RECOMMENDATIONS AND GUIDELINES FOR PERINATAL MEDICINE

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and

MATRES MUNDI INTERNATIONAL

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and

- International Society «The Fetus as a Patient»

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FOREWORD

by FRANK A. CHERVENAK

President Elect of World Association of Perinatal Medicine (WAPM)

Given Foundation Professor and Chairman
New York Presbyterian Hospital
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The most perilous journey in everyone's life is the joumey from conception through the perinatal period. During the past generation, in the developed countries, tremendous advances have been made in perinatal medicine, both before and after birth. To optimize the care of fetal and neonatal patients, all perinatologists should practice medicine to the highest standards of care. Such standards are constantly evolving and require excellent clinical judgement to compliment the best available evidence.

Unfortunately the situation in the developing countries is very different. The above mentioned advances, have only been applied partially in those regions, so the rates of maternal and perinatal mortalities continue to be very high.

Such dramatic situation of the maternal and infant health in those countries, obbligues as to elaborate guidelines and clinical recommendations adapted to the resources and possibilities of the Health Systems in those geographical areas. Of course, the aim is to obtain the best possible perinatal results with the intelligent application of the scarce present means. And definitively this is also the objective of this book.

To compile the best available evidence in a readable and clinically useful, succinct manner, is a challenge for the brightest minds in the field. The Editors J. M. Carrera, X. Carbonell, and E. Fabre have coordinated such an effort, utilizing the talents of the foremost obstetricians and neonatologists that the world has to offer. Countless hours of literature review, discussion, and synthesis were necessary to produce the outstanding result.

The fjrst section introduces the work with an overview of important background topics, such as terminology and statistics that set the stage for later sections. Pregnancy is then covered by addressing the spectrum of topics that affect the fetal patient. The section on labor and operative obstetrics deals with labor and delivery issues, which are especially important in the increasing medical-Iegal environment. The puerperal period follows with a discussion of the important complications which may occur. Focus is then directed on the low-risk and high-risk neonatal patient. The volume ends with an original and challenging section on recommendations to diminish both maternal and perinatal mortality.

«Recommendations and Guidelines for Perinatal Medicine» is an intemational tour-de-force that should be read by every physician and health care provider who cares for maternal, fetal, and neonatal patients. The world of perinatal medicine is grateful to Drs. Carrera, Carbonell, and Fabre and the many authors for their commitment and devotion to this project and the evolving challenge of improving perinatal medicine throughout the world.

New York, July 2007

PREFACE

by José M. Carrera

Chairman of the Solidarity Committee of the World Association of Perinatal Medicine (WAPM)

Secretary General of WAPM

President of MATRES MUNDI INTERNATIONAL

The decision to write and publish this work was taken by the Board of the World Association of Perinatal Medicine (WAPM) at it ordinary meeting held in Prague (Czech Republic, May 2006). At this meeting, MATRES MUNDI INTERNATIONAL, WAPM's solidarity agency, was entrusted with taking all the necessary steps to make this project a reality. The decision arose from the WAPM's desire to provide perinatologists in developing countries with a useful tool for laying down suitable guidelines for health care workers on maternal wards.

Readers thus have before them a very special book. Its title, «Recommendations and Guidelines for Perinatal Medicine», is fairly self-explanatory. However, unlike other books of its kind it is not addressed to obstetricians and neonatologists in developed countries, but to mother and child health care professionals in low and medium-low income countries, which in politically correct terms are known as developing countries. Therefore, in theory at least, these guidelines should prove to be useful for perinatologists in most countries in Africa, Asia, Australasia and Latin America.

Current existing guidelines may be divided into two categories: those for high income western countries, which therefore describe state-of-the-art protocols that are completely unattainable by professions in poor countries; and those based on recommendations issued by the WHO and its agencies, which include very simple practices and procedures whose sole objective is to prevent the dramatic mother and child health care scenario in low income countries from deteriorating any further. As mentioned above, this work is somewhat different as it should prove to be useful to between 60 and 70% of the world's population with limited resources whose health care professionals wish to practise Perinatal Medicine in a straightforward but effective manner. This explains why, as the reader will find out, physiopathological treatises have been omitted, the description of the various nosological case studies are intentionally straightforward, the recommended technological resources are limited to the most accessible ones available, whilst emphasis has been placed on the most practical aspects of perinatal practices. This does not however detract from its high degree of scientific learning. To give just one very obvious example, the level of technological sophistication does not go beyond ultrasonography, and on no account are more complex, expensive diagnostic procedures included.

A doubtless riches of this book consist in the great number of prestigious perinatologists (obstetricians and neonatologists, etc.) that have collaborated in it.

But this fact also conditions some of its weaknesses: overlaping, differences of criteria, and above all several points of view concerning the desirable level of one text destineted to the low o medium-low income countries. These circumstances have conditioned that

the editorial coordinators have had to modify, change, amplify or parcial amputate the text of some chapters in order to assure a minimal coherence. A necessary intervention for which i personally ask for comprehension, tolerance and benevolence to the authors.

Just over one year ago, the collaboration between the WAPM and Matres Mundi made possible the publication of a work entitled «Maternal and Infant Health in the World», which was received with great interest not just by mother and child health care professionals but also by humanitarian associations and agencies that work in the field of health. By revealing the scandalous proportion of maternal and perinatal mortality and the sad reality of health care that prevails in the world's poorest countries, this publication to some degree contributed to the spirit of solidarity with these countries that has emerged. As a result of this, MATRES MUNDI and scientific societies worldwide involved in mother and child health care have drawn up an «Integral Plan for the Reduction of Maternal Mortality in Central Africa», which is about to be implemented. Other projects will follow this one that will progressively be set in motion in the most deprived areas in the world. This book goes some way to forming part of the practical resources that have been devised for the above-mentioned Plan, as it is widely believed that the good training of doctors, midwives and nurses in developing countries is the key factor for improving mother and child health care in these countries.

The authors who have made contributions to this work are all members of the World Association of Perinatal Medicine (WAPM), which is a scientific society that brings together all of the perinatologists in the world. They therefore come from the four corners of the earth. It is a telling fact that the Supervising Committee of this work is made up of the leading figures on the WAPM Board and its International Council. These people are drawn from the world's most prestigious departments of obstetrics, neonatology and perinatal medicine.

MATRES MUNDI INTERNATIONAL, the humanitarian association that acts as the WAPM's solidarity agency, sets the benchmark for NGOs worldwide that work in the field of mother and child health care. It has deployed its infrastructures to ensure the publication of this work. The financial backing needed was provided by ORDESA Foundation. The book will therefore be available free of charge to all hospitals worldwide that request it. All mother and child health care professionals in the world will also be able to download the full version of the book from the Matres Mundi and WAPM websites at: **www.matres-mundi.org** and **www.wapm.info.**

It cannot be too strongly stressed that this book is a good example of the synergies that may be achieved between scientific institutions, humanitarian associations and benefit foundations. It also illustrates how these synergies can bear fruit.

Thus, as the coordinating editor of this book, I wish to express my thanks to the institutions that have made its publication possible and I am particularly indebted to the authors and supervisors of the work. I hope that the efforts made live up to the expectations of perinatologists in developing countries.

Barcelona, July 2007

GENERAL PART

CHAPTER 1

Terminology in perinatal medicine

D. Orós López | S. Rueda Marín | E. Fabre González

GENERAL PART

INTRODUCTION

The term perinatology was introduced in 1936 by the German paediatrician Pfaundler to define a period around the birth, characterize by a high fetal and neonate mortality, but with death causes different from those observed in older infants[1]. Perinatal medicine has as aim to improve the quality of life from its beginnings, through the fetal and newborn care.

A precise terminology is required in order to describe all the events associated with perinatal outcome. International comparison of perinatal and neonatal mortality and its components is important. That information allows identifying problems, tracking temporal and geographical trends and disparities and assessing changes in public health policy and practice[2].

TERMINOLOGY

DELIVERY

Delivery is the main event of perinatology, marking the end of the fetal life. Very high risk is associated with the moment of delivery. Legal and medical implications forced to pay attention at the definition criteria of delivery[3].

Delivery: «The complete expulsion or extraction from its mother of a product of conception with a weight of 500 g or more, regardless of the gestational age, whether or not the umbilical cord has been cut or the placenta is attached[3].»

Newborns that weights less than 500 g should not be included in the perinatal statistics. In case of the birth weight was unknown, 500 g of fetal weight is assumed as 22 weeks of gestation. If both birth weight and gestational age were unknown, a crown-heel length of 25 cm is equivalent to 500 g.

BIRTH WEIGHT

Birth weight is an important perinatal variable, strongly correlated with overall morbidity and mortality outcomes. The highest mortality rate occurs in the newborns weighing less than 1.000 g[4]. As it is an easy parameter to obtain, it is together, with gestational age, the main data to record for perinatal statistics.

Birth weight: «Birth weight is defined as the first weight of the fetus or newborn obtained after birth. For live births, birth weight should preferably be measured within the first hour of life before significant postnatal weight loss has occurred. While statistical tabulations include 500 grams groupings for birth weight, weights should not be recorded in those groupings. The actual weight should be recorded to the degree of accuracy to which it is measured[3].»

In order to study and predict bad neonatal outcomes, birth weight may be catalogue as:

LOW BIRTH WEIGHT

Birth weight less than 2500 g (up to and including 2.499 g).

VERY LOW BIRTH WEIGHT

Birth weight less than 1500 g (up to and including 1.499 g).

EXTREMELY LOW BIRTH WEIGHT

Birth weight less than 1.000 g (up to and including 999 g).

These definitions do not constitute mutually exclusive categories. Below the set limits they are all-inclusive and therefore overlap.

GESTATIONAL AGE

Pregnancy control turns around the evolutionary process of fetal development. Gestational age at delivery is well correlated with perinatal morbidity and mortality. Only less than one in ten births are preterm, but these newborns undergo almost two thirds of perinatal mortality. Even not been always feasible, it is very important define as more accurately as possible the gestational age.

Gestational age: «The duration of gestation is measured from the first day of the last normal menstrual period. We could express gestational age in completed days or completed weeks[3].»

For the purposes of calculation of gestational age from the date of the first day of the last normal menstrual period and the date of delivery, it should be borne in mind that the first day is day zero and not day one; days 0-6 therefore correspond to «completed week zero»; days 7-13 to «completed week one»; and so on. In order to avoid misunderstanding, tabulations should indicate both weeks and days.

Measurements of fetal growth, as they represent continuous variables, are expressed in relation to a specific week of gestational age (e.g. the mean birthweight for 40 weeks is that obtained at 280-286 days of gestation on a weight-for-gestational age curve).

Nowadays it is assumed that the ultrasound assessment is the best way to confirm the first day of the last menstrual period. In case that ultrasound measurement or the date of the last normal menstrual period are not available, gestational age should be based on the best clinical estimate.

According to the gestational age at delivery, different periods of pregnancy may be defined[5]:

PRE-TERM

When delivery occurs before 37 completed weeks (less than 259 days) of gestation.

TERM

When delivery occurs from 37 completed weeks to less than 42 completed weeks (259 to 293 days) of gestation.

POST-TERM

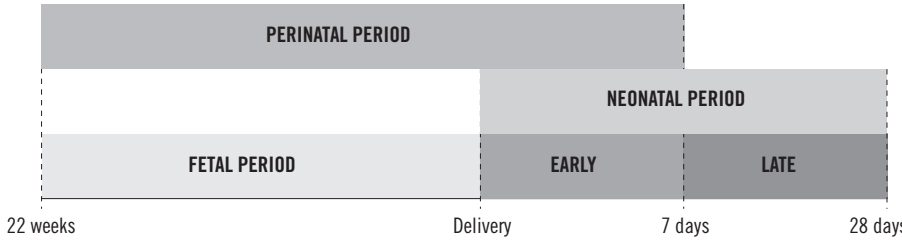
When delivery occurs after 42 completed weeks or more (294 days or more) of gestation.

PERINATAL PERIOD

Fetal life and early neonate life are the periods studied by perinatolgy.

Perinatal period: «The perinatal period commences at 22 completed weeks (154 days) of gestation. As it has been said before, this is the time when birth weight is normally around 500 grams, and ends seven completed days after birth[3].»

Perinatal period is divided in:



FETAL PERIOD

The fetal period starts at 22 completed weeks (154 days) of gestation, and ends with birth.

NEONATAL PERIOD

The neonatal period commences at birth and ends 28 completed days after birth. Neonatal period is also divided in:

EARLY NEONATAL PERIOD

Early neonatal period commences at birth and ends 7 completed days after birth.

LATE NEONATAL PERIOD

Late neonatal period commences 7 completed days after birth and ends 28 complete days after birth. It is important to remark that late neonatal period is not included in the perinatal period.

FETAL AND NEWBORN MORTALITY

Because of its high incidence, perinatal mortality is not everywhere perceived as a problem. Perinatal mortality is an important indicator of maternal care, and the quality of obstetric and paediatric care available, playing an important role in providing the information needed to improve the health status of pregnant women and newborns.

There are great differences in the way in which stillbirths and neonatal deaths are recorded. It is very important improve the quality of reporting and clinical diagnosis of causes of perinatal death[6].

Live birth: «Live birth is the complete expulsion or extraction from its mother of a product of conception, irrespective of the duration of the pregnancy, which, after such separation, breathes or shows any other evidence of life, such as beating of the heart, pulsation of the umbilical cord, or definite movement of voluntary muscles, whether or not the umbilical cord has been cut or the placenta is attached; each product of such a birth is considered liveborn[3].»

Fetal death (stillbirth): «Fetal death is death prior to the complete expulsion or extraction from its mother of a product of conception, irrespective of the duration of pregnancy; the death is indicated by the fact that after such separation the fetus does not breathe or show any other evidence of life, such as beating of the heart, pulsation of the umbilical cord, or definite movement of voluntary muscles[3].»

Intrauterine death occurs either before onset of labour, antepartum death, or during labour, intrapartum death. While international attention and interventions focus on liveborn infants, stillborn infants have largely been overlooked. Stillbirths represent more than half of perinatal deaths. More than one third of stillbirths take place intrapartum, during delivery, and are largely avoidable[2].

$$\textbf{Stillbirth mortality rate} = \frac{\text{Stillbirth}}{\text{Total newborns}} \times 1.000$$

Intrapartum death rate is a very important indicator enabling health personnel to take the most appropriate measures to prevent such deaths. Consequently the risk of an intrapartum stillbirth is on average 14 times greater in developing than in developed countries, increasing up to 17 times this value in the least developed countries[7].

PERINATAL MORTALITY

The perinatal mortality covers the deaths ocurred during fetal period leading up to birth and the first week of life. Deaths occurring in this period are largely due to obstetric causes.

$$\textbf{Perinatal mortality rate} = \frac{\text{Stillborn} + \text{Early neonatal death}}{\text{Total newborns}} \times 1.000$$

Perinatal mortality rate is one of the best perinatal health indicators, because:

- Death is a specific and easy recognisable event.
- The cause of death it is not needed to calculate it.
- Perinatal mortality rate groups together the stillbirths and early neonatal deaths.

On the other hand, perinatal mortality rate is not a precise indicator, since it ignores an amount of factors associated with perinatal deaths:

- Gestational age and birth weight, main factors correlated with perinatal death, are not reflected.
- Perinatal mortality rate does not give any information about the cause of death, and avoidable deaths.
- There is a communication bias, due to lower than real registration of perinatal mortality in many areas.

NEONATAL MORTALITY

Neonatal mortality relates to the death of live-born infants during the neonatal period, which begins with birth and covers the first four weeks of life.

Neonatal mortality may be subdivided into early and late neonatal deaths. In developing regions, the risk of death in the neonatal period is more than six times that of developed countries. In the least developed countries, it is more than eight times higher[2].

EARLY NEONATAL MORTALITY

Early neonatal mortality relates to the death of live-born infants during the first week of life, which is also part of the perinatal period. Age at death during the first day of life, day zero, should be recorded in units of completed minutes or hours of life. For the second and followed days, age at death should be recorded in days[8].

$$\textbf{Early neonatal mortality rate} = \frac{\text{Early neonatal death}}{\text{Live births}} \times 1.000$$

The majority of deaths occur soon after birth, some just before birth. All over the world, early neonatal mortality represents about three quarters of neonatal mortality. Obstetric origins of early neonatal deaths and stillbirth are similar.

LATE NEONATAL MORTALITY

Late neonatal mortality relates to the death of live-born infants during the period between the first and fourth weeks of life. Late neonatal mortality is not part of the perinatal period.

OTHER RECOMMENDATIONS

«World Health Organization recommends that, if possible, all fetuses and infants weighing at least 500 g at birth, whether alive or dead, should be included in the statistics. The inclusion in national statistics of fetuses and infants weighing between 500 g and 1.000 g is recommended both because of its inherent value and because it improves the coverage of reporting at 1.000 grams and over. For international comparison, 1.000 g and/or 28 weeks gestation is recommended[5].»

The legal requirements for registration of fetal deaths and live births vary between and even within countries. Cultural and religious backgrounds may affect the decision whether to classify a delivery long before term as a spontaneous abortion or as a birth.

MATERNAL MORTALITY

The death of a mother is a terrible tragedy. Maternal mortality is one of the best parameters in perinatal health evaluation.

Maternal mortality: «Maternal death is the death of a woman while pregnant or within 42 days of the end of the pregnancy, irrespective of the duration and the site of the pregnancy, due to any cause related to or aggravated by the pregnancy or its management, but not from accidental or incidental causes[6].»

The above definition requires that there be both a temporal and a causal link between pregnancy and the death. When the woman died, she could have been pregnant at the time, that is, she died before delivery, or she could have had a pregnancy that ended in a live or stillbirth, a spontaneous or induced abortion or an ectopic pregnancy within the previous 6 weeks. The pregnancy could have been of any gestational duration.

In addition, the death was caused by the fact that the woman was or had been pregnant. Either a complication of pregnancy or a condition aggravated by pregnancy or something that happened during the course of caring for the pregnancy caused the death. In other words, if the woman had not been pregnant, she would not have died[6].

$$\textbf{Maternal mortality ratio} = \frac{\text{Number of mother deaths}}{\text{Live births}} \times 100.000$$

When time is take into consideration:

LATE MATERNAL DEATH

Deaths occurring between 43 days and one year after abortion, miscarriage or delivery. They can be due to direct or indirect causes. Identifying late maternal deaths makes it possible to take into consideration deaths in which a woman had problems that began during pregnancy, even if she survived for more than 42 days after its termination.

Maternal deaths can be subdivided into further groups:

DIRECT MATERNAL DEATHS

Those resulting from conditions or complications, or their management, which are unique to pregnancy and occur during the antenatal, intrapartum or postpartum period.

INDIRECT MATERNAL DEATHS

Those resulting from previously existing disease or disease developing during pregnancy which was not due to direct obstetric causes, but which was aggravated by physiologic effects of pregnancy. Examples of indirect deaths include epilepsy, diabetes, cardiac disease and hormone-dependent malignancies.

OTHER MATERNAL MORTALITY INDICATORS

LIFETIME BIRTHS PER WOMAN

The total fertility rate, defined as the number of children a woman would have if current age-specific fertility rates remain constant throughout her childbearing years[9].

PERCENT OF BIRTHS ATTENDED BY SKILLED PERSONNEL

Skilled personnel include doctors, nurses, and midwives[10].

LIFETIME CHANCE OF DYING FROM MATERNAL CAUSES

The probability that a woman will die during her lifetime from causes related to pregnancy and delivery. The measure combines the probability of becoming pregnant and the risk of death from each pregnancy[9].

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CHAPTER 2

Recommendations for collection and elaboration of reproductive health statistics

GENERAL PART

D. Orós López | S. Rueda Marín | E. Fabre González

INTRODUCTION

Reproductive health is a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity, in all matters relating to the reproductive system and to its functions and processes. Reproductive health therefore implies that people are able to have a satisfying and safe sex life and that they have the capability to reproduce and the freedom to decide if, when and how often to do so. It also includes sexual health, the purpose of which is the enhancement of life and personal relations[1, 2].

In fact, reproductive health affects the lives of women and men from conception to birth, through adolescence to old age, and includes the attainment and maintenance of good health.

Major changes are taking place in the area of maternal and child health all over the world. The need for evaluation and information has, therefore, become increasingly apparent. Research provides evidence of health care practices and interventions. Different approaches can be used for reviewing a wide range of aspects of health, but the general principles in perinatology, are obviously the same as in other scientific fields[3]:

1. Identify the research question.
2. Acquire the information.
3. Analyze the information.
4. Apply the results and disseminate the findings.
5. Evaluate the actions

IDENTIFY THE RESEARCH QUESTION

The first step and a central methodological issue in all research actions, is identify the research question. The research question must have genuine medical, social and/or scientific value that the research methods used give a good chance of obtaining findings that

are trustworthy, and that the value and quality of the new knowledge gained or set risks to the subjects of participating in the study[4]. The final purpose of any research action in medicine is to improve the health. All the actions executed during the research development, should be distinguishable, justifiable, and compatible with the needs of the patient or population.

A good medical research question must take in consideration[5]:

- Patient target.
- Intervention to analyze.
- Comparison (not always).
- Outcomes.

ACQUIRE THE INFORMATION

Acquire the information is an important and unfortunately often difficult process in perinatology. Following steps could be helpful in collecting the information.

DEVELOPMENT OF THE RESEARCH PROTOCOL

Once the research question is well defined, a protocol plan should be considered. When planning the investigation, a number of questions must be taken into consideration[6]:

- What is the objective of the study?
- How will cases be identified?
- Where and by whom will cases be examined?
- How many cases are expected and what is the workload likely to be?
- What resources are available?
- Who can act on the results?
- What or who is the driver for change?
- Who are the key stakeholders?

It is essential that a good quality study report the exact enrolment procedures used by the study investigators. Ideally, a study protocol should not only give the report for purposes of inclusion or exclusion, instead, the clinical workup and diagnostic criteria need to be described sufficiently well so that a reader would be able to replicate the study's enrolment procedures[4].

Retrospective studies sometimes present more difficulties in preparing the research approach, because existing records may only document incompletely or inconsistently information. Prospective studies, particularly clinical trials, are more likely to employ uniform procedures for screening and enrolment.

Legal and ethical considerations are important when investigating perinatal events. Investigation protocol must always respect both. The laws and customs of a particular country or culture can have a significant impact on the process of investigation, helping or hindering access to information, the involvement of the population and professionals, the conduct of the investigation, and the ways the findings are used[6].

DEFINE THE OUTCOMES

Objectives are an essential component in the aims of the research. In order to quantify the purpose of the study, outcomes must be well choose in order to be powerful enough indicators able to answer the research question.

Indicators are markers of health status, service provision or resource availability, designed to enable the monitoring of service performance or programme goals[1]. An awareness of an indicator's inherent limitations is crucial to ensuring its effective use. Most importantly, indicators should be regarded as indicative or suggestive of problems or issues needing action. In some cases, indicators are measurements that have the power to summarize, represent or reflect certain aspects of the health of persons in a defined population. In other cases, they may simply serve as indirect or proxy measurements for information that is lacking. Indicator must be able to «measure progress» towards agreed goals. Several indicators could be chosen to study the perinatal health status. As an example, United Nation suggests the most important reproductive health indicators (table I).

Table I. Indicators for global monitoring of reproductive health. The Millennium Declaration. United Nations[1]

1. Total fertility rate.
2. Contraceptive prevalence.
3. Maternal mortality ratio.
4. Antenatal care coverage.
5. Births attended by skilled personnel.
6. Availability of basic essential obstetric care.
7. Availability of comprehensive essential obstetric care.
8. Perinatal mortality.
9. Prevalence of low birth weight.
10. Prevalence of positive syphilis serology in pregnant women.
11. Prevalence of anaemia in women.
12. Percentage of obstetric and gynaecological admissions owning to abortion.
13. Reported prevalence of women with genital mutilation.
14. Prevalence of infertility in women.
15. Reported incidence of urethritis in men.
16. Prevalence of HIV infection in pregnant women.
17. Knowledge of HIV-related preventive practices.

A good outcome should answer to these questions[2]:

- Are the outcome measures meaningful?
- Are the outcome measures sensitive enough to detect important changes?
- How are outcomes going to be compared?

Best outcome as possible must be selected in order to answer the main research question (table II).

Table II. Characteristics of an optimum indicator[2]

Scientifically robust	An indicator must be a valid, specific, sensitive and reliable reflection of that which it purports to measure.
Valid	An indicator must actually measure the issue or factor it is supposed to measure.
Reliable	An indicator must give the same value if its measurement were repeated in the same way on the same population and at almost the same time.
Sensitive	An indicator must be able to reveal important changes in the factor of interest.
Specific	An indicator must reflect only changes in the issue or factor under consideration.
Useful	An indicator must be able to act as a «marker of progress» towards improved reproductive health status, either as a direct or proxy measure of impact or as a measure of progress towards specified process goals.
Representative	An indicator must adequately encompass all the issues or population groups it is expected to cover.
Understandable	An indicator must be simple to define and its value must be easy to interpret in terms of reproductive health status.
Accessible	The data required should be available or relatively easy to acquire by feasible data collection methods that have been validated in field trials.
Ethical	An indicator must be seen to comply with basic human rights and must require only data that are consistent with the morals, beliefs or values of the local population.

DATA COLLECTION

Contextual considerations primarily involve the source and method of data collection. Deciding which of the approaches to use is influenced by two considerations, which level is appropriate for the review, and what kind of cases will be studied. In terms of level, the communities, health care facility, district, regional or national are the options. In choosing which cases to study, a decision needs to be taken whether these will be outcomes or processes. Not all locations are suited to reviewing all types of cases. In resource-poor countries, it is unlikely to be possible to review severe complications or clinical practice at the community level[6].

Reliability of data depends on reliable reporting and recording. Underreporting and misclassification are common, originating both with the mother and with the recording mechanism. The reason for underreporting may be due to tedious process of registration, ignorance of requirements, or economical causes. Normally, live births are more likely to be reported than stillbirths or early neonatal deaths. Stillbirth data are available for fewer countries and are less consistent than early neonatal and neonatal mortality data[2].

DATA SOURCES

It is important to identify what types of information are available. Health care planners, managers and professionals have access to multiple sources and types of information useful in planning the activities. Information could be obtained from different stratus. Population-based data, as well as vital registration systems, can provide information on the population as a whole. Routine health information activities and systems provide health service-related information (table III).

Reliable vital registration is available for only about one third of the world's population. Many countries have information systems, which are useful for international reporting.

Table III. Different approaches to data sources

General population data	*Censuses or health surveys*
Community identification	Disease surveillance systems: government-run disease surveillance systems to which certain specified diseases or conditions must be reported on a routine, timely basis with obliged declaration.
Vital records	Reporting of vital events refers to the outcomes of live births, such as the birth and death of an infant or death later in life.
Facility-based surveys	Patient records: from hospitals or other health care facilities. Offers trustable information depending on the quality of health facilities.
Community-based surveys	Verbal autopsy: a community-based case review (RAMOS).

Unfortunately, such systems in most developing countries are inadequate. International comparability may be undermined, however, by variations in the reliability and heterogeneity of the basic data. The analysis of these sources should therefore be treated with a certain degree of caution[7].

DATA FORMS

Once the approach to implement is known, standardized questionnaires for data collection need to be developed. When developing the form, it is important to bear in mind the purpose of the survey and have a clear understanding of what the plan is for analysing the data. The forms should be developed and tested before the general implementation.

POPULATION SAMPLE

Bigger is not always better. The number of cases investigated will depend on the number of cases identified and the resources available. The number should be large enough to provide information on a variety of factors associated with death or severe morbidity and to allow conclusions to be drawn.

ANALYSIS

The interpretation of reproductive health indicators is currently a challenge. Quantitative and qualitative analysis must be done. Quantitative analysis shows which groups of the population studied may be at higher risk, such as women from specific ethnic groups or places of residence, or who have other characteristics in common. Qualitative analysis provides more detailed information on the precise causes of the target for each individual.

Important bias can result where the analysis methodology does not reflect the study design. The key is to distinguish between real and artificial differences. Nevertheless, it is important to bear in mind that explanations for change reflected by health indicators are usually multiple and interrelated.

Some frequent errors are[1]:

- Low precision of sample.
- Changes in reporting bias over time.

- Changes in procedures for data collection.
- Revisions in definitions and values related to health.
- Changes in the socioeconomic characteristics of the population.
- Long-term stability of aggregate levels of health statistics.
- Lack of data to control for confounding factors.

APPLY THE RESULTS AND DISSEMINATE THE FINDINGS

All the work should be directed to taking actions. Action taken may depend on the approach used, who was responsible for the investigation, stakeholder involvement and the findings of the analysis.

Science's base is dissemination of the knowledge. A plan to disseminate the results of any investigation should be determined in advance, although flexibility should be built in, particularly in the face of unexpected results. The format and dissemination of the report depends on the circumstances in which it will be produced and the resources available. The team involved in undertaking the work should be fully involved in developing and implementing the recommendations.

EVALUATE THE ACTIONS

Last step of the process is evaluating the impact of the recommendations that were made. The main purpose of evaluation is to consider if the process improved the perinatal health, well-being and safety of pregnant women and their offspring.

The process can be evaluated by looking for improvements in the community, in the health care system, or in society in general. Depending on what factors were found to be responsible the morbidity and what actions were taken, different aspects of the overall process might be evaluated.

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CHAPTER 3

GENERAL PART

Health education during pregnancy

L. S. Voto | M. J. Mattioli

INTRODUCTION

There are several situations not linked to the presence of different pathologies during gestation, and often regarded as independent of medical care, which can significantly impact the course of pregnancy and which are mainly associated with the patients' mental health and socio-cultural status.

In this context, Healthcare Education plays a crucial role within the routine prenatal visit. It conveys basic information about lifestyle choices and attitudes to promote both the mother's and baby's good health.

Additionally, Healthcare Education aims to encourage not only the mother but the whole family to change old practices and acquire new behaviors to maintain a healthy lifestyle. It should also advocate the active role of the father and other family members during prenatal care in order to attain the necessary emotional support for the mother and build stronger bonds with the newborn.

HEALTH CARE DURING PREGNANCY

THE PRE-CONCEPTION VISIT

The pre-conception visit allows the healthcare provider to obtain information about several physical, mental and social aspects as well as other everyday life issues which could impact the future pregnancy and fetal development.

Its main objectives are:

- To diagnose the patient's individual risks and/or those associated with her environment.
- To provide general health information to the future parents.

- To give counsel regarding lifestyle changes.
- To warn about the possibility of having to progressively reduce the amount of physical activity (work).
- To prescribe folic acid to prevent neural tube defects (NTD). Information about the benefits of taking folic acid should be given to all future mothers. Those patients who had babies with neural NTD should be advised of the higher risk of recurrence in their future pregnancies and should be offered continued folic acid supplement[1].

PRENATAL CARE

This is the time for healthcare providers to answer all the questions and queries that the parents may have which may prevent them from fully enjoying pregnancy.

NUTRITION

This is a very important aspect of Healthcare Education. Nutrition excesses or deficits can have serious consequences during gestation. An adequate nutrition plan should ensure the normal growth and development of the fetus. The diet should be well balanced and include four meals and two snacks a day. Overall weight gain should not exceed 10 to 12 kilograms and should be more pronounced during the last months of pregnancy, when the fetus grows in volume.

Calories:

— Do not increase calorie intake during the first trimester of pregnancy.

— Increase 300 calories during the second and last trimesters of pregnancy.

— Emphasize that diets of less than 1,600-1,700 calories should not be followed due to the possible production of ketonic bodies which produce psychomotor damage in the fetus.

— The recommended percentages of macro nutrients in the Total Caloric Value are:

- Carbohydrates: 55% (increase intake of complex carbohydrates, grains, fruits and vegetables).
- Proteins: 15% (recommended daily intake: 60 grams per day).
- Fat: 30% (increase intake of omega 3 and 6 fatty acids).

Water. Water intake is necessary due to the increment of blood and fluids during pregnancy. A daily intake of 2 liters of water promotes proper renal function and prevents infections. The water requirement should be higher in patients engaging in strenuous physical activity.

Fiber. An adequate intake of fiber maintains the healthy peristaltic activity of the colon. A diet that incorporates 25 to 35 grams of fiber daily prevents constipation, a condition that is very common during pregnancy

Vitamins. Vitamins are essential for tissue metabolism, especially during growth. Therefore, the requirement of vitamins increases during pregnancy. It is important to consider the potential vitamin toxicity —the fetus could be more susceptible to this condition than the mother.

LIFESTYLE

For decades, the consumption of illegal drugs was linked to people morally weak, teenagers, or criminals. Today, that concept proves to be obsolete, as illegal drugs consumption is widespread among the population.

Several studies have shown that substances considered harmless to the mother could have unwanted effects on the fetus. Prenatal exposure to alcohol, nicotine, and illegal drugs has been associated with adverse perinatal outcomes.

Caffeine. It is recommended to limit the consumption of caffeine during pregnancy. Excessive intake can disrupt the heart and breathing rates of the fetus. Caffeine is known to cross the placenta; therefore, its intake should not exceed 400 milligrams a day, at least until definitive answers about its toxicity for the fetuses are found.

Alcohol. Alcohol drinking is embedded in our culture. This interferes with the efforts to limit its consumption during and out of gestation. According to data provided by the Center for Disease Control and Prevention (CDC)[2], 13% of pregnant women consume alcohol, and 3% do it excessively (5 or more alcoholic beverages at a time) or frequently (7 or more alcoholic beverages per week). Alcohol consumption during pregnancy can cause a myriad of birth defects, ranging from those with little significance to lasting disabilities.

The term Fetal Alcohol Spectrum Disorders describes all disorders associated with fetal exposure to alcohol before birth. The most serious one is the Fetal Alcohol Syndrome (FAS), which presents with a combination of physical and mental birth defects. Its prevalence is estimated to be from 0.2 to 1.5/1,000 liveborns, which translates to 1,000 to 6,000 babies born with FAS per year. In addition, the CDC also estimates that the cases of babies born with less significant complications (consequences) related to alcohol are three-fold. FAS is one of the leading causes of mental retardation and the only one that is completely preventable. Consumption of alcohol during pregnancy increases the chances of spontaneous miscarriage, low weight births (less than 2,500 grams) and stillbirths.

It is likely that birth defects associated with alcohol intake (such as cardiac and facial defects) are linked to its consumption during the first trimester of pregnancy. However, alcohol consumption in any stage of pregnancy can negatively affect the brain as well as growth. Since it has not been established what a «safe dose» of alcohol consumption during pregnancy would be, it is imperative to advocate abstinence during the course of pregnancy.

Tobacco. The CDC, in its report Births 2002[3], stated that in the USA, at least 11% of pregnant women smoke. Moreover, it found that 12.2% of babies born to smokers suffered from low birth weight (less than 2,500 grams), in contrast to 7.5% of babies born to nonsmokers.

Tobacco consumption is also linked to spontaneous abortion (genetically normal embryos), placenta previa, placental abruption, premature rupture of membranes, preterm delivery, intrauterine growth restriction, birth defects, and sudden infant death. It is also responsible for 15% of all preterm deliveries, 20 to 30% of low birthweight newborns, and a 150% increase in global perinatal deaths.

Interventions designed to decrease tobacco consumption during pregnancy often result in permanently quitting smoking, which reduces the risk of low birth weight by 20% and of preterm deliveries by 17%[4].

Consequently, patients should be warned of the risks associated with smoking during pregnancy. They should also be informed of the increased incidence of respiratory disorders and sudden infant death in babies that grow and live in smoking households.

Illegal Drugs. The consumption of illegal drugs by pregnant women is unequivocally associated with a clear increase in birth defects, such as cardiac and musculoskeletal defects, and absence of limbs. In many cases it triggers miscarriages and stillbirths, or is allied to malnourished newborns.

Although many studies have focused on the consequences of the exposure to high doses of illegal substances, recent findings suggest that more attention should be given to fetal exposure to low or moderate doses of those agents[5].

Given that illegal drugs consumption is generally kept private, it is very likely that pregnant women will not talk freely about their addiction. This topic should be included in the initial questionnaire of prenatal care visits.

The patients should be counseled about the risks that the consumption of illegal drugs pose for the mother-to-be and the fetus. It is also important, as is in the case of tobacco and alcohol consumption, to assess the roots of such behaviors, which are frequently associated to underlying social or family pressures or depression.

EXERCISE

Several studies suggest that regular exercise during pregnancy may carry many important benefits not only for the mother, but for the fetus as well. For the mother, exercise would help her control weight gain and the build-up of body fat, reduce the incidence of gestational diabetes and stress, and boost her feeling of well being. For the fetus, exercise would control the build-up of body fat and enhance neurological development, both up to 5 years of age[6].

The American College of Obstetricians and Gynecologists (ACOG)[7, 8] drew up guidelines on recommended exercise during pregnancy, which were later questioned on the basis of lack of scientific evidence after a systematic revision carried out by Cochrane[9].

ACOG GUIDELINES (1994)

- Given its beneficial cardiovascular, metabolic and biomechanical effects, regular exercise is recommended to healthy women with low risk pregnancies.
- Exercise should be done regularly, three or more times per week, with a moderate intensity that should not cause fatigue. If the patient exercised regularly before becoming pregnant, she can follow a more intensive exercise regime.
- Exercise sessions must be of limited duration and intensity, and should be carried out in an optimal environment with respect to hydration and nutrition.
- Each exercise session should be preceded by a warm-up period and followed by a subsequent cool-down time.
- The type of exercise should minimize fetal risk and maternal injury. Stationary bicycles and swimming are strongly recommended.
- Pregnancy complications or chronic diseases are relative or absolute contraindications of physical activity.

WORK

Pregnant women are faced with the challenge of balancing a career and domestic duties, such as caring for children and household chores, which are oftentimes more demanding than their own job.

Many countries base the legislation that sets labor standards during pregnancy on the provisions of the International Labor Organization (ILO). Treaty concerning the protection of maternity (revised), 1952 (number 103), and the recommendation to protect maternity, 1952 (number 95), which guarantee safe labor conditions and the right to maternity leave for all the women in the world[10].

The medical recommendations proposed by ACOG and NIOSH (National Institute for Occupational Safety and Health) concerning work during pregnancy can be grouped into three different categories:

- «Healthy women who have no complications during their pregnancy, whose jobs do not pose more risks than those of every day life, and who can work without interruptions up to their labor day, and can return to work a few weeks after delivery without any complications» (Isenman and Warshaw, 1977). This is the scenary of the majority of the cases.
- Pregnant women who can continue to work but only after adjustments in their work environment or modifications of their activities are carried out in order to eliminate all risks to their pregnancies.
- Pregnant women who should not work by medical prescription, whose health care providers consider their jobs a risk to their health or to that of their developing fetus.

Recommendations should not only specify the adjustments that need to be made at work, but also a time frame for them to be completed and the date of the next prenatal visit.

These recommendations serve as guidelines for the health care professional, who can categorize each patient and offer her appropriate advice.

The American Medical Association created the following recommendations for working pregnant women.

- Take breaks every two hours
- Take a longer break and eat every four hours
- Drink plenty of fluids during the work day
- Change positions frequently while at work: sitting to standing and walking.
- Lifting heavy objects and bending down should be kept to a minimum

In July 2006, the First Consensus of Preterm Labor took place in Argentina, sponsored by the Buenos Aires Society of Obstetrics and Gynecology (SOGIBA). Considering the relationship between work and pregnancy, the consensus argued for the importance of bed rest. It is crucial to progressively reduce the hours of physical work during pregnancy. If the job requires intense physical activity, and no modifications can be made, rest should be prescribed.

ACCIDENT PREVENTION

The most serious injuries sustained by pregnant women are usually caused by automobile accidents. It is vital to advise patients to drive carefully and always buckle up. The vertical

band of the seat belt should be positioned between the breasts and the horizontal band adjusted across the lap, avoiding any pressure on the abdomen. Air bags should not be deactivated; it has been proven that air bags save lives. It is not the impact against the air bags that causes injuries to the fetus, but the impact of the car crash itself.

If the pregnant woman is not driving, her safest place is sitting in the back seat, with the seat belt on.

If the pregnant woman is involved in an car accident, she should never underestimate it, as many fetal injuries may present with no clear symptoms, and especially if the accident occurs after the sixth month of gestation.

MATERNITY READINESS PROGRAM

In May 2005, the Ministry of National Health (Argentina) crafted guidelines for maternity readiness[11], a proposal that aims to bring together professionals of different areas (obstetricians, neonatologists, physical therapists, nutritionists, social workers and psychologists) in order to promote an interdisciplinary approach.

These guidelines suggest that the healthcare team should:

- Foster the patient's self-care capabilities.
- Strengthen mutual support of parents and other members of the family.
- Protect the family environment where the new baby will grow.
- Establish guidelines for baby care.
- Restore the woman's leading role during delivery.

Consequently, the healthcare team will focus their work on three distinctive areas:

- Promotion of breastfeeding.
- Training and support for the parents-to-be.
- Training of the accompanying partner for the delivery room.

PROMOTION OF BREASTFEEDING

In the Experts Consensus of Geneva, in March 2001, the World Health Organization (WHO) recommends breastfeeding exclusively for the first six months, and continuing breastfeeding with a complementary diet up to two years of age[12].

The Baby Friendly Health Initiative (BFHI) was implemented in 1989 following a joint proposal by the WHO and UNICEF (United Nations Children's Fund). A year later, the Innocenti Declaration was signed and adopted. It establishes new and demanding guidelines to define national support for breastfeeding in thirty different countries. Currently, more than 20,000 hospitals in up to 150 countries adhere to the BFHI proposal. The BFHI program has been recognized as one of the most successful international programs for the protection, promotion and support of breastfeeding. From 1990 to 2000, this program, along with the Innocenti Declaration[13], was responsible for the 15% increase worldwide in breastfeding rates among infants less than four months of age (from 46% to 53%) and by 5% among infants less than six months of age (from 34% to 39%), especially in developing countries.

There are several factors that influence a mother's decision to breastfeed, such as socioeconomic status (family structure, income, family support and healthcare nets), cultural issues, and, in the case of working women, plans to return to work after maternity leave, and working conditions (longer work days and conditions at work which favor breastfeeding).

Consequently, it is imperative to offer patients the appropriate counselling about breastfeeding as part of the Maternity Readiness Program. Moreover, during the patient's prenatal visits, the obstetrician must conduct a breast examination (proven to positively influence nursing), educate about proper breast and nipple hygiene and care, explain the physiology of nursing so the mother understands the importance of breastfeeding on demand, counsel on adequate hydration and nutrition, show the different nursing positions, promote the active participation of the father in the nursing process and encourage his collaboration at home, and offer information about how to face the mother's return to work without compromising breastfeeding.

TRAINING AND SUPPORT FOR PARENTS-TO-BE

This is a series of workshops aimed to prepare the mother-to-be, physically and mentally. They begin at 26th week of gestation (sixth month) and are structured around as group work.

Topics to be explored include:

- Human reproduction mechanisms.
- Pregnancy stages and their normal signs.
- Risk factors and warning signs during the different stages of the reproductive process.
- Importance of early, regular and complete prenatal care.
- Physical activities to improve posture, muscle strengthening and stretching, and relaxation and breathing techniques.
- Sexuality during pregnancy.
- Characteristics and functioning of Labor and Delivery rooms and hospital stay after delivery, ideally with guided tours.
- Tips on care during normal pregnancy and puerperium.
- Mother-newborn-father relationship.
- Typical fears during pregnancy.
- Care, nursing and special characteristics of the newborn.
- Birth control during puerperium and nursing.

TRAINING OF THE ACCOMPANYING PARTNER FOR THE DELIVERY ROOM

Based on the concept proposed by the WHO in 1985, «birth is not a disease», new lines of thought have placed the family at the center of birth, giving the healthcare team a secondary role. This is the foundation of the idea of «Family centered maternity care», which is intended to promote activities that lessen the mother's fears, anxiety and stress that originate from the lack of knowledge about the environment and characteristics of labor

and delivery[14]. One of the proposals, to which we adhere, was to include an accompanying partner (mother/father, husband, another family member or friend) in the delivery room.

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CHAPTER 4

Demographic, educative, social and economic factors: influence in perinatal outcomes

GENERAL PART

D. Orós López | S. Rueda Marín | E. Fabre González

INTRODUCTION

Of the 136 million babies born every year, 3.2 million are stillborn and 4 million die in the first month of life, 98% of whom live in low-income and middle-income countries. Neonatal deaths contribute 38% of deaths in those younger than 5 years. There are 559 million children under 5 years in developing countries, 156 million of whom are stunted and 126 million are living in absolute poverty. Disadvantaged children in developing countries who do not reach their developmental potential are less likely to be productive adults. Two pathways reduce their productivity: fewer years of schooling, and less learning per year in school. Both stunting and poverty are associated with reduced years of schooling. Several studies show that, on average, each year of schooling increases wages by 10%[1].

In the same way, a quarter of women in developing countries suffer illness, injury, or disability, often hidden, as a result of pregnancy and childbirth. They are denied their sexual and reproductive health rights and subjected to appalling gender inequalities.

Nowadays, good evidence shows that poor women have bad reproductive health outcomes and that early and unintended childbearing leads to poverty. Adolescent pregnancy can lead to reduced educational opportunities for both mother and child. Short intervals between births are associated with prematurity, low birthweight, and an increased risk of infant death. Campaigners for HIV and AIDS have been successful in demonstrating links between HIV and AIDS, and poverty[2]. Although mother and child outcomes are associated across the whole life-cycle and into the next generation, the most radical effects of maternal mortality on child survival are in the pregnancy and neonatal period[3].

Like it or not, sexuality is an essential part of human behaviour and it is difficult to talk about, especially for politicians. Sexual and reproductive rights are an integral component of basic human rights. The fundamental right to health was first codified in the Universal Declaration of Human Rights of the UN General Assembly in 1948, and explicitly recognised in 1968 at the World Conference on Human Rights in Tehran and in the International Conference on Population and Development (ICPD) in 1994, in Cairo[4].

Unfortunately, in general, we have just a few data about worldwide perinatal problems. Variety of conditions that prevail in different population groups, small consensus on a core set of indicators and cultural roots of many sexual and reproductive health problems are some of the reasons.

DEMOGRAPHIC FACTORS

Between 1960 and 2005, the global population rose by 114%, from 3 billion to nearly 6.5 billion. Over the next 45 years, the percentage increase is expected to be much lower, around 40%, but still will remain huge in absolute numbers, about 2.6 billion. Under these assumptions, world population is expected to be a little over 9 billion in 2050. Half the expected increase will come from Asia and 36% from sub-Saharan Africa. Even after allowing for immigration, Europe's share of total population is expected to decline from 20% in 1960 to 7.2% in 2050, whereas sub-Saharan Africa's share will rise from 7.5% to 18.6% over the same period[5]. With these differences in regional growth rates, the populations of many of the poorest countries will double or triple over the next 40-50 years, making it far harder to reduce poverty and keep pace with the necessary investment in basic services, such as health and education[6].

High proportion of the population in the reproductive age range, and high desired family size, are some of the factors of demographic increased in developing countries. It is known that children from large families might also be disadvantaged in terms of nutrition, healthcare, and education. Access to family planning would reduce population growth by about 20%.

FAMILY PLANNING

Unsafe sex is the second most important risk factor for disease, disability, or death in the poorest communities. Sexual and reproductive ill health accounts for almost 18% of all lost disability-adjusted life-years[6].

High population growth is one of the most important factors contributing to economic, environmental, social, and political strain in several countries. In 18 African countries less than 10% of married women use any contraception, and in 22 countries less than 10% are using modern methods. Adolescents often face many obstacles when seeking contraception. Little knowledge and little access to services result in low uptake and high rates of ineffective use. Teenager's sexual education is crucial, preventing sexual diseases and unwanted pregnancies. In the developing world, girls aged less than 15 years are more likely to have premature labour and are four times more likely to die from pregnancy-related causes than are women older than 20 years. Young women are less likely to receive antenatal care and are more likely to undergo unsafe abortion. Sexual activity in the teenage years is generally unsafe[2].

Family planning is one of the most cost-effective ways of reducing maternal, infant and child mortality. Promotion of family planning is unique among medical interventions in the breadth of its potential benefits: reduction of poverty and maternal and child mortality, empowerment of women by lifting the burden of excessive childbearing, preventing sexually transmitted infections and enhancement of environmental sustainability by stabilising the population of the planet[7]. Improving sexual and reproductive health is also important for national development and economic growth. In 2000, about 90% of global

abortion-related and 20% of obstetric-related mortality and morbidity could have been averted by use of effective contraception by women wishing to postpone or cease further childbearing. A total of 150,000 maternal deaths, 32% of all such deaths, could have been prevented with high cost-effectiveness.

Family planning also brings large potential health and survival benefits for children, mainly as a result of wider intervals between births. Cross-sectional surveys and prospective surveillance suggest that about 1 million of the 11 million deaths per year of children younger than 5 years could be averted by elimination of interbirth intervals of less than 2 years. Findings of studies in both rich and poor countries show that conceptions taking place within 18 months of a previous livebirth are at greater risk of fetal death, low birthweight, prematurity, and being of small size for gestational age. The mechanisms underlying this association are thought to include postpartum nutritional depletion, especially folate deficiency[8]. Sex is an uncomfortable topic for politics. Cultural and religious barriers often obstruct family planning programs, stealing to these women their sexual rights.

UNSAFE ABORTION

The frequency of unsafe abortion in a country is affected by the effectiveness of its family planning programmes, the abortion legislation and its implementation, and the availability and quality of legal abortion services. About 80 million women each year have unwanted or unintended pregnancies, 45 million of which are terminated. Of these 45 million abortions, 19 million are unsafe, 97% of these are in developing countries, 40% of them are done on women aged under 25, and about 68,000 women die every year from complications of unsafe abortion. In many countries, access to safe abortion is restricted and, in some of those, unsafe abortion causes more than 30% of maternal deaths[2].

Deaths due to unsafe abortion are arguably the most preventable of all maternal deaths[7]. Evidence suggests that unintended pregnancy and unsafe abortion are associated with violence and sexual coercion. Legal obstacles to provision of safe abortion services force women to resort to unsafe abortion when faced with an unwanted pregnancy.

UNDERNUTRITION

In developing countries, intrauterine growth restriction is mainly due to poor maternal nutrition and infections. Intrauterine growth restriction indicates constraints in fetal nutrition during a crucial period for brain development. Up to 11% of births in developing countries are growth restricted. Low-birthweight infants with intrauterine growth restriction had lower developmental levels and lower cognitive scores[9].

A third of children younger than 5 years in developing countries have linear growth retardation or stunting. Longitudinal studies show more problems with conduct, poorer attention, and poorer social relationships at school age in stunted children.

Many cross-sectional studies of high-risk children have noted associations between concurrent stunting and poor school progress or cognitive ability[10]. Stunted children also learn less per year in school. This reduction is equivalent to two fewer years of schooling. Assuming that every year of schooling increases adult yearly income by 9%, the loss in adult income from being stunted but not in poverty is 22.2%, the loss from living in poverty but not being stunted is 5.9% and from being both stunted and in poverty is 30.1%.

Taking into account the number of children who are stunted, living in poverty, or both the average deficit in adult yearly income for all 219 million disadvantaged children is around 20%. The children will subsequently do poorly in school and are likely to transfer poverty to the next generation[10]. The total cost to society of poor early child development is enormous. Sub-Saharan African countries have the highest percentage of disadvantaged children but the largest number live in south Asia.

There is increasing evidence that early interventions can help to prevent the loss of potential in affected children and improvements can happen rapidly. Randomised trials that provide food supplements to improve children's nutritional status and development show concurrent benefits to motor development, mental development, and cognitive ability. Additionally in children who received high levels of supplementation from birth to 2 years showed greater social involvement and less anxiety. Children who received iodine supplementation averaged 8 points higher than those who did not. Large supplementation trials in infants in developing countries show benefits of iron, especially on motor and social-emotional outcomes. An easier intervention as breastfeeding could benefit development through nutrients in milk, especially essential fatty acids, reducing infant morbidity[9].

POVERTY

Poverty and associated health, nutrition, and social factors prevent mothers and children in developing countries from attaining their developmental potential. Poverty and the socio-cultural context increase young children's exposure to biological and psychosocial risks that affect development through changes in brain structure and function, and behavioural changes. Several longitudinal studies have assessed the association between wealth at birth and later educational and cognitive attainment. Poverty is the main problem. Poverty is associated with undernutrition, infections, violence, dangerous environmental exposure, and difficult the access to sanitary resources[10].

SKILLED SANITARY ATTENTION

Every year, an estimated 210 million women have life threatening complications of pregnancy, often leading to serious disability, and a further half a million women die in pregnancy, childbirth, and puerperium. More than 99% of these deaths are in developing countries. Three million babies die in the first week of life and about 3.3 million infants are stillborn every year[2]. The burden of maternal morbidity and mortality shows one of the largest differentials between rich and poor countries. The long-term consequences are not only physical, but are also psychological, social, and economic. Consistent findings show reduced levels of cognitive function and higher levels of behaviour problems in young children of depressed mothers. Good maternal health is crucial for the welfare of the whole household, especially children who are dependent on their mothers to provide food, care, and emotional support. The death or chronic ill-health of a mother increases the probability of death and poor growth and development of her children[3].

Third part of maternal deaths is attributable to postpartum haemorrhage. Additionally, anaemia, infections or sepsis, obstructed labour, hypertensive disorders, and now HIV infection, are the most important causes of maternal death[11]. The three biggest causes of neonatal death are preterm delivery, complications of presumptive birth asphyxia, and infection. If we can achieve high coverage of intrapartum care based in health centres, a

qualitative change in labour monitoring and in early care for preterm newborn babies is likely to translate into a fall in early neonatal mortality[12].

Skilled birth attendance is particularly advantageous for both maternal and neonatal survival. Associations between skilled attendant and neonatal deaths are similar to those for maternal deaths. Cheap and effective interventions to prevent and treat pregnancy complications have existed for many years. Yet, in the developing world, a third of all pregnant women receive no health care during pregnancy, 60% of deliveries take place outside health facilities and only about 60% of all deliveries are attended by trained staff. Ninety per cent coverage of facility-based clinical care alone could reduce neonatal mortality by 23-50%. If outreach and family-community care were added and achieved similar coverage, the reduction would be 31-61%.

Women are intensely vulnerable to the effects of costs incurred during childbirth. User fees, especially high for emergency or technological procedures, the fear of anticipated pay, and the costs of transport and companion time can also delay access to emergency life-saving care, and sometimes push families into poverty[10].

In countries with similar amounts of economic development, maternal mortality is inversely proportional to women's status. Female ownership of assets and secondary education increases use of maternal services, even in adverse family or socioeconomic situations. Women in many developing countries have less freedom to act, less personal autonomy, and less access to information than their male partners or husbands[3]. Antenatal and postnatal care provides opportunities to deal with recurrent problems and can also represent an opportunity for other actions, such as birth planning.

INFECTIONS

Around 340 million new cases of common sexually transmitted bacterial and protozoal infections, 5 million new HIV infections and 257,000 deaths from cervical cancer, are estimated to be acquired every year. At least a third of sexually transmitted diseases affect people aged under 25. Globally, about 20% of women aged under 24 years have a prevalent HPV infection and more than 25% in populations older than 40 years have been infected with HSV-2. The yearly number of sexually transmitted infections acquired easily exceeds 1 billion (more than one infection for every three adults aged 15-49 years), which is probably an underestimate. Infections arising as a result of unsafe abortion or as a complication of pregnancy and childbirth not infrequently lead to chronic disability and death in some places[2].

After pregnancy-related causes, sexually transmitted infections (syphilis, gonorrhoea, and chlamydia) are the second most important cause of healthy life lost in women, accounting for 8.9% of all disease burdens in reproductive age women. However, if one includes sexually transmitted HIV infection, sexually transmitted infections and HIV easily become the leading cause of healthy life lost in many countries.

A third of the world's population is infected with at least one species of intestinal helminth. At least 2 million children younger than 14 years are estimated to be living with HIV/AIDS. HIV infection in infancy can lead to severe encephalopathy with catastrophic outcomes. Even in children without severe outcomes there is increased risk of delays in several developmental domains[9]. Worldwide, up to 4,000 newborn babies go blind every year because of maternal gonorrhoea; an unknown number are affected by neonatal herpes or chlamydial conjunctivitis. Untreated early syphilis results in a stillbirth rate of 25%

and a perinatal mortality of about 20 %. Tuberculosis kill more women worldwide than all causes of maternal mortality[3]. More than 40 % of the world's population lives with the risk of malaria. There are 300-660 million clinical episodes of malaria every year, and severe malaria accounts for up to 40 % of paediatric admissions in parts of sub-Saharan Africa. Neurological and cognitive impairments associated with severe or cerebral malaria have been reported in numerous studies.

Several actions are effective in reducing the infectious disease damage. An effective screening and treatment programme for syphilis in pregnancy in Africa could prevent close to half a million fetal deaths a year. Treating intestinal infection in children improves neurological development. Malaria and HIV programmes benefit from the relatively high coverage of antenatal care, for example through intermittent preventive treatment of malaria for pregnant women and distribution of insecticide-treated nets, and through improved access to intrapartum care for HIV-positive mothers.

VIOLENCE

Violence against women is an important contributor to sexual and reproductive health. Such violence is a human rights abuse, a consequence, and a cause, of gender inequality. The most common and better documented types of violence are intimate-partner violence and sexual violence. In developing countries, between 13 % and 61 % of women who were or had been married reported physical abuse by an intimate partner in their lifetime, and between 6 % and 59 % reported sexual violence[2]. Large numbers of children from developing countries are exposed to war or to community and political sectarian violence. The negative effect of exposure to violence is likely to be increased when family cohesion or the mental health of primary caregivers is disrupted. Prevalence varies widely between countries and between regions within countries.

Growing evidence suggests that women who suffer violence are often unable to make sexual and reproductive choices, putting them at great risk of early and unwanted pregnancy and sexually transmitted infections, including HIV. Sexual abuse during childhood is associated with high-risk behaviours later in life, including alcohol and drug use, early consensual sexual experience, and a high number of partners.

Sadly, most women remain silent about violence by an intimate partner and do not seek help. They frequently think that this violence is normal or even justified. More than 20 % of women in a WHO study, thought that wife-beating were justified if a wife disobeyed her husband, or failure to complete her housework.

Female genital mutilation is also prevalent many in countries, especially in sub-Saharan Africa and some countries in Southeast Asia. The procedure is often done to girls before they reach age 10 years, and under unhygienic conditions. Many girls go on to have chronic morbidity, including recurrent urinary tract infections, reproductive tract infections, dyspareunia, and sometimes vesicovaginal fistula.

ENVIRONMENTAL EXPOSURES

Environmental degradation in less developed countries is more often the result of poor people struggling to acquire basic essentials, such as food, water, shelter, and fuel. The world's richest countries, home to 20 % of the world's population, account for 86 % of to-

tal private consumption. Millions of people live without access to clean water or adequate sanitation, which puts them at high risk for diarrhoeal diseases.

Worldwide prevalence of raised lead levels in children are estimated to be around 40%, with children in developing countries being at greater risk of exposure to environmental lead than those in developed countries. Lead exposure is associated with small decrements in intelligence. At least 30 million people in Southeast Asia use water from wells that exceed standards for arsenic. Arsenic exposure, via drinking water or industry, has a known cognitive effect in adults[9].

CONCLUSION

Cheap and effective interventions have existed for more than 50 years, but which are not available in many parts of the world because governments do not care enough. Perinatal problems have been forgotten because the world thinks the problem has been solved or because the problem makes the world feel uncomfortable.

Individuals should behave more responsibly, but for that, people should have the skills and resources at their disposal to behave in that way. Health systems in developing countries face many challenges: severe and long-term underfunding, deteriorating infrastructure, unreliable or inadequate supplies of essential drugs, weak institutions and governance, increasing shortages of trained health workers, particularly in under-served rural areas, and weak information systems needed to monitor progress. Many organisations work with the governments of developing countries in uncoordinated and often competitive ways, taking up valuable time and resources. Researchers, clinicians, health administrators, academics, religious leaders, funding governments... We all have the responsibility of providing information, and work in the same direction to improve perinatal health all over the world. In view of the high cost of poor perinatal development, and the availability of effective interventions, we can no longer justify inactivity.

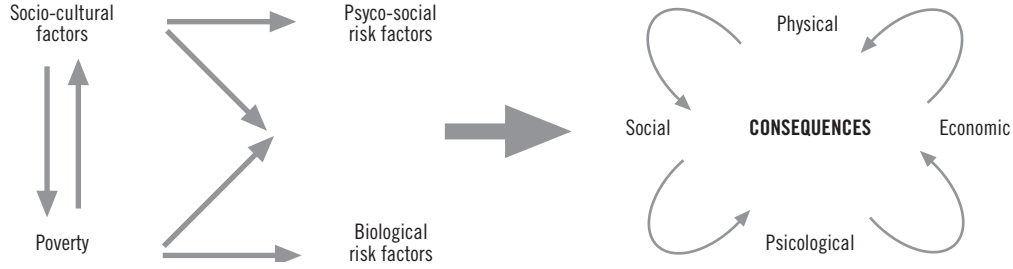

Figure 1. Social factors and its consequences.

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CHAPTER 5

Medicines, drugs and radiations in perinatal period

GENERAL PART

J. Mallafré | B. Serra

INTRODUCTION: Medicines and drugs

Although pregnancy is a period of woman's life where women try to improve their daily habits, in many occasions they could not avoid being exposed to treatments with different drugs or to radiations. Even sometimes women are exposed to these agents before they become aware of their pregnancy.

The use of medicines during pregnancy can imply a potential risk to the fetus and to the mother. It is therefore mandatory to evaluate the possible benefits and drawbacks in order to decide whether to treat or not and which is the most appropriate drug or treatment to be used. Nevertheless it should not be forgotten that any women that becomes pregnant has a baseline risk of having a fetus with a congenital defect of 1-3 %. In fact less than 1 % of all malformations could be attributed to a teratogenic effect of a drug. Most congenital defects are of multifactorial or genetic origin.

In turn, the teratogenicity of a given drug may be evident in terms of pregnancy loss, growth restriction, congenital defects or carcinogenicity.

CLASSIFICATION OF DRUGS

Drugs have been classified by US FDA in five categories depending on its teratogenicity (A, B, C, D, X) as follows:

US FDA risk classification in pregnancy[1]

Category	*Explanation*
A	Controlled studies in women fail to demonstrate a risk to the fetus in the first trimester; possibility of foetal harm appears remote.
B	Either animal studies do not indicate a risk to fetus and there are no controlled studies in women or animal studies have shown an adverse effect, but controlled studies in women failed to demonstrate the risk.

C	Either animal studies indicate a fetal risk and there are no controlled studies in women, or studies in women and animals are not available.
D	There is positive evidence of fetal risk, but benefits may be acceptable despite de risk.
X	There is definitive fetal risk based on studies in animals or Humans or based on human experience, and the risk clearly outweighs any possible benefit.

In turn, the category of a given drug can vary depending on the trimester of pregnancy at which it is administered to the woman or if it is used during lactation. Therefore not only the drug, but also the chronology of pregnancy has to be taken in account when treating pregnant women.

Women who receive long term treatments, like for example patients with epilepsy, clotting disorders, high blood pressure, etc, should plan her pregnancy if the treatment that is being used has to be changed, in order to use another drug with a better security profile.

Some drugs must also be avoided several months, even years, before becoming pregnant. It is the case of different retinoid derivates (etretinate, acitretine, tazarotene) that are used to treat skin disorders[3].

Even treatments used by the male couple can have teratogenic effects on the offspring. That is the case of finasteride (inhibitor of 5-alfa reductase), or other drugs that accumulate and are excreted in the seminal fluid, as for example gliseofulvin.

In general new medicines should be avoided in favour of those with a known security profile and special efforts should be directed to discourage self medication in pregnant women.

The next table provides information about the teratogenic classification of currently used drugs.

DRUGS, THEIR CATEGORY & THEIR EFFECTS ON FETUS[2, 3]

When a pregnant woman has been exposed to one or more drugs with unknown effects on the fetus, she should be referred to a specialized prenatal care centre. If this option is not feasible, as it happens in most rural areas of developing countries, local health providers should make on-line searches in order to obtain updated information regarding the use of the drug that have risen concern. The following websites contain useful information:

http://www.perinatology.com/exposures/druglist.htm

http://www.otispregnancy.org/

http://www.motherisk.org/drugs/index.php3

As most of health facilities in developing countries also don't have internet facilities, national health systems should provide teratogenic information by telephone or even radio, or provide local health facilities with updated treatment guides for pregnant women.

If the drug to which the patient has been exposed during pregnancy is associated with an increased risk of congenital malformations that could be prenatally diagnosed, the women has to be advised and available prenatal diagnosis techniques capable to diagnose the related malformations should be recommended to the patient.

Drugs	*Category*	*Effects on fetus*
Acetaminophen/codeine	C	Is considered safe for the fetus.
Acetaminophen/hydrocodone	C	
Acetaminophen/ oxycodone	C	
Albuterol	C	Experience in early pregnancy is limited, no malformations reported. During treatment of premature labour, fetal heart rate and blood sugar are increased.
Amoxicillin	B	Penicillin antibiotics are usually considered safe for the fetus.
Ampicilin	B	Penicillin antibiotics are usually considered safe for the fetus.
Azithromycin	B	
Beclomethasone nasal	C	
Cephalexin	B	Penicillin antibiotics are usually considered safe for the fetus.
Codeine/guaifenesin	C	Some studies have found an increase in malformations afterits use in early pregnancy,cough mixtures and expectorants, as separate groups, are each associated with an increased risk of an eye and ear abnormalities.
Erythromycin oral	B	Is considered safe for the fetus, effects on mother: liver damage is reported in pregnant women treated with erythromycin stolate.
Hydrocortisone topical	C, D	1st trimester.
Hydroxyzine	C	
Ibuprofen	B/D	Premature closure of the ducts arteriosous and foetal death have been reported (3rd trimestrer).
Insulin, isophane	B	Most evidence indicates the rate of malformations is not different than the rate of malformations in unexposed diabetic pregnancies.
Levothyroxine	A	Adverse effects to the fetus are not expected.
Metoclopramide	B	Safety or risk has not been established.
Metronidazole oral	B	No increased risk of malformation.
Metronidazole, topical, vaginal	B	Most evidences indicated no increased risk of malformations, miscarriage or stillbirth after exposure to metronidazol.
Nitrofurantoin	B	Is considered safe for the fetus.
Penicillin	B	Penicillin antibiotics are usually considered safe for the fetus.
Prednisone	B/C and D	1st trimestrer. Several studies do not indicated an increased risk of malformations.
Prochlorperazine	C	Most evidence indicates that the risk of births defects is low, however there is some controversy.
Progesterone	B	
Promethazine	C	Most evidences indicate with fenotiatines and ant emetics is low, however there are controversies.
Sulfamethoxazole		Interferes with folic-acid activity on the mother.
Sulfamethoxazole/ trimethoprim	C	Most evidence does not indicate an increased risk of malformation; however some malformations have been reported.
Terbutaline	B	Malformations have not been.
Terconazole		Topical vaginal.
Triamcinolone, topical	C/D	1rd trimester.

RADIATIONS AND NUCLEAR MEDICINE

On human tissues the X and gamma rays could cause biological and genetic effects in a dose-dependent way. During the peri-implantation (0-14 days) and immediate post implantation (14-21 days) periods, radiation has an all or none effect. Exposure in this phase is likely to cause miscarriage, although in those embryos that do survive, there is no risk increase of congenital malformations or growth restriction.

Exposure to radiation during organogenesis (3 to 9 weeks), could cause a wide range of congenital malformations and severe growth restrictions.

Exposure during the fetal stage (9-40 weeks) could cause growth restriction. As the Central Nervous System (CNS) specially develops from week 8 to 25, exposure during this period of pregnancy could cause disturbances in the posterior neurobehavioral development of the fetus or newborn.

Again it should be taken in account that the baseline risk of suffering a spontaneous abortion is 15%, and of having a fetus with a major malformation or a restricted fetal growth of 3-4% each[7, 8]. The risk that can be attributed to a radiation exposure during pregnancy depends on several factors, including radiation doses, time lapse in which the patient is exposed to the radiation, the exposed area, etc.

The mean radiation doses to which the fetus is exposed during diagnostic radiological examinations vary between less than 0,01 mGy for a chest exploration and 7,5 mGy for several projections of the lumbar spine. A colecistography implies a 0,6 mGy exposure, that rises to 6,1 mGy if a barium enema is done. Fetal exposure during a CT scan varies between 3,6 mGy for a liver exploration and 89 mGy for a pelvic one.

The most common possible effects of **diagnostic radiation** are:

1. RISK OF MALFORMATIONS AND MENTAL RETARDATION

The risk of malformations after exposure to radiological imaging doesn't increase significantly, although decline in intellectual coefficient (IQ) has been estimated to be about 30 IQ points per Grey[8] during the most sensitive period, that is between 8 and 15 weeks post conception

2. RISK OF RESTRICTED GROWTH OR DEATH

Permanent growth restriction was apparent in children who where within 1,500 m of the hypocenter of Hiroshima's nuclear bomb 17 years after the exposure to ionizing radiation. These exposed children were on average 2,25 cm shorter, 3 kg lighter, and had a 1.1 cm smaller head than age-matched children. Diagnostic radiation seems not to be associated with an increase of the incidence of intrauterine growth restriction or perinatal mortality[9].

3. RISK OF CANCER

The National Radiological Protection Board (USA) has estimated an excess absolute risk (EAR) coefficient for cancer incidence under 15 years of age following low dose intrauterine irradiation of 0,006% per mGy compared to 0,0018% per mGy for a exposition just after birth.

Different studies have failed to prove any significant risk increase of suffering a malignancy in childhood, including leukaemia, central nervous system tumours or other malignancies, after the intrauterine exposition to diagnostic X-rays[10].

4. RISK OF IN HEREDITARY DISSEASES.

No significant excess risk for any genetic disorder has been found in inhabitants of areas with high-background radiation (Chernobyl, Hiroshima, Nagasaki). The risk of genetic disorders has been estimated to be between 0,112% and 0,099% for every 10 mGy exposure[11]. The exposure to diagnostic irradiation during pregnancy has therefore a light impact in terms of hereditary injuries[12].

Irradiation of males may produce possible genetic injuries. Therefore it is recommended to delay conception after radiotherapy at least 6 months. In those settings where it is possible, advise regarding the frozen storage of semen obtained prior to the irradiation should be given.

RADIOTHERAPY DURING CONCEPTION AND THE TWO FIRST TRIMESTERS OF GESTATION.

Radiotherapy is contraindicated during pregnancy, although in certain clinical situations it may be administrated. The incidence of cancer during pregnancy is quite frequent: cervical cancer (0,5 ‰ to 0,08‰), Hodgkin lymphomas (1‰-6‰), breast cancer (0,3‰ to 0,1‰) and melanoma (0,2‰). In turn, radiotherapy plays a major role in the multidiciplinary treatment of most of them. With an appropriate[11] abdominal shielding, the estimated fetal exposure can be reduced by more than 50% in most cases. Modern imaging and irradiation techniques allow calculating the irradiation doses to which the fetus is going to be exposed.

NUCLEAR MEDICINE

Radionucleotides used in medicine like tecnetium-99 have short disintegration times and do not cross the placenta. Its use therefore doesn't cause a great exposure of the fetus to radiation, as this latter proceeds from the surrounding tissues of the mother. The exposure can be reduced hydrating the mother and placing a urinary catheter to avoid the accumulation of the radionucleotide in the bladder.

The use of radioisotopes is contraindicated during pregnancy. Therapeutic abortion may be considered when the fetus is supposed to have been exposed to radiation doses exceeding 150 mGy between the second and the 15th week of conception. If the exposure ranges between 50 and 150 mGy pregnancy termination should only be considered in case of added compromising circumstances[7]. The fetal exposure to less than 50 mGy only implies a minimal risk and doesn't justify a therapeutic abortion.

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PREGNANCY

CHAPTER 6

Antepartum care

M. Tajada Duaso | L. Ornat Clemente | B. Carazo Hernández | E. Fabre González

INTRODUCTION

Pregnancy is a natural process for women. It must not be considered as an illness although, occasionally, some complications may occur during pregnancy. The majority of pregnancies have a normal evolution but, even under ideal conditions, a certain amount of risk for the heath of the mother and the foetus is always present. Therefore, the provision of special care for women during pregnancy through the public health services in every country and all communities is one of the objectives of the World Health Organization (WHO).

Antenatal care consists in a number of visits, ideally performed before and along the gestation period, in order to minimize the maternal and foetal morbidity and mortality by:

1. Detection of high risk pregnancies.
2. Detection of congenital anomalies.
3. Prevention of obstetric complications.
4. Promotion of sanitary and nutritional education.
5. Preparation to affront labour.
6. Puerperal instructions, recommendations for breastfeeding and new born necessities.

The majority of antenatal interventions known to be effective can be delivered by a midwife or nurse or indeed, lower level health care workers, provided they have the necessary training, equipment and supplies and are appropriately supervised. However, for complicated cases, it is important to be able to draw upon more specialized skills such as those of a doctor (general practitioner) or even an obstetrician.

Few life-threatening complications for the mother can be prevented antenatally; the majority of them require interventions at the time of delivery and the immediate postpartum period[1]. Reduction of maternal mortality depends on ensuring that the most of the wo-

men benefit from the care of a skilled professional during delivery. Meanwhile, care during the antenatal period represents an opportunity to improve maternal health, perinatal health and, more than likely, neonatal survival.

The antenatal period offers opportunities for delivering information and services that can significantly enhance the health of women and their infants. Other important sanitary programs such as nutrition, malaria, HIV/AIDS and tuberculosis may be introduced to the mothers through antenatal visits.

Data for 1990-2001 show that just over 70% of women worldwide have at least one antenatal visit with a skilled provider during pregnancy[2]. A schedule of antenatal appointments is determined by the function of them. In the standard antenatal care model currently in use, periodicity of visits for uncomplicated pregnancies is as follow:

- Till week 36: every 4-6 weeks.
- 37 to 40 weeks: every 2 weeks.
- Since 40 weeks: weekly until delivery.

Women attending clinics of this model have a median of eight visits during her pregnancy. A new WHO antenatal care model[3] limits the number of visits to the clinic to five and restricts the test, clinical procedures and follow-up actions to those that have been shown to improve outcomes for women and newborns.

THE NEW WHO ANTENATAL CARE MODEL
(Appendix 1)

This new model is based on the following principles:

1. An antenatal care model should include a simple form that can be used easily to identify women with special health conditions and/or those at risk of developing complications; such women need to be referred to a higher level of care.
2. The identification of women with special health conditions or risk factors for complications should be done very carefully. Such women should be referred to higher levels of care.
3. Health care providers should make all pregnant women feel welcome at their clinic. The opening hours of clinics providing antenatal care should be as convenient as possible for women to come to the clinic.
4. Only examinations and tests that serve an immediate purpose and that have been proven to be beneficial should be performed.
5. Whenever possible, rapid and easy-to-perform tests should be used at the antenatal clinic or in a facility as close as possible to the clinic. When test results are positive (e.g. positive for syphilis), treatment should be initiated at the clinic the same day.

At the first antenatal visit to the clinic the new WHO antenatal care model proposes a classifying form used to decide which women will follow the basic component of the new WHO model and which will require special care (figure 1). These women who need special care will represent, on average, approximately 25% of all pregnant women initiating antenatal care. The other 75% will follow the basic component.

Figure 1. Criteria for classifying women for the basic component of the new WHO antenatal care model.

Name of Patient ..... Clinic record number ☐☐☐☐☐☐☐

Address ..... Telephone .....

Instructions: Answer all the following questions by place a cross mark in the corresponding box

OBSTETRIC HISTORY	no	yes
1. Previous stillbirth or neonatal loss?	☐	☐
2. History of 3 or more consecutive spontaneous abortions?	☐	☐
3. Birth weight of last baby < 2500 g?	☐	☐
4. Birth weight of last baby > 4500 g?	☐	☐
5. Last pregnancy: hospital admission for hypertension or pre-eclampsia/eclampsia?	☐	☐
6. Previous surgery on reproductive tract?	☐	☐
(Myomectomy, removal of septum, cone biopsy, classical CS, cervical cerclage)	☐	☐

CURRENT PREGNANCY	no	yes
7. Diagnosed or suspected multiple pregnancy?	☐	☐
8. Age less than 16 years?	☐	☐
9. Age more than 40 years?	☐	☐
10. Isoimmunization Rh (−) in current or in previus pregnancy?	☐	☐
11. Vaginal bleeding?	☐	☐
12. Pelvic mass?	☐	☐
13. Diastolic blood pressure 90 mm Hg or more at booking?	☐	☐

GENERAL MEDICAL	no	yes
14. Insulin-dependent diabetes mellitus?	☐	☐
15. Renal disease?	☐	☐
16. Cardiac disease?	☐	☐
17. Know «substance» abuse (including heavy alcohol drinking)?	☐	☐
18. Any other severe medical disease or condition?	☐	☐

Please, specify .....

.....

A «Yes» to any ONE of the above questions (i.e. ONE schaded box marked with a cross) means that the woman is not elegible for the basic component of the new antenatal care model.

Is the woman elegible? (circle) NO YES

If NO, she is referred to .....

Date ..... Name..... Signature

(staff responsible for ANC)

Women with risk factors for complications during delivery only (e.g. previous caesarean section) or those with a history of intrapartum complications, but with otherwise normal pregnancies, should follow the basic component of the new model. However, in such cases, the place of delivery should be selected carefully; arrangements should be made in advance to ensure that appropriate facilities for delivery and possible complications will be available and that the woman will be able to reach them in a timely manner.

THE FIRST VISIT

Ideally, the first visit should occur in the first trimester, around, or preferably before, week 12 of pregnancy. However, regardless of the gestational age at first enrolment, all pregnant women coming to the clinic for antenatal care will be enrolled and examined according to the norms for the first, and subsequent, visits.

Certain factors, such as a strenuous workload, can identify women who may be at risk for pregnancy complications. Work that is physically hard, requires lengthy standing positions, or entails exposure to teratogenic agents (heavy metals, toxic chemicals, ionizing radiation) could adversely affect maternal and neonatal outcomes. Other problems that need to be identified and for which support should be provided include: poverty, young age of the mother, women suffering domestic or gender-based violence, and women living alone.

Individual interaction between the patient and health care provider is essential. Sufficient time must be made during each visit for discussion of the pregnancy and related issues with the patient. Instructions should include general information about pregnancy and delivery as well as any specific answers to the patient's questions.

Written instructions should accompany all verbal advice. Simple written instructions in the local language should be available, even for illiterate women as family members or neighbours can often read. When necessary, materials appropriate for an illiterate audience should be available, such as simple pictures and diagrams describing the advice given at each visit.

INFORMATION RECORDED ON ANTENATAL CARD

1. PERSONAL HISTORY

a) Name, age and marital status.

b) Address and telephone number.

c) Tobacco use or use of other harmful substances.

d) Housing: type, size, number of occupants.

e) Sanitary conditions: type of toilet and source of water; electricity.

f) Educational level and economic resources.

g) Type of work and position of patient and husband.

2. MEDICAL HISTORY (IDENTIFY SPECIFIC DISEASES AND CONDITIONS):

a) Tuberculosis, heart disease, chronic renal disease, epilepsy, diabetes mellitus.

b) Sexually transmitted diseases. HIV status, if known.

c) Other specific conditions depending on prevalence in study site (for example, hepatitis, malaria, sickle cell trait).

d) Other diseases, past or chronic.

e) Allergies.

f) Operations other than caesarean section.

g) Blood transfusions. Rhesus (D) antibodies.

h) Current use of medicines.

i) Periods of infertility: duration, and causes if known.

3. OBSTETRIC HISTORY

a) Number of previous pregnancies.

b) Date and outcome of each event (live birth, preterm birth, stillbirth, abortion, ectopic, hydatidiform mole).

c) Birth weight (if known).

d) Sex.

e) Periods of exclusive breast-feeding.

f) Special maternal complications and events in previous pregnancies:

- Recurrent early abortion.
- Induced abortion and any associated complications.
- Thrombosis, embolus.
- Hypertension, pre-eclampsia or eclampsia.
- Placental abruption.
- Placenta praevia.
- Breech or transverse presentation.
- Obstructed labour, including dystocia.
- Third-degree tears.
- Third stage excessive bleeding.
- Puerperal sepsis.
- Gestational diabetes.

g) Obstetrical operations:

- Caesarean section (indication, if known).
- Forceps or vacuum extraction.
- Manual/instrumental help in vaginal breech delivery.
- Manual removal of the placenta.

h) Special perinatal complications and events in previous pregnancies:

- Twins or higher order multiples.
- Low birth weight (2.500 g).
- Intrauterine growth retardation.
- Rhesus-antibody affection (erythroblastosis, hydrops).
- Malformed or chromosomally abnormal child.
- Macrosomic newborn (> 4.500 g).
- Resuscitation or other treatment of newborn.
- Perinatal, neonatal or infant death.
- History of present pregnancy.
- Date of last menstrual period (LMP).
- Habits: tobacco, alcohol, drugs (frequency and quantity).
- Any unexpected event (pain, vaginal bleeding...).
- History of malaria attacks.

CLINICAL EXAMINATION

Chest and heart auscultation is convenient for all women as well as checking for signs of severe anaemia. The measure of blood pressure allows identification of patients in risk of developing pre-eclampsia or eclampsia.

Maternal weight and height should be measured to assess the mother's nutritional status. Repeated weighing during pregnancy should be confined to circumstances where clinical management is likely to be influenced[4].

Only one routine vaginal examination during pregnancy is recommended. This includes taking a sample for Pap smear if the patient has not had it done elsewhere during the past two years. Identification and treatment of symptomatic sexually transmitted infections should be done concomitantly. Female genital mutilation may be identified at this moment if suspected by ethnicity and it allows planning intrapartum defibulation if needed.

The measurement of symphysis-fundal distance must be performed each antenatal appointment since week 20 to detect small or large for gestational-age infants (figure 2).

Distance from symphysis to fundus of the uterus measured in centimetres is equivalent to the weeks of gestational age (figure 3).

Figure 2. Uterine height values by weeks of gestation.

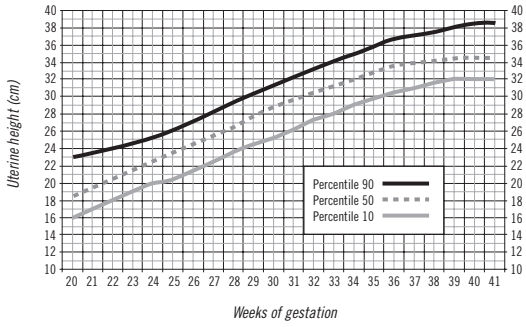
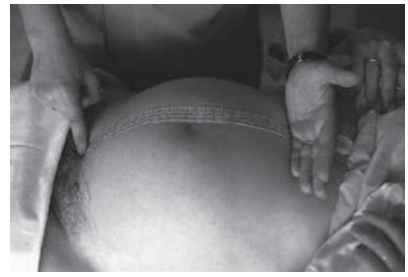


Figure 3. Measure of uterine height.



Picture courtesy of *Sociedad Española de Ginecología y Obstetricia (SEGO).*

ANALYSIS

Urine: multiple dipstick test for bacteriuria and test for proteinuria to all women are recommended.

Blood: syphilis (rapid test), blood-group typing (ABO and rhesus) and haemoglobin. The New WHO Antenatal Care Model offers screening for anaemia only in the presence of some signs or symptoms: pale complexion, fingernail, oral mucosa and shortness of breath. Neither the routine screening for gestational diabetes mellitus is included in the new WHO protocol[3].

INTERVENTIONS AND ADVICES

Iron and folate supplements are recommended to all pregnant women: one tablet of 60 mg elemental iron and 250 micrograms folate one–two times per day. If Haemoglobin <70 g/l: dose must be doubled.

In malaria endemic areas: sulfadoxine/pyrimethamine, three tablets once in second trimester and repeat in third trimester (check current recommendations for timing and dosage). Inject first doses of tetanus toxoid.

Give advice on safe sex. Emphasize the risk of acquiring or transmitting HIV or other sexual transmitted infections without the use of condoms.

Advise women to stop the use of tobacco, alcohol or other harmful substances.

Advise women on breast-feeding: When to stop breast-feeding previous child and when to begin breast-feeding the expected child.

Give advice on whom to call or where to go in case of bleeding, abdominal pain and any other emergency. Give advice on birth plan, including special transport to delivery institution.

THE SECOND VISIT

The second visit should be scheduled close to week 26. The examinations and tests are restricted to measuring blood pressure and uterine height, and performing a multiple dipstick test for bacteriuria. Testing for proteinuria should only be performed for nulliparous women and those women with a history of hypertension or pre-eclampsia/eclampsia. A blood test should be performed to determine haemoglobin if clinically indicated. Check compliance with iron intake.

THE THIRD VISIT

The third visit should take place in or around week 32. If the second visit was missed, the third visit should also include all the activities of the second visit. The examinations and tests are restricted to measuring blood pressure, uterine height, performing a multiple dipstick test to detect bacteriuria, and haemoglobin for all women. Testing for proteinuria should only be performed for nulliparous women and those with a history of hypertension, pre-eclampsia or eclampsia. Special attention should be directed toward discovery of twins during the external abdominal examination and uterine height measurement. Hand-held Doppler or Pinard stethoscope[5] to detect foetal heart sounds is required only if no foetal movements are seen, the woman feels less foetal movement or if she requests it (figure 4). Valuate presence of generalized oedema and other alarming signs of disease: shortness of breath, cough, vaginal bleeding or spotting…

Picture courtesy of *Matres Mundi International.*

Figure 4. Press with the ear. Do not touch stethoscope. Face to the feet of the woman.

Continue iron intake and proceed to second injection of tetanus toxoid.

Some women will go into labour and deliver before the next scheduled visit. Therefore, extra attention must be paid in providing instructions and advice in the event labour starts (e.g. what to do in the event of abdominal pain or leaking of amniotic fluid) and to ensure they have a skilled attendant for the birth.

The woman should also be encouraged to discuss birth spacing and contraceptive options with her partner and be encouraged to leave the clinic with her preferred method of choice. Waiting for a postpartum visit to talk about contraception may be too late. Still, the importance of a postpartum visit, including recommendations for lactation and contraception, should be stated in order to ensure that the woman is seen at the clinic within one week of delivery.

THE FOURTH VISIT

The fourth should be the final visit of the basic component and should take place between weeks 36 and 38. At this visit, it is extremely important that women with foetuses in breech presentation should be discovered and referred for obstetric evaluation. An external cephalic version or elective caesarean section should be considered.

Physical examination will be similar to third visit and the woman must be inquired for some common symptoms and events that may occur close to delivery like abdominal pain, contractions, bleeding or vaginal discharge.

Women should be advised that if they have not delivered by the end of week 41 they should go directly to the hospital/maternity centre for evaluation and possible induction of labour by the best method available. This is recommended considering the unproven benefit of all methods of foetal surveillance for post-term pregnancy commonly used in prolonged pregnancies. The number of women who will not have delivered by the end of week 41, and to whom this would apply is estimated at between 5% and 10%. Although routine induction is not always recommended, available evidence demonstrates that induction of labour after 41 completed weeks is not associated with any major risks. Rather, it reduces the risk of meconium-stained amniotic fluid and perinatal death and does not increase caesarean section rates even in women with an unfavourable cervix.

During this visit patients should be again informed of the benefits of lactation and contraception, as well as the availability of contraceptive methods at the postpartum clinic.

THE POSTPARTUM VISIT

Although a postpartum visit is universally recommended, it is seldom done in most developing countries. The importance of this visit should be stressed as short birth intervals and pregnant women with ages of less than 20 or more than 30 years have been demonstrated in developing countries to increase the risk of intrauterine growth restriction and prematurely born infants.

A special effort should therefore be made to schedule such a visit. The visit should take place within one week of delivery and include activities aimed at the prevention of future unplanned pregnancies; reinforcement of breast-feeding; complete tetanus immunization for late attendants to antenatal care clinics; and folate supplementation for women with previous neuro-tubal defective infants; continuation of iron supplementation for women who are anaemic, or with heavy blood loss in labour; prevention of infection; and finally planning any continued postnatal surveillance, if required. No routine vaginal examination is recommended; it should only be conducted if there are clinical indications.

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Apendix 1. New WHO Antenatal Care Model basic component checklist.

FIRST VISIT for all women at first contact with clinics, regardless of gestational age. If first visit later than recommended, carry out all activities up to that time DATE: / /	*Visits*			
	1st <12 weeks	2nd	3rd	4th
Classifying form which indicates eligibility for the basic component of the programme				
Clinical examination				
Clinically severe anaemia? Hb test				
Ob. exam: gestational age estimation, uterine height				
Gyn. exam (can be postponed until second visit)				
Blood pressure taken				
Maternal weight / height				
Rapid syphilis test performed, detection of symptomatic STIs				
Urine test (multiple dipstick) performed				
Blood type and Rh requested				
Tetanus toxoid given				
Fe / Folic acid supplementation provided				
Recommendation for emergencies/hotline for emergencies				
Complete antenatal card				
SECOND VISIT and SUBSEQUENT VISITS ***Gestational age-approx. # of weeks*** DATE: / / **26wks 32wks 38wks**				
Clinical examination for anaemia				
Ob. exam: gestational age estimation, uterine height, fetal heart rate				
Blood pressure taken				
Maternal weight (only women with low weight at first visit)				
Urine test for protein (only nulliparous women / women with previous pre-eclampsia)				
Fe/Folic acid supplementation given				
Recommendation for emergencias				
Complete antenatal card				
THIRD VISIT: add to second visit DATE: / /				
Haemoglobin test requested				
Tetanus toxoid (second dose)				
Instructions for delivery/plan for birth				
Recommendations for lactation / contraception				
FOURTH VISIT: add to second and third visits DATE: / /				
Detection of breech presentation and referral for external cephalic version				
Complete ANC card, recommend that it be brought to hospital				

CHAPTER 7

Antepartum fetal assessment

PREGNANCY

L. Cabero | M. Goya

INTRODUCTION

Prenatal assessment of the fetal condition has two main phases: in the first half of pregnancy, assessment is done to exclude fetal abnormality and, in a limited way, fetal infection. In the second half of pregnancy, the priority is to monitor the condition of the presumed normal fetus, with a view to determining the optimum time for delivery.

The ideal monitoring system of antepartum fetal assessment would gather a wide range of information, with versatility for all maternal and fetal conditions and flexibility for all gestational ages, allowing for varying degrees of onset, severity, and duration of intrauterine challenges[1]. In meeting these objectives, an ideal antenatal monitoring system would do the following[2]:

— **Detect fetal peril** with specificity, sensitivity, and timeliness to allow preventive intervention. These qualities imply:

  - Correlation with measurable standards of fetal compromise.
  - Proportionality between test results and outcome.
  - A low false alarm rate, especially as prematurity deepens.
  - Application to all ranges of perinatal morbidity and basic perinatal mortality.
  - A reliable relationship to compromise that yields intervention early enough to prevent permanent damage but late enough to be certain of the need for intervention and to minimize the risks of prematurity.

— **Reliably exclude stillbirth** or permanent injury over a significant period of time. However, allowing for the possibility of acute change such as placental abruption, a normal test must exclude abnormal outcomes for a clinically important length of time, most commonly 7 days.

— **Exclude lethal congenital anomalies.**

— **Incorporate multiple variables:** this principle reflects the only way in which a monitoring system can address the interwoven cycles of behaviors and the many ways in which the normal fetus can manifest that normality.

— **Apply to fetal compromise from a variety of basic sources,** including asphyxia, poisoning, metabolic abnormalities, anemia, and chance obstetric factors such as cord accident to address the many origins of adverse outcome.

— **Have measurable benefits to high-risk populations,** in reduction of perinatal mortality and perinatal morbidity.

No single variable or measurement could possibly meet these objectives in the context of the great variability in normal behavior, the complex cascades of responsiveness to abnormal conditions, in the complicated balance between stillbirth from intrauterine decompensation and neonatal death from prematurity. Only by integration of information from multiple physiologic sources, with multiple time periods, can the assessment of fetal health reach these goals.

INDICATIONS FOR FETAL ASSESSMENT

The most common and conventional methods of fetal assessment in **low risk pregnancies** are the following:

— Maternal monitoring of fetal movement.

— Measurement of symphysis-fundal height.

— Auscultation of the fetal heart.

No evidence supports the use of routine ultrasound to screen for fetal compromise in low risk pregnancies[3-5].

Pregnancies with risk factors for fetal compromise **(high risk pregnancies)** can be divided in two different categories:

— ***DISEASE IN THE FETUS:***

- **Triploidy** is associated with severe asymmetrical growth restriction and abdominal measurement that lags many weeks behind the head measurement. The diagnosis is easily made by recognizing this and identifying the multicystic appearance of the placenta. The diagnosis is confirmed by placental biopsy. These fetuses are nonviable. Other aneuploidies, such as trisomy 13, trisomy 18, and to a lesser extent, trisomy 21, are associated with lesser degrees of growth restriction. These can be diagnosed by identifying the typical anatomic features on ultrasound and by placental biopsy.
- **Confined placental mosaicism** explains some cases of growth restriction. Most specific syndromes associated with uniparental disomy (UPD), such as Prader-Willi syndrome (maternal UPD15). Uniparental disomy of other chromosomes has been described in growth-restricted patients without additional phenotypic abnormalities. However, with current searching techniques, few cases can be explained by uniparental disomy, usually for chromosome 16.
- **Growth restriction** is a feature of intrauterine infection with toxoplasmosis, cytomegalovirus, and rubella. However, this type of infection accounts for few cases of isolated

growth restriction. In areas and settings in which they are prevalent, malaria and HIV infection are also important causes.

- **Multiple pregnancies** are associated with an increased risk of fetal compromise from either uteroplacental vascular disease or twin-twin transfusion syndrome.

— ***DISEASE IN THE MOTHER.*** Two types of patients can be identified: those with a specific pathology, and those with no known pathology, but with a risk of adverse fetal outcome.

- *Risk with specific pathology*
  - Essential hypertension and preeclampsia and renal and autoinmmune diseases, especially systemic lupus erythematosus, are associated with an increased risk of growth restriction in association with uteroplacental vascular disease. Many types of thrombophilia, such as lupus anticoagulant and factor V Leiden homozygosity, are associated with growth restriction.
  - Maternal diabetes tipically causes fetal macrosomia and risk of fetal death (probably from a combination of fetal hypoxia, acidemia, and hyperglucemia), especially in women with microvascular complications.
  - Drugs and toxins can reduce fetal growth. Important examples include anticonvulsivants, especially phenytoin; smoking; cocaine use; and excessive alcohol intake.
  - Other maternal factors associated with increased fetal risk are thyroid disease (transplacental transfer of thyroid-stimulating antibodies that cause fetal thyrotoxicosis), isoinmunization (fetal haemolytic anemia), maternal heart disease and inadequate nutrition.
- *Risk with no known pathology*
  - Risk with no known pathology include the following:
    - Reduced fetal movements.
    - Vaginal Bleeding.
    - Prolonged pregnancy.
    - Abdominal pain of uncertain cause.
    - Ruptured membranes.

In high-risk pregnancies, the **following methods** are often used to assess fetal health:

— Biophysical profile.

— Fetal heart rate monitoring.

— Measurement of fetal growth.

— Measurement of amniotic fluid volume.

— Umbilical artery Doppler.

— Measurement of middle cerebral artery blood flow.

— Regional Blood Flow: Venous Waveforms.

— Uterine artery Doppler.

— Placenta Grading.

— Biochemical Tests.

EVALUATION OF FETAL ASSESSMENT METHODS

MATERNAL MONITORING OF FETAL MOVEMENTS

Obtaining a total daily count is time-consuming and unnecessary for most pregnancies in which movement is normal. A better method is for women to count 10 movements and to record how long it took for these movements to occur (the «count to 10» chart). Inability

to count 10 movements in a 12-hour period is associated with an increased likelihood of fetal death, although randomized trials of this policy have not shown improvement in fetal outcome with this approach. The autors of the largest randomized study suggested that the failure to reduce the death rate was mainly caused by false reassurances or innappropiate interpretation of subsequent studies, including fetal heart rate monitoring (cardiotocography and nonstress testing)[6].

SYMPHYSIS-FUNDAL HEIGHT MEASSUREMENT

Inspection and informal palpation of the abdomen alone detect only 30% of fetuses that are small for gestational age. Formal measurement of symphysis-fundal height (the distance in centimetres from the top of the uterus to the pubic bone) is not more effective and did not improve the perinatal outcomes measured in the one controlled trial found during systematic review[7].

AUSCULTATION OF FETAL HEART SOUNDS

No studies have examined whether auscultation of fetal heart sounds identifies fetuses at risk or improves fetal outcome. Nevertheless, it is recommended as standard practice. In theory, fetal arrhythmia, such as congenital heart block or tachyarrhythmia, could be identified, although detection of such rare conditions would require routine and regular documentation of fetal heart rate.

BIOPHYSICAL PROFILE

The biophysical profile score (BPS) presumes that multiple parameters of well-being are better predictors of outcome than single parameters as a multivariable fetal assessment. table 1 lists the BPS variables. Important interpretive points are expanded upon here.

Table 1. Interpretation of BPS variables

Fetal Variable	*Normal Behavior (score = 2)*	*Abnormal Behavior (score = 0)*
Fetal breathing movements	Intermittent multiple episodes of more than 30-sec duration, within 30-min BPS time frame. Continuous FBM for 30 min = exclude fetal acidosis	Continuous breathing without cessation. Completely absent breathing or no sustained episodes.
Body or limb movements	At least four discrete body movements in 30 min. Continuous active movement episodes = single movements. Includes fine motor movements, rolling movements, and so on, but not REM or mouthing movements.	Three or fewer body/limb movements in a 30-min observation period.
Fetal tone/posture	Demonstration of active extension with rapid return to flexion of fetal limbs and brisk repositioning/trunk rotation. Opening and closing of hand, mouth, kicking, and so on.	Low-velocity movement only. Incomplete flexion, flaccid extremity positions, abnormal fetal posture. Must score = 0 when FM completely absent.
Cardiotocogram	Normal mean variation (computerized FHR interpretation), accelerations associated with maternal palpation FM (accelerations graded for gestation), 20-min CTG.	Fetal movement and accelerations not coupled. Insufficient accelerations, absent accelerations, or decelerative trace. Mean variation <20 on numerical analysis of CTG
Amniotic fluid evaluation	At least one pocket >3 cm with no umbilical cord.	No cord-free pocket >2 cm or elements of subjectively reduced amniotic fluid volume definite.

Amniotic fluid volume less than 2 cm or greater than 8 cm is not normal, and a detailed evaluation of the fetus must be carried out to exclude anatomic and anomalous explanations. In normal fetuses, moderate hydramnios (amniotic fluid largest pocket depth, 8 to 12 cm), anatomic issues, idiopathic hydramnios, and fetal macrosomia due to maternal diabetes are the most common explanations, and fetal testing will likely reflect fetal neurologic status accurately. For pockets greater than 12 cm in depth in singleton pregnancies, neurologic issues, and structural defects associated with aneuploidy, are much more likely, in wich case biophysical profile scoring may be invalid. Thus, one variable may lead to suspicion about the validity of testing and call for additional evaluation. Amniotic fluid pockets are identified in real time, and clear fluid is proven because the fetus readily moves through it. When there is doudt, a cord-free pocket is confirmed by pulse Doppler. There is evidence that routine application of continuous color imaging may lead to the false impression of oligohydramnios.

Fetal breathing movements. The presence of rhythmic fetal diaphragm contractions and/or hiccups lasting more than 30 seconds constitutes a normal score. Isolated individual breaths and/or hiccups do not. Fetal «gasping» is a rare phenomenon, probably related to serious acidosis in the near-term fetus. This must be verified by observations of the fetal face and neck, which show the facial equivalent of gasping, not the vigorous diaphragmatic movement of the hiperglycemic fetus of a diabetic mother. Because the amplitude of fetal breathing depends on gestational age, maternal glucose, exposure to increased oxygen concentrations, and many medications, careful evaluation of all parameters is necessary before intervention is precipitated.

Fetal movement and tone. One of the interpretative pitfalls of biophysical profile scoring is that at least some movements must be necessary to evaluate tone. It is emphasized that tone is not simply the flexed posture of a normal fetus. Although the evaluation of tone is indeed subjective, there must be at least some movements to assess it. The original description of movement called for large amplitude movements of the fetal body and/or limbs: since ultrasound was primitive at that time it was sometimes difficult to tell if the fetus was moving at all.

Systematic recording of the FHR with simultaneous documentation of uterine activity constitutes **cardiotocography.** When spontaneous contractions occur and are sufficiently well-defined to document their time, a spontaneous contraction stress test (CST) is denoted. The same pattern elicited by intravenous infusion of oxytocin is called an oxytocin challenge test (OCT). When criteria relating fetal movement to standardized interpretation of FHR accelerations are applied, a NST is defined. Finally, these data can be digitally acquired by a computerized system that interprets not only accelerations and decelerations, but also numerically analyzes FHR variability within gestational age-normalized paradigms.

Interpretation of the BPS is meant to dictate action according to the systematic application in table 2. More detailed instructions on the application of biophysical profile scoring are available elsewhere[8,9]. The correlation between abnormal scores and high risk of poor outcome has been demonstrated in large population studies and produces a characteristically shaped outcome curve. Before acting, however, one must consider the differential diagnosis of this abnormal behavior. Because so many factors may influence biophysical profile scoring (table 3), prolonged testing, retesting after a brief interval, or adding ancillary tests are important steps before the action illustrated in the systematic response for equivocal scores. When the score is 0 to 4/10, especially in the fetus with reduced fluid, IUGR, and in whom serial observations have previously been normal, undue delay in delivery for these ancillary tests would not be reasonable. Thus, confirmatory tests are applied if diagnosis is uncertain but not as a complicated formula of responses in the biophysical profile scoring system.

Table 2. Systematic application of biophysical profile scoring.

Biophysical Profile Score	*Interpretation*	*Predicted PNM/1.000**	*Recommended Management*
10/10 8/8 8/10 (AVF normal)	No evidence of fetal asphyxia present.	Less than 1/1.000	No acute intervention on fetal basis. Serial testing indicated by disorder-specific protocols.
8/10-OLIGO	Chronic fetal compromise likely.	8-9/1.000	For absolute oligohydramnios, prove normal urinary tract, disprove asymptomatic rupture of membranes, then deliver at any viable gestation
6/10 (AFV normal)	Equivocal test, fetal asphyxia is not included.	Depends on progression (61/1.000 on average)	Repeat testing immediately, before assigning final value. If score is 6/10, then 10/10, in two continous 30-min periods, manages as 10/10. For persisten 6/10, deliver the mature fetus, repeat within 24 hr in the immature fetus, then deliver if less than 6/10.
4/10	Acute fetal asphyxia likely. If AFV-OLIGO, acute or chronic asphyxia very likely.	91/1.000	Deliver by obstetricially appropriate method, with continuous monitoring.
2/10	Acute fetal asphyxia, most likely with chronic decompesation.	125/1.000	Deliver for fetal indication (usually caesarean section)
0/10	Severe acute asphyxia virtually certain.	600/1.000	Delivery immediately by caesarean section.

* Per 1.000 live births, within 1 week of the test result shown, if no intervention. For scores of 0, 2, or 4, intervention should commence virtually immediately, provided the fetus is viable. PNM, perinatal mortality.

Table 3. Many factors influence BPS performance.

Agent	*Fetal Effect*
Drugs Sedatives/sedative side effects Excitatory Street drugs Indomethacin	 Diminished activity of all varieties; abolition of none. Continous «picket fence» FBM Rachitic, rigid, furious, bizarre FM Oligohydramnios
Maternal Cigarrette Smoking	Various observations: FBM abolished or attenuated but some report no change FM reduced
Maternal Hyperglycemia	Sustained FMB/acidosis, diminution or abolition of FM/FT/CTG-reactivity
Maternal Hypoglycemia	Abnormal paucity of all behaviors, normal AFV
Single Parameter Removed by Perinatal Condition Persistent fetal arrhythmia Spont premature rupt of membranes Periodic deceleration	 Uninterpetable CTG Obligatory oligohydramnios CTG defined as nonreactive
Acute Disasters (Eclampsia, Abruptio Placentae, Ketoacidosis)	Invalidates BPS predictive accuracy

AFV, amniotic fluid volume; BPS, biophysical profile store; CTG, cardiotocogram; FBM, fetal breathing movements; FM, fetal movement; FT, fetal tone.

FETAL HEART RATE MONITORING

The isolated use of Fetal Heart Rate (FHR) testing, whether by classic non-stress test (NST) or by the introduction of contraction challenges, is not considered standard of care for high-risk fetuses. There may be economic or logistic reasons why ultrasound is not available to women undergoing routine prenatal care with no identificable risks, but even in that population there are substantial problems with using the NST as the only method of surveillance (table 4).

Table 4. Problems with non-stress test alone.

Method Fails to detect	
• Oligohydramnios.	• Twin demise.
• Lethal anomalies.	• Anomalies requiring intervention.
• Cord presentation, abnormalities.	• Overall sensitivity 50 % (all outcomes).
• Placental abnormalities.	
Nonreactive Test	
• Poor specificity for compromise.	• Poor specificity for fetal death.
Reactive Test	
• False-reassuring rate 6/1.000	• Unreliable as a backup test*

* False reassuring rate for post-dates pregnancy 20/1.000, false reassuring rate for decreased fetal movement 24/1.000.

The classic accepted criteria for a reactive NST are at least two FHR accelerations lasting at least 15 seconds and rising at least 15 beats/min above the established baseline heart rate. Beyond 30 weeks, the normal baseline is between 120 and 160 beats/min, the baseline variability is more than 5 beats/min, and there is a 20 to 30 minute cycle of sleep activity. During the active phase of the cycle, the fetal heart rate accelerates in response to uterine contractions and fetal movement. On the other hand, preterm fetuses, IUGR fetuses at similar gestations, or fetuses with maternal medication such as sedatives or magnesium sulphate will frequently have paired accelerations-movements that do meet these criteria. Modification of these criteria in biophysical profile scoring (e.g., including accelerations of 10 beats/min lasting 10 seconds on a background of normal FHR variability) accepts the principle that earlier fetuses have smaller accelerations but that they should always demonstrate some degree of FHR acceleration with palpated fetal movements.

False reassuring NSTs do exist, at a rate od 4 to 5 per 1.000 in the largest studies. These are most problematic in fetuses with IUGR, oligohydramnios, and metabolic problems associated with severe macrosomia. In other words, NST has significant liabilities among the highest risk groups. It should not be used in isolation in determining antenatal status of such fetuses.

Because most normal fetuses will demonstrate normal ultrasound variables in biophysical profile scoring within 15 minutes, the additional time to perform non-stress testing is optional and unnecessary in a large number of monitored fetuses. It is economical, therefore, to start antenatal testing with the ultrasound biophysical variables, proceeding to NST if not all of these are normal.

MEASUREMENT OF FETAL GROWTH

A systematic review showed no evidence from randomized trials that the use of fetal growth assessment reduce important adverse outcomes in either high-risk or low-risk pregnancies. Most trials were of isolated measurement of fetal size, usually abdominal circumference. Because single measurements of abdominal circumference are poor predictors of fetuses with pathologic growth, serial measurements may be better. In fact, serial measurements can show a decline in growth as a fetal measurement crosses percentile lines. This approach may be superior to waiting until the absolute measurement is below a particular cutoff value[10].

MEASUREMENT OF AMNIOTIC FLUID VOLUME

Amniotic fluid volume cannot be measured accurately in clinical practice. Ultrasound measurement of amniotic fluid volume is the best reproducible method. There are two ways in which this can be measured with ultrasound: the single maximum pool diameter and the amniotic fluid index (the sum of the maximum vertical pool in each of four uterine quadrants, excluding those containing fetal limbs or cord). A systematic review with a meta-analysis of 18 studies involving more than 10.000 pregnancies showed that oligohydramnios (defined as an amniotic fluid index below the third percentile) was associated with an increased risk of a 5-minute Apgar score of less than 7[11]. However, a low Apgar score is considered fairly poor outcome endpoint. In that systematic review, only one study looked at the predictive value of the amniotic fluid index for neonatal acidosis, and this study reported a poor correlation between the two.

UMBILICAL ARTERY DOPPLER RECORDINGS

As gestation advances, placental resistance decreases, and in the normal fetus, considerable forward movement of blood occurs in the umbilical artery throughout the cardiac cycle. Therefore, the systolic-to-diastolic ratio is low. In normal pregnancy, the S/D decrease with increasing gestational age. In placental insufficiency, the S/D ratio increases until forward flow ceases at the end of diastole (absent end diastolic flow) and flow reverses later (reversed end diastolic flow). Perinatal mortality and morbidity rates increase with the degree of abnormality of umbilical artery Doppler recording. Karsdorp and associates estimated that the odds ratios for perinatal mortality in pregnancies complicated by absent and reversed end diastolic flow were 4 and 11, respectively. Fetal umbilical artery Doppler blood flow waveform is the only test that has been evaluated in randomized trials that included a reasonable number of pregnancies. These studies support the conclusion that its use in high risk pregnancies reduces the rates of perinatal morbidity (defined as admission to antenatal units and induction of labor) and mortality[12]. However, no evidence showed that supports the use of umbilical artery Doppler recordings in screening low risk pregnancies[13].

MEASUREMENT OF MIDDLE CEREBRAL ARTERY BLOOD FLOW

The middle cerebral artery is the easiest fetal cerebral vessel to visualize. Vasodilatation in the cerebral vasculature occurs during mild to moderate hypoxemia. With severe hypoxemia and acidemia, the reduction in middle cerebral artery pulsatility index (PI) reaches a limit that may represent maximum vessel dilatation and redistribution. Ussually, a cutoff value of less than 2 standard deviations from the mean for gestational age is used. Several comparative studies examined high risk pregnancies with redistribution and correlated this finding with perinatal outcome. As with umbilical artery Doppler assessment, the fetus with small for gestational age and middle cerebral artery PI in the normal range is at lower risk perinataly than the fetus with abnormal middle cerebral artery PI[14].

However, cerebral redistribution of fetal blood flow during hypoxia is probably associated with peripheral vasoconstriction. Therefore, the ratio between cerebral arterial PI and umbilical artery PI may be a more sensitive indicator of redistribution. The ratio between blood flow velocity of the umbilical artery and that of the middle cerebral artery does not appear to depend on gestational age. A cerebroplacental ratio of less than 1 indicates redistribution.

REGIONAL BLOOD FLOW: VENOUS WAVEFORMS

The development of abnormal waveforms in the umbilical vein, inferior vena cava, and ductus venosus indicate a late stage of progressive deterioration of the fetal condition and severe fetal compromise. However, venous Doppler waveforms can be difficult to obtain, and in some series, valuable waveforms were achieved in only approximately 75% of cases.

UTERINE ARTERY DOPPLER WAVEFORMS

The uterine artery waveform is used more often to predict disease in late pregnancy than to assess the fetal condition directly. An abnormal waveform at 11 to 14[15] weeks or at 23[16] weeks identifies a high proportion of cases of severe preeclampsia or fetal growth restriction. After 34 weeks, abnormal uterine artery Doppler waveforms at diagnosis are associated with a fourfold increased risk of adverse neonatal outcome[17].

CONCLUSIONS

1. Maternal monitoring of fetal movements is useful for identifying fetuses at increased risk for fetal death. Further study is needed to determine the best method for subsequent fetal monitoring when women report reduced fetal movements.
2. Symphysis-fundal height measurement has considerable limitations when used as the sole screening test for pathologic fetal growth. It has low sensitivity, a high false-positive rate and significant intraobserver and interobserver variation. Customized serial measurements give a better clinical prediction.
3. Auscultation of the fetal heart gives information only about fetal viability. There is no evidence that it identifies at-risk fetuses or improves fetal outcome. Routine recording of the fetal heart rate helps to identify fetal arrhythmias.
4. A biophysical profile score is not recommended for routine screening in low risk pregnancies. However, it is useful adjunct to umbilical artery Doppler recording in high risk pregnancies, particularly because of its high negative predictive value. It is predominantly an acute measure of fetal well-being, giving short-term information and reassurance. In high risk cases, an abnormal biophysical profile score usually predicts imminent fetal death.
5. Cardiotocography analysis predicts outcome. However, like the biophysical profile score, in most cases, carditocography provides information about the acute status of the fetus. The findings become grossly abnormal late in the process of fetal deterioration. Arguably, it should be used only in combination with test of chronic fetal health (e.g. measurement of fetal growth, umbilical artery Doppler).
6. Ultrasound assessment of fetal growth and size in a high risk pregnancy predicts fetal outcome, but there is no evidence that this strategy alters outcome.

7. Amniotic fluid volume less than the third percentile is associated with an increased risk of poor perinatal outcome. It is not clear whether this association is valid if it is an isolated finding.
8. Umbilical artery Doppler recordings in high risk pregnancies are a useful screening tool and reduce perinatal morbidity and possibly mortality rates. There is no agreement about the optimum frequency of use of this modality. No evidence supports the use of umbilical artery Doppler recordings in screening low risk pregnancies.
9. There is no evidence that the use of the regional blood flow recordings in patients with chronic hypoxia and anemia improves pregnancy outcomes, although these recordings indicate the degree of fetal compromise.
10. Uterine artery Doppler recordings obtained before 24 weeks can identify an increased risk of intrauterine growth restriction and preeclampsia. There is evidence that their use improves pregnancy outcome, although the degree of improvement needs further research.

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CHAPTER 8

Evaluation and classification of high risk

PREGNANCY

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INTRODUCTION

One of the most important parts of any health program designed to reduce adverse outcomes of pregnancy anywhere in the world is the detection of the population that has a higher probability to suffer complications. But the objectives of the evaluation and classification of the risk related to pregnancy differ substantially between countries and parts of the world. Broadly speaking, countries can be divided in developed and developing ones.

In developed countries, almost all pregnancies are supervised by gynecologists or midwifes with appropriate prenatal diagnosis facilities and protocols, and the deliveries take place in hospitals or under medical supervision, generally with adequate facilities to confront any complication. The main objective of obstetric care and therefore of risk assessment in these countries, where the maternal mortality rates range between 5 and 15/100.000 births, is the reduction of perinatal mortality and morbidity. On the other hand in developing countries the challenge is firstly to reduce maternal mortality and morbidity figures, that are horrifying in most Sub-Saharan and some Asiatic countries (figure 1 and 2), and in second place to improve the perinatal results.

In developing countries, an adequate selection of high risk patients and the adaptation of the prenatal care programs to facilitate a better detection of and assistance to these especially vulnerable women would have a major impact on maternal and perinatal mortality and morbidity, as an important percentage of these deaths could be avoided by assigning the supervision of their pregnancies and deliveries to trained health providers in adequately equipped centers.

CLASSIFICATION OF FETAL RISK

The aim of this chapter is not only to reach obstetricians or perinatologists, but specially general practitioners, who constitute the fundamental in situ components of the health facilities of most developing countries and therefore should be responsible for the identification of high risk patients and their referral to second line health centers.

Figure 1. Maternal Mortality ratio per 100.000 livebirths.

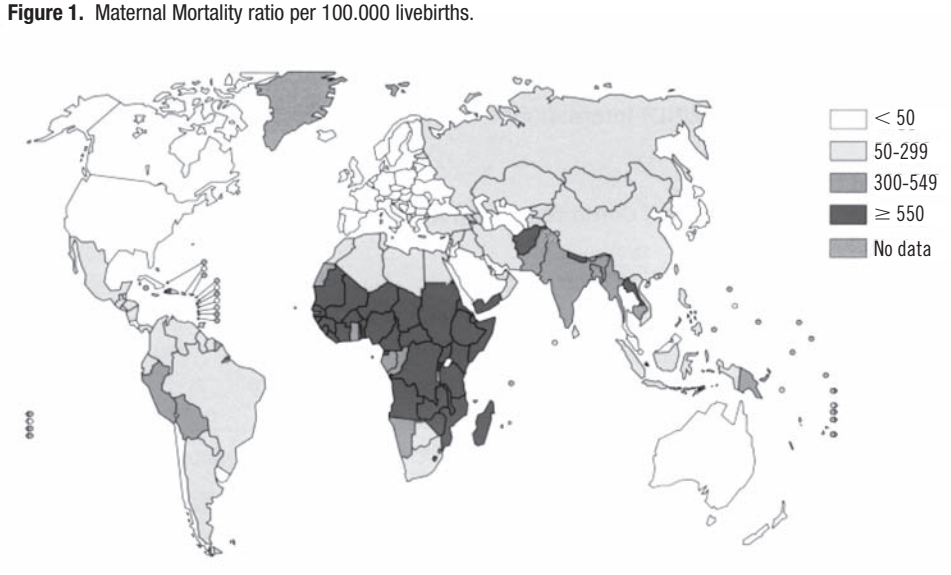

Figure 2. Neonatal Mortality ratio per 1.000 livebirths.

In Perinatal Medicine high risk means a higher probability of adverse results in terms of maternal, fetal or postnatal morbidity or death. But the different pathologies that have been associated with high risk in pregnancy have usually neither high sensitivities nor specificities and, in turn, they could be present with different intensities or even combined. Moreover the same risk factor could have different effects on different populations, not only depending on the characteristics of the population itself, but also of the heath facilities. Therefore it is extremely difficult to establish risk factors and risk scoring systems which could be used in different populations and health settings with different expectations.

Every specific country or region should therefore reach a consensus on which risk factors should be evaluated in their pregnant population to try to reduce those adverse outcomes that are more worrisome due to its frequency or severity, and how many risk categories should be considered, according to the organization of the health system. In general risk scales should include 3 categories: 1.- Low risk; 2.- Intermediate risk and 3.- High risk. In developing regions with rudimentary health structures without third-level hospitals, patients should be divided into low or high risk patients, whereas in developed countries a 4th category of very high risk pregnancies should be considered. Pregnant women should be assigned to the low risk group if no risk factor has been identified. Patients with risk factors that have a low sensitivity and specificity should be assigned to the intermediate risk group. Finally those with risk factors that have a relatively high sensitivity and specificity for severely adverse outcomes should be classified in the high risk group.

In several countries (e.g. Catalunya, Spain), the risk classification of pregnant women reached by consensus of a group of experts under the auspices of the local government includes four categories that are presented in table 1.

Table 1. Classification of fetal risk.

Risk 0:	**High Risk or risk 2:**
Patients with no risk factors identified of all those detailed in the following levels.	Threat of Premature Birth
	Cardiac diseases II
Medium Risk or risk 1:	Prolonged pregnancy
Pelvic anomaly	Second and third trimesters hemorrhage
Cardiac disease I	Oligoamnios
Insufficient prenatal control	Fetal malformation suspicion
Age < 16 or > 35 years	Previous uterine surgery
Uncertain last period date	Anomalous presentation
Twins	Light hypertension
Rh incompatibility	Anemia
Excessive weight gain	Drug adddiction/Alcohol
Urinary infection	Endocrine diseases
Obesity	Hydramnios
Inter pregnancy interval < 12 months	Bad obstetrical background
Short height	Uterine malformation
Social class IV and V	Recurrent perinatal death
Diabetes A	IUGR Risk
Previous sterility	**Very high Risk or risk 3:**
Smoker	Cardiac Diseases III and IV
First trimester hemorrhage	Hypertensive disorders
Insufficient weight gain	Linked serious pathology
Maternal infection	IUGR
Multi-parity	Diabetes B or more serious
Positive VDRL	Isoimmunization
	Placenta previa

The identification of several risk factors means inclusion in the highest group.
The risk level should be revised in each prenatal visit and also at delivery.
VDRL: Veneral Disease Research Laboratory / IUGR: Intrauterine growth restriction.

Risk factors could be detected before pregnancy based on the previous obstetric history or the existence of maternal diseases, or during the progress of pregnancy due to the appearance of obstetric pathologies like hypertensive disorders, intrauterine growth restriction, gestational diabetes, etc. It is important to point out that women with known risk factors

should be counseled before becoming pregnant about the prognosis of a future pregnancy and the follow-up strategy that would be recommended, so that they could freely decide to assume the risks associated to pregnancy or not. In this latter case counseling regarding appropriate family planning should be provided.

Other risk factors appear unexpectedly during pregnancy and could only be detected if the patients are aware of the symptoms or signs that should move them to seek medical assistance, or if pregnant women are regularly controlled by sanitary staff. Therefore adequate health educational programs, not only for first line health providers but also for the general population are of paramount importance in those regions where pregnant women are usually not followed up during their pregnancies.

Once women are classified as high risk patients, specific control and treatment protocols should be applied to reduce the incidence, progression or consequences of the pathology at risk. In many occasions the impact of risk factors on pregnancy is reciprocal; the prognosis of the pathology that constitutes a risk factor for adverse perinatal outcomes can in turn worsen as the result of the pregnancy itself. This could be the case in patients with heart insufficiency, for example.

RISK FACTORS FOR MATERNAL MORBIDITY AND DEATH

The risk of a woman dying as a result of pregnancy or childbirth during her lifetime is about one in six in the poorest parts of the world compared with about one in 30.000 in Northern Europe[1]. Maternal deaths are classified as direct (e.g. hemorrhage, eclampsia, etc.), indirect (e.g. cardiac, renal, etc.) or coincidental (e.g. accidents). Within the group of direct causes also those should be contemplated that derive from the omission or application of incorrect medical or surgical treatments. They can occur in pregnancy, within 42 days of delivery (early) or after 42 days to 1 year (late). Declines in direct mortality may be associated with surveillance and related improvements in obstetric care. The important role of indirect deaths from HIV/AIDS, sickle cell disease, cardiac disease and asthma between others suggests the need to improve collaboration with medical teams to implement guidelines to care for pregnant women with chronic diseases.

The majority of **epidemiological studies** on mortality related to pregnancy have identified the following risk factors:

1. **Socioeconomic and educational status.** In all ethnic groups a low economical and generally related educational status increases the maternal mortality rate[2].
2. **Marital status.** Maternal mortality is three times higher in unmarried patients or patients without couple. This group of patients concentrates near 50 % of all maternal deaths related to abortion or ectopic pregnancy.
3. **Ethnic group.** Apparent health inequality persists with indigenous mothers continuing to have a higher risk of maternal death in different continents.
4. **Age.** Until 30 years of age maternal mortality remains stable, but from then on it rises progressively.
5. **Parity.** The lowest maternal mortality is found in relation with the second and third delivery. With further deliveries the risk increases noticeably, overcoming that of the first delivery.

6. **Insufficient prenatal care.** The risk of maternal mortality is significantly higher in patients without or with poor prenatal control.

7. **Distance to hospital and hospital level.** hospitals with few deliveries have a higher rate of maternal deaths, generally due to the absence of blood banking facilities and the availability of skilled birth attendants. The higher maternal mortality rates found in referral hospitals has to be attributed to the high percentage of high risk pregnancies and deliveries that are attended in these institutions.

On the other hand there are several **medical factors** which could have a live threatening impact on the mother. Main causes of maternal death vary between developed and developing countries. Hemorrhage and hypertensive disorders of pregnancy constitute pathologies that have an important protagonism in both settings, whereas infective complications, including those derived from unsafe abortions, have a great impact in developing countries and thromboembolic events are the leading causes of maternal deaths in some developed countries. The following are some of the medical factors that have a closer relationship with adverse maternal outcomes, and affected women should be controlled during their pregnancies and deliveries by skilled health providers:

1. **Diabetes.** Prior to the discovery of insulin diabetic patients died before reaching the reproductive age, and those who did not, suffered a near 50 % mortality rate during pregnancy. Despite the introduction of insulin and the great advances in the knowledge of the pathogenesis and treatment of the diabetes, this pathology remains related to a higher risk of complications, especially if the control of the glycemia is suboptimal.

2. **Hypertension and hypertensive disorders of pregnancy.** Patients with chronic hypertension have an increased risk of preeclampsia/eclampsia, that by themselves imply a higher mortality risk[3].

3. **Multiple pregnancy.** Compared with singleton gestations, women with multiple gestations have a twofold risk of death, preeclampsia, and postpartum hemorrhage and a three fold risk of eclampsia. There is also a significant association between multiple gestation and increased incidence of preterm labor, anemia, urinary tract infection, puerperal endometritis, and cesarean delivery[4].

4. **Obesity.** Compared to women with normal BMI, the following outcomes were significantly more common in obese pregnant women: gestational diabetes mellitus, proteinuric pre-eclampsia, postpartum hemorrhage, genital tract infection, urinary tract infection and wound infection[5].

5. **Stillbirth.** Stillbirth and maternal mortality rates are strongly correlated, with about 5 stillbirths for each maternal death. However, the ratio increases from about 2 to 1 in least developed countries to 50 to 1 in the most developed countries[6].

6. **Previous cesarean section.** Compared with mothers who have had primary vaginal births, mothers who have had primary caesarean section and undergo labor in the second birth are at increased risk of uterine rupture, hysterectomy, postpartum hemorrhage, infection and intensive care unit admission[7].

7. **Previous obstetric complications.** In a recent study conducted in Mexico, the history of complications in previous pregnancies was the risk factor for maternal death with the highest odds ratio, followed by pre-existing medical conditions[8].

8. **Preexisting medical conditions.** Infectious, hematological, endocrine, renal, hepatic, neurological, cardiac, pulmonary and immunological diseases. Especially in pandemic areas, HIV/AIDS and malaria.

RISK FACTORS FOR ADVERSE PERINATAL OUTCOMES

All risk factors for adverse maternal outcomes enumerated in the previous section have also a negative impact on the perinatal figures. But on the other hand there are some risk factors that have a specific impact on perinatal outcomes without influencing maternal health. The most common causes of stillbirths were conditions originating in the perinatal period: intrauterine hypoxia and asphyxia. Congenital malformations, including deformities and chromosomal abnormalities, and disorders related to slow fetal growth, short gestation, low birth weight, birth trauma and infections were the most common causes of neonatal deaths.

1. **Congenital defects.** In developed countries where pregnancy interruption for fetal congenital defects is legally accepted, fetal malformations have reduced its impact on perinatal mortality, but in developing ones, malformations constitute one of the important causes of perinatal deaths. Reduction of its contribution to perinatal mortality can only be achieved implementing prenatal diagnosis strategies and referring patients to referral hospitals where affected newborns could be adequately treated.
2. **Preterm delivery.** Despite great efforts, prematurity rates remain unchanged in the last decades. Different screening and prevention strategies have been proposed without great impact on its incidence. Adequate dating of the gestation is of great importance to refer the patients with preterm labor to be delivered in adequate health centers. The challenge of perinatal medicine in this field is to improve the neonatal outcome, especially in poor resource settings. One promising approach consists in managing low birth weight and preterm neonates in home setting by the mother and trained village health workers[9].
3. **Intrauterine growth restriction.** Infants with intrauterine growth restriction are at risk for increased perinatal mortality, birth adaptation complications, including perinatal acidosis, hypoglycemia, hypothermia, coagulation abnormalities, and selected immunologic deficiencies. IUGR infants also appear to be at great risk for complications of prematurity, including chronic lung disease and necrotizing enterocolitis and an increased risk of neurological disorders, including cerebral palsy and poor neurodevelopmental outcome[10].
4. **Intrauterine infections.** The failure to apply known effective antiretroviral and antimalarial interventions to infected mothers through antenatal programs continues to contribute substantially to infant deaths globally[11], especially in pandemic areas.
5. **Birth trauma.** Although some are not predictable, antepartum obstetric evaluation of the prognosis of a vaginal delivery, birth assistance by trained health providers, adequate referral protocols and the possibility to perform a caesarean section are some alternatives to lover the impact of birth trauma not only on perinatal but also on maternal outcomes.
6. **Rh alloimmunization.** The formation of maternal antibodies when any fetal blood group factor inherited from the father is not possessed by the mother, also known as alloimmunization, may lead to various degrees of transplacental passage of these antibodies into the fetal circulation. Depending on the degree of antigenicity and the amount and type of antibodies involved, this transplacental passage may lead to hemolytic disease in the fetus and neonate. Undiagnosed and untreated, alloimmunization can lead to significant perinatal morbidity and mortality[12].

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CHAPTER 9

Haemorrhage in the first term of the pregnancy

E. Bescós Santana | P. Ibáñez Burillo | M. Tajada Duaso | E. Fabre González

INTRODUCTION

Haemorrhage is the main cause of maternal mortality around the world. The most common bleeding event during gestation is the early miscarriage or abortion followed by ectopic pregnancy. Trophoblastic illness or other causes of vaginal or cervical haemorrhage are less frequent.

MISCARRIAGE

Miscarriage or spontaneous abortion is the natural or spontaneous end of a pregnancy at a stage where the embryo or the foetus is incapable of surviving, generally defined at a gestation of prior to 20 weeks. Miscarriages are the most common complication of pregnancy.

Determining the prevalence of miscarriage is difficult. Many miscarriages happen very early in the pregnancy, before a woman may know she is pregnant. Prospective studies[1] using very sensitive early pregnancy test have found that 25% of pregnancies are miscarried before the sixth week of gestation. The risk of miscarriage decreases sharply after the 8th week. Clinical miscarriages occur in 8% of pregnancies[2]. The prevalence of miscarriage increases considerably with age of the parents.

CAUSES

Miscarriages can occur for many reasons, not all of which can be identified. Most miscarriages (more than three-quarters) occur during the first trimester. Chromosomal abnormalities are found in more then half of embryos miscarried in the first 13 weeks. Another cause of early miscarriage may be progesterone deficiency.

Up to 15% of pregnancy losses in the second trimester may be due to uterine malformation, growths in the uterus (fibroids) or cervical problems. These conditions may also contribute to premature birth. Other causes are: gestational diabetes, high blood pressure, tobacco, hypothyroidism, autoimmune diseases...

DIAGNOSE

The most common symptom of a miscarriage is bleeding. Symptoms other than bleeding are not statistically related to miscarriage[3]. However the patient may refer moderate or mild pelvic pain, her cervix can be dilated and her uterus can be enlarged in an extent appropriate or minor for gestational age of the pregnancy. A pregnancy test will be positive.

Pelvic ultrasound is used to visualize foetal heartbeat and to determine whether a pregnancy is still viable. The measure of the embryo length determines its gestational age. We have to differentiate if it is a threatened miscarriage (uterine bleeding with embryo alive), complete miscarriage (products of conception have emptied out of the uterus) or incomplete miscarriage (products of conception persist in the uterus).

Blood levels of serial human chorionic gonadotrophin (hCG) may help to determine the viability of a pregnancy if the ultrasound examination is inconclusive.

TYPES OF MISCARRIAGE

THREATENED MISCARRIAGE

Uterine bleeding at early pregnancy that may be accompanied by cramping or lower backache. The cervix remains closed. This bleeding is often the result of implantation.

INEVITABLE OR INCOMPLETE MISCARRIAGE

Abdominal or back pain accompanied by bleeding whit an open cervix. Miscarriage is inevitable when there is a dilation or effacement of the cervix and/or there is rupture of the membranes. Bleeding and cramps may persist if the miscarriage is not complete.

COMPLETE MISCARRIAGE

The embryo or products of conception have emptied out of the uterus. Bleeding should subside quickly, as should any pain or cramping. It can be confirmed by an ultrasound or by having a surgical curettage performed.

MISSED MISCARRIAGE

Women can experience a miscarriage without knowing it. Embryonic death has occurred but there is not any expulsion of the uterus. It is not known why this occurs. Signs of this would be a loss of pregnancy symptoms and the absence of fetal heart tones found on an ultrasound.

RECURRENT MISCARRIAGE

Defined as three or more consecutive miscarriages. This can affect 1 % of couples trying to conceive.

BLIGHTED OVUM

Also called anembryonic pregnancy. A fertilized egg implants into the uterine wall, but foetal development never begins. Often there is a gestational sac with or without a yolk sac, but there is an absence of foetal growth[4].

TREATMENT

Avoid or restrict some forms of exercise is recommended to manage threatened miscarriage. Not having sexual intercourse is usually recommended until the warning signs have disappeared.

No treatment is necessary for a diagnosis of complete abortion (as long as ectopic pregnancy is ruled out).

In cases of an incomplete abortion, empty sac, or missed abortion there are three treatment options[5]:

- With no treatment, most of these cases (65-80 %) will pass naturally within two to six weeks. This path avoids the side effects and possible complications from medications and surgery.
- Medical management usually consists of using oral or vaginal prostaglandins (misoprostol) to encourage completion of the miscarriage. About 95 % of cases treated with misoprostol will complete within a few days.
- Surgical treatment, most commonly dilation and curettage (D&C) is the fastest way to complete the miscarriage. It also shortens the duration and heaviness of bleeding, and is the best treatment for physical pain associated with the miscarriage.

If women's blood group is Rh negative, they will also need the Rhogam shot within 72 hours of the abortion[4]. Although a woman physically may recover from a miscarriage quickly, psychological recovery for parents in general can take a long time.

ECTOPIC PREGNANCY

In an ectopic pregnancy, a fertilized egg has implanted outside the corps uterus (figure 1). The egg settles in the fallopian tubes more than 95 % of the time. This is why ectopic pregnancies are commonly called «tubal pregnancies». The egg can also implant in the ovary, abdomen or the cervix.

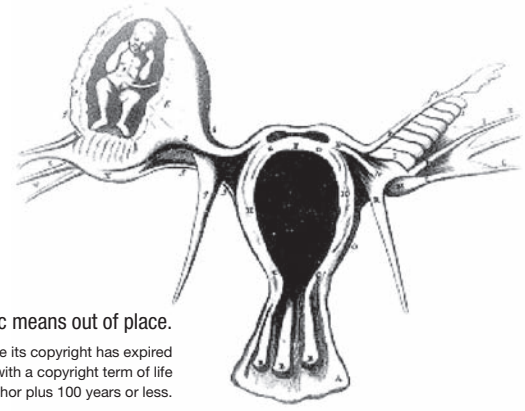

Figure 1. Ectopic means out of place.

None of these areas has as much space or nurturing tissue as a uterus for a pregnancy to develop. As the foetus grows, it will eventually burst the organ that contains it. This can cause severe bleeding and endanger the mother's life. A classical ectopic pregnancy never develops into a live birth.

The ectopic pregnancy incidence is between 1 % and 2 % of all pregnancies.

CAUSES

The causes of ectopic pregnancy are unknown. After fertilization of the oocyte, the egg takes about nine days to migrate down the tube to the uterine cavity at which time it implants. Wherever the embryo finds itself at that time, it will begin to implant:

- Previous surgery or inflammation of the Fallopian tubes (pelvic inflammatory disease) can increase the risk of and ectopic pregnancy.
- If a woman has previously had an ectopic pregnancy, the chances of another one in the same Fallopian tube and in the other tube are increased.
- Contraceptive coil or the progestogen-only contraceptive pill (mini-Pill) could be the cause of an ectopic pregnancy.

However, many women experiencing an ectopic pregnancy do not have any of these risk factors.

DIAGNOSE

An ectopic pregnancy has to be suspected in any woman with lower abdominal pain and/or unusual bleeding who is or might be sexually active and whose pregnancy test is positive.

Early symptoms in ectopic pregnancy are either absent or subtle. Clinical presentation of ectopic pregnancy occurs at a mean of 7,2 weeks after the last normal menstrual period, with a range of 5 to 8 weeks. Later presentations are more common in communities deprived of modern diagnostic ability (ultrasound and determination of hCG levels).

Patients with a late ectopic pregnancy typically have pain and bleeding. This bleeding will be both vaginal and internal and has two discrete pathophysiologic mechanisms:

a) External bleeding is due to the falling progesterone levels.

b) Internal bleeding is due to haemorrhage from the affected tube.

The vaginal bleeding can be indistinguishable from an early miscarriage or the implantation bleed' of a normal early pregnancy.

The pain and discomfort are usually mild. A *corpus luteum* on the ovary in a normal pregnancy may give very similar symptoms.

A urine test for pregnancy will nearly always be positive but it might be only weakly positive. In cases of doubt, a blood pregnancy test may be performed, which is always positive in ectopic pregnancy.

The uterus will often be smaller than expected for the number of weeks since the woman's last period. During the exploration it might be felt a tender swelling corresponding to an ectopic pregnancy[4].

COMPLEMENTARY TESTS

Transvaginal ultrasound is a valuable diagnostic tool. The presence or absence of an intrauterine sac must be documented. A β-hCG >2.400 mIU/ml with no intrauterine sac present is diagnostic of an abnormal pregnancy and highly suggestive of an ectopic pregnancy[6]. The hCG discriminatory concentration is dependent on the hCG standard utilized in any given laboratory. In addition, ultrasonic detection of adnexal cardiac activity is useful in determining the appropriate therapy for ectopic pregnancy.

Culdocentesis may be used to look for internal bleeding. In this test, a needle is inserted into the space at the very top of the vagina, behind the uterus and in front of the rectum. Any blood or fluid found there likely comes from a ruptured ectopic pregnancy. A **laparoscopy** or laparotomy can also be performed to visually confirm an ectopic pregnancy.

TREATMENT

If left untreated, about half of ectopic pregnancies will resolve without treatment. These are the tubal abortions. The advent of methotrexate (MTX) treatment for ectopic pregnancy has reduced the need for surgery; however, surgical intervention is still required in cases where the Fallopian tube has ruptured or is in danger of doing so.

MTX, long used in treatment of gestational trophoblastic neoplasia, is also effective in treating ectopic pregnancy. It is particularly effective as primary treatment when the diagnosis can be made without surgery. MTX may be administered intramuscularly in either single[7] or alternate day doses[8]. However, the optimal dose and time of MTX has yet to be determined.

If haemorrhaging has already occurred, surgical intervention may be necessary if there is evidence of ongoing blood loss. The option to go to surgery is thus often a difficult decision to make in an obviously stable patient with minimal evidence of blood clot on ultrasound. Surgeons use laparoscopy or laparotomy to gain access to the pelvis and can either incise the affected Fallopian and remove only the pregnancy (salpingostomy) or remove the affected tube with the pregnancy (salpingectomy).

If women's blood group is Rh negative, they will also need the RhoGam shot. The chance of future pregnancy depends on the status of the tube(s) that are left behind, but is decreased. The chance of recurrent ectopic pregnancy is about 10% and is independent of whether the affected tube was repaired (salpingostomy) or removed (salpingectomy).

MOLAR PREGNANCY

A molar pregnancy is an abnormality of the placenta, caused by a problem when the egg and sperm join together at fertilization. Molar pregnancies are rare, occurring in 1 out of every 1.000 pregnancies. Molar pregnancies are also called hydatidiform mole or simply referred as a «mole».

The complete mole, this occurs when the nucleus of an egg is either lost or inactivated. The sperm then duplicates itself because the egg was lacking genetic information. Usually there is no foetus, no placenta, no fluid and no amniotic membranes. The uterus is rather filled with the mole that resembles a bunch of grapes. The fluid filled vesicles grow rapidly, which can make the uterus seem larger than it should be for gestational age.

The partial mole, this most frequently occurs when two sperm fertilize the same egg. There may be partial placentas (figure 2), membranes or even a foetus present in a par-tial mole. However, there are usually genetic problems with the baby.

The gestational trophoblastic diseases (GTD) include complete and incomplete molar pregnancy. The term gestational trophoblastic neoplasia (GTN) replaces the terms chorioadenoma destruens, metastasizing mole and choriocarcinoma. These were pathologic diagnoses.

DIAGNOSE

The main symptoms of a molar pregnancy are increased nausea and vomiting, vaginal bleeding, and increased hCG levels with a rapidly growing uterus; but no foetal movement or heart tone is detected. It is frequent to find pregnancy induced hypertension prior to 24 weeks and hyperthyroidism. Pulmonary embolization may also occur.

Ultrasound can also help determine a molar pregnancy. The typical «snow storm effect» may be seen on the screen.

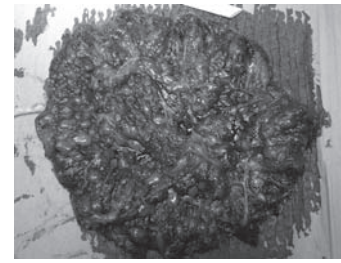

Figure 2.
Courtesy of HCU of Zaragoza.

TREATMENT

If the pregnancy has not ended on its own, suction is usually used to evacuate the mole from the uterus.

Ongoing treatment includes β-HCG levels to be taken two times a week, then weekly, until they are «normal» for three weeks. Afterwards it will be tested monthly for six months, and every two months until a total of one year has passed. Pelvic exams should be done too. A rising level of β-HCG and an enlarging uterus could indicate the presence of a choriocarcinoma. If women's blood group is Rh negative, they will also need the RhoGam shot. Pregnancy should be avoided for the period of one year. Any method of birth control, with the exception of an intrauterine device, is acceptable.

Table 1. Differential diagnosis of haemorrhages of the first term of the pregnancy.

Threatened miscarriage	*Ectopic pregnancy*	*Molar pregnancy*
Genital bleeding	Pelvic pain	Uterus bigger than gestational age
Embryo with/without beating	Uterus is empty and there is a tubal increase	«snow storm effect» with/without embryo
β-HCG according or lower to gestational age	Lower increase of β-HCG	β-HCG very increased

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CHAPTER 10

Intrauterine growth restriction

G. P. Mandruzzato

INTRODUCTION

In normal conditions the fetal growth process depends on many factors mainly maternal and constitutional or racial. Many pathological conditions can alter the normality of this process in defect and in excess as well.

Since a long time it is well recognized that perinatal mortality and morbidity are significantly increased in case of birthweight (BW) below the 10th percentile for the gestational age. These newborns are defined as Small for Gestational Age (SGA). Moreover it has been shown that the perinatal mortality rate is inversely proportional to the BW. For a long time SGA newborns have been considered the consequence of intrauterine growth restriction (IUGR) and the two terms became synonymous. After the introduction in clinical practice of ultrasonic fetal biometry it became possible to assess the fetal size and monitor with good accuracy the patterns of fetal growth before birth. As a consequence it becames clear that IUGR and SGA are different clinical conditions.

It has been suggested that IUGR should refers only to the fetus and SGA only to the newborn[1].

The assessment of the BW has lost part of his importance as a factor influencing the perinatal outcome as it is now evident that the adverse outcome is the consequence of the growth restriction.

In fact looking at the «growth» and not at the «weight» it is possible to have IUGR presenting a BW within the range of statistical normality (AGA) but that are affected in same way as the IUGR-SGA.

Moreover due to the improvement in fetal instrumental semeiotic it is now clear that IUGR and SGA are neither a diagnosis nor a disease per se. They must be considered as symptoms of a possible disease that has affected the inherent growth potential of the fetus indicating an increased risk of poor perinatal outcome. In fact IUGR are not representing an homogenuos fetal/neonatal population as the causes of growth restriction

can be different. Anyway it is obvious that in order to apply any management (when available) the prenatal recognition of the IUGR is fundamental.

The aim of this chapter is to present and discuss definition, etiology, fetal and neonatal complications, prenatal recognition, diagnosis and management of IUGR.

DEFINITION

The ACOG has proposed the following definition of IUGR: a fetus that fails to reach his potential growth.

At the moment this definition seems to be the more satisfactory. In fact it is implicit that in this way the weight or size, being a function of growth, has only importance when compared to an expected value. This consideration has practical implications that will be discussed when dealing with the recognition of IUGR.

Anyway it should be now clear that it is not correct to describe as IUGR fetuses or newborns only on the basis of the estimated fetal weight (EFW) or BW only below any predefined threshold.

ETIOLOGY

The fetal growth restriction can be the consequence of maternal, fetal or placental abnormal conditions.

a) Many **medical maternal conditions** can be associated with IUGR: hypertension and preeclampsia, renal diseases, antiphospholipid syndrome, cyanotic heart disease, lung diseases, hemoglobinopathies, severe anemia. Lyfestile (substance abuse and smoking), severe malnutrition and low socioeconomic status can also negatively influence fetal growth process.

b) **Fetal malformations, chromosomal aberrations and infections** are recognized as causes of IUGR.

   It is estimated that less than 5% of IUGR are consequence of viral infections (mainly rubella and cytomegalovirus). Congenital Toxoplasmosis can be associated with IUGR. Malformations are also associated with IUGR but that risk is largely different according to the severity of the abnormality.

   A major etiology of IUGR is represented by chromosomal aberrations. Some medications administered to the mother can induce growth restriction. This association is documented for anticonvulsivant drugs.

c) **The placenta** is the organ that allows normal nutrient and oxygen supply from the mother to the fetus. Therefore placental diseases are the most frequent cause of IUGR. Abnormal placental implantation (like placenta praevia) or structure (like chorioangioma) can be associated with IUGR.

   Confined placental mosaicism is observed in case of IUGR with significantly increased frequency as compared to case presenting normal growth.

The most important placenta disease responsible of more than 35% of IUGR is represented by the obliterative vasculopathy. It is the consequence of insufficient secondary trophoblastic invasion occurring in the late 1st and early 2nd trimester. In this condition maternal-fetal exchanges are reduced and growth restriction first occurs, followed by chronic fetal hypoxaemia (CFH) and acidaemia, in case of worsening condition.

FETAL AND NEONATAL COMPLICATIONS

First of all it is necessary to remember that IUGR is not «per se» a disease. Therefore fetal and neonatal complications and outcome are strongly dependent on the primary etiology and on its severity. Moreover it is necessary to remember that the factor that principally influences the perinatal outcome is the gestational age at birth.

When IUGR is the consequence of fetal malformations, chromosomal aberrations and infections, the outcome will depend on the natural history of these diseases and their severity. In case of maternal pathological conditions inducing IUGR the fetal/neonatal complications can be mainly represented by prematurity if the maternal situation indicate the delivery remote to term.

When CFH occurs the fetal outcome depends on the level and duration of oxygen supply reduction.

The fetus first adapts to the adverse condition performing blood flow redistribution. In this way more oxygenated blood is directed toward brain, heart and lung while blood flow to splancnic and somatic structure is reduced. This phenomenon is called «brain sparing effect» and it is observable by using Doppler technology. The peripheral resistance to flow increases in the fetal thoracic descending aorta and other vessel while the resistance is reduced in cerebral arteries. This is a mechanism of defense. If the hypoxaemia lasts for a long time or is worsening heart function is altered than tissue and organ damage can occur particularly at the level of the brain.

Intrauterine fetal death can occur. In fact it has been observed that 52% of the unexplained stillbirths is associated with IUGR[2].

Also many complications can be observed in the neonatal life. Low Apgar Scores and acidaemia are frequently observed. Moreover hyperbilirubinemia, hypoglicemia. polyccythemia and hypothermia are frequent. As far as the postnatal catch up in growth is concerned the results are controversial. Anyway it has been shown that neurologic sequelae prevalence in case of IUGR is doubled as compared to normally grown newborns. It has also been suggested that adult diseases, like cardiovascular complications and hypertension, can be a consequence of fetal growth restriction.

PRENATAL RECOGNITION

Taking into account the ACOG definition the criteria that should be used to suspect or recognize an IUGR fetus are obvious. The task in fact is not to recognize SGA fetuses but to detect the failure of that fetus of reaching his potential growth. As growth is a dynamic process in order to detect any possible deviation it is fundamental to have an exact start point that is represented by a precise assessment of gestational age. It can be easily done by performing

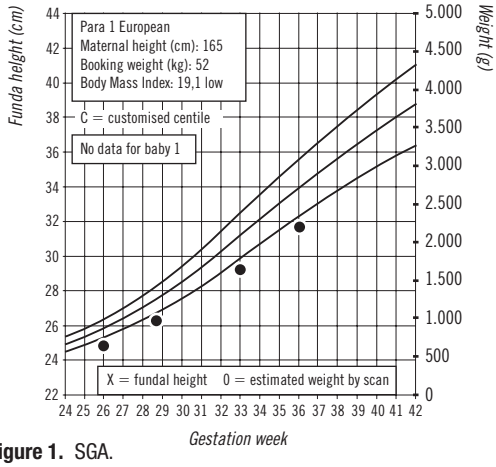

Figure 1. SGA.

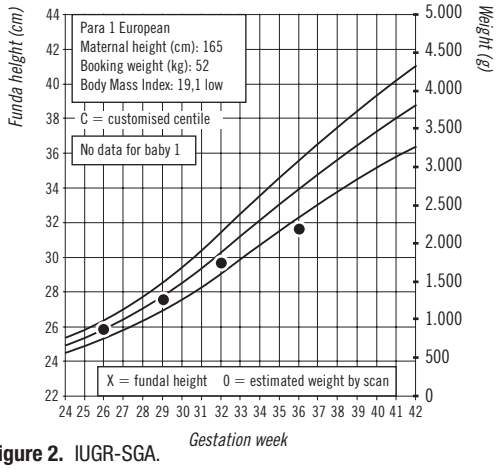

Figure 2. IUGR-SGA.

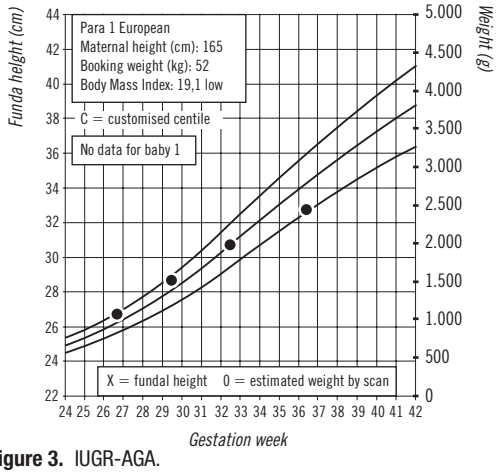

Figure 3. IUGR-AGA.

an US scan in the 1st trimester by measuring the crown-rump length or before 20 gestational week the biparietal diameter(BPD). The accuracy of these measurements is plus/minus 4 days. In this way it is possible, at a later scan, to observe if the individual growth is deviating from the expected. The commonly used parameters of the fetal biometry are the abdominal circumference (AC), the BPD and the femur length or the estimated fetal weight (EFW). The formulas commonly used for EFW are the ones proposed by Shephard[3] and Hadlock[4]. **When a significant deviation from the expected value is observed IUGR should be suspected.** Apparently an easy task. But it is necessary to remember that the «inherent potential growth» of any individual is dependent in normal conditions on many factors: maternal, constitutional and racial. Therefore in order to achieve a better assessment the use of «customized» growth charts has been proposed[5]. It has been suggested to consider IUGR the fetus presenting an EFW inferior to the 10th percentile for the gestational age.

Unfortunately any proposed formulas for EFW are affected by an error, in excess or defect as well, between 7,5% and 10%. Therefore taking into consideration that the abdominal circumference is strongly correlated with the fetal weight and that its measurement is highly reliable this simple method could be a better way for monitoring fetal growth. It is advisable to compare the obtained values with charts built on data of the population that is object of evaluation. As the fetus should be his own control by comparing serial measurements a better assessment of his growth can be obtained. **The interval between measurement should not be inferior to two weeks in order to avoid false positive results[6].** But if the suspicion of IUGR is based on the observation of a biometric value (AC or EFW or FH) below the 10th percentile a significant number of IUGR will be missed as only SGA will be detected. It has been shown that IUGR signs can be present also if the weight is within the range of normality. Therefore plotting serial biometric values against expected values it is possible to observe SGA presenting normal growth patterns (figure 1), IUGR-SGA (figure 2) and IUGR-AGA (figure 3) fetuses.

SCREENING FOR IUGR

About 50% of IUGR are not recognized until birth and the majority are observed in pregnancies that are not presenting risk factors. It has been also shown that perinatal mortality is significantly lower in SGA cases detected before birth as compared to those undected[7]. Therefore a timely prenatal recognition of IUGR is fundamental for improving the outcome when an appropriate management is available.

Fundal height measurement (FH) has been proposed as a screening method for IUGR. It is easy to perform and unexpensive but its efficacy for early detection of IUGR is not satisfactory. More sophisticated methods for using FH have been proposed but their efficacy must be tested.

When available the ultrasound fetal biometry should be considered the method of choice.

Evidence has been given that by using mass screening with scans performed at 30-32 and 36-37 weeks the detection of IUGR fetuses and their outcome are improved[8].

IUGR DIAGNOSIS

As already said IUGR nor SGA are a diagnosis. They must be regarded as a symptom of a possible maternal, fetal or placental disease. Therefore after suspicion of growth restriction it is fundamental to identify his etiology in order to optimize the clinical management.

1. **Exhaustive clinical and immunological examinations** of the maternal conditions must be carried out in order to detect factors possibly inducing IUGR. Viral or protozoal infections must be identified or excluded.
2. **A complete careful examination of the fetal anatomy** must be performed for excluding or detecting malformations. Kariotyping should be carried out especially in cases of early onset of IUGR. It can be done by amniocentesis or chordocentesis. The last offers a quicker result but carries an increased fetal risk. In the same way in case of suspected infections the fetal involvement can be better assessed.
3. **Characteristics of the placenta** (morphology and localisation) must be checked. In order to assess placental function Doppler Blood Flow on the umbilical arteries must be carried out.. In this way it is possible to detect possible reduction of blood supply to the fetus.

IUGR PREVENTION

The only available method for IUGR prevention of known efficacy, is represented by the modification of the maternal lifestyle, when considered as potential risk for IUGR. Probably the modification should start in the preconceptional period.

IUGR MANAGEMENT

When the primary etiology are maternal diseases the management of course will performed following the maternal indications. When the cause of IUGR is fetal chromosomal

aberrations, malformations or infections little can be done to improve significantly the outcome.

On the contrary when the etiology is the placental obliterative vasculopathy inducing CFH and acidaemia the management can be optimized and the outcome improved using as a clinical guidance a close monitoring of the CFH. When a fetus is facing CFH he adapts to the situation by altering his vital functions. Haemodynamic changes occur, heart rate can be altered, amniotic fluid production is reduced (inducing olygohydramnios) and fetal movements are also reduced. Moreover the fetal behaviour can be altered. Therefore the clinical management is mainly based on the monitoring of these changes, especially haemodynamic and heart activity.

HAEMODYNAMIC CHANGES

a) **Peripheral resistance in the umbilical arteries** is progressively reduced in normal evolving pregnancies. This fact can be easily assessed by measuring the Pulsatility Index(PI) on these vessels.

   In case of obliterative placental vasculopathy the PI increases and this increase is proportional to the obliteration of the placental vascular bed. In this case the oxygen supply to the fetus is reduced and CFH occurs. Therefore the investigation on the umbilical arteries is in condition to distinguish between affected IUGR and those that are not. In fact this method is considered the best available test for placental function.

b) In **normal conditions the PI in the fetal arterial vessels shows a fairly trend to reduction.** When CFH occurs the PI rises in somatic vessels and decreases in cerebral arteries. By studying these changes it is possible to evaluate the fetal response and adaptation. In very severe cases the blood flow can be absent or reversed in the diastolic phase. These patterns are called ARED flow (end diastolic absent or reverse flow). In this particular haemodynamic condition perinatal mortality and morbidity are very high.

   Also venous fetal vessels undergo changes. The Ductus venosus (DV) has been object of many studies and it has been shown that abnormal Doppler findings are strong predictors of adverse outcome. At the moment the clinical utility of DV haemodynamic changes for the management must be assessed.

FETAL HEART RATE (FHR)

FHR is also altered in case of CFH. The most sensible parameter, showing a strong correlation with the levels of hypoxaemia and acidaemia is the reduction of the FHR variability. By using cardiotochography (CTG) it is easy to observe such a reduction. But the conventional CTG has a limitation as it is difficult to quantify precisely this reduction. By using computer assisted CTG it is possible to evaluate it precisely on line obtaining also a numerical value. Short term and long term variability values and their trend along time are usually the basis for choosing the timing of the delivery. **Therefore when available the computerized CTG should be the method of choice for the management of the hypoxaemic fetus.**

It must be remembered that the only available cure for the hypoxaemic IUGR is the delivery. But it must also be kept in mind that IUGR is not per se an indication to delivery and also in cases of CFH and abnormal Doppler findings aggressive management (caesarean section) is necessary with different frequence according to the severity of the

compromise. When ARED flow are observed, if no other contraindications are present, timing of the delivery must be considered. The management anyway must be different in case of End Diastolic Flow Absent or Reverse Flow[9]. When PI superior to the 2nd SD are observed CS is needed in 70% of the cases and if abnormal PI is only observed in the fetal aorta but is still normal in UA spontaneous vaginal delivery is achievable in more than 65% of the cases[10].

AMNIOTIC FLUID

In case of blood flow redistribution when CFH occurs in IUGR also the amniotic fluid amount is reduced. This reduction is consequence of reduced fetal urine production. This phenomenon is easily observable by obstetric ultrasound. The amniotic fluid index (AFI) or the measurement of the deepest amniotic fluid pocket are used for a quantification of the olygohydramnios. The timing of the delivery should not be based only on the amniotic fluid assessment.

FETAL BIOPHYSICAL PROFILE (FBP)

There is no evidence that the use of the FBP improves the outcome is risk pregnancies.

When the GA is low it necessary to make a compromise between the risk of intrauterine life in adverse conditions and the risk of the large prematurity.

Whenever possible the fetal management and the delivery should take place in tertiary level Center.

SUMMARY

Fetal growth restriction is a major problem in perinatal medicine. The prevalence is about 8-10% of a general population. Perinatal mortality and morbidity are significantly increased as compared to normally growing fetuses. The etiology is multifactorial and must be carefully assessed as the outcome is strongly dependent on it. In fact IUGR in itself is not a disease but can be the symptom of a pathological condition maternal, fetal or placental. As in some situations, like placental obliterative vasculopathy, the outome can be improved, a timely recognition of IUGR is of paramount importance. After that by using second level tests like Doppler flowmetry it is possible to identify the fetuses that are affected by chronic hyopoxaemia. The clinical management is based on the monitoring of hypoxaemia and cardiotochography, when available computer assisted, is usually the principal guide for choosing the time of the delivery when necessary.

RECOMMANDATIONS

1. IUGR is not synonymous of SGA and should be used only when referring to the fetus.
2. Screening for IUGR is highly advisable. The method of choice should be serial ultrasonic biometry. If this facility is not available FH can be used.
3. After IUGR suspicion the etiology (maternal, fetal, placental) must be assessed.
4. Doppler flowmetry on umbilical arteries should be performed for assessing placental function.

5. If abnormal Doppler findings are detected on umbilical arteries, the fetal response to CFH must be assessed.In this case the clinical management is based on close monitoring of CFH.
6. Whenever possible the delivery should take place in tertiary level centers.

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Diabetes and pregnancy

CHAPTER 11

PREGNANCY

F. A. Van Assche

INTRODUCTION

Substantial progress has been made in understanding the physiopathology and management of diabetes and pregnancy, however major problems remain unsolved.

Pre-gestational and gestational diabetes remain an important medical complication, with consequences for the mother and the child in the short and long term.

The care of the pre-gestational diabetes has improved, but major complications, such as congenital malformations, sudden fetal death and the association with pre-eclampsia, need better understanding. Obesity is becoming a major problem not only in relation to the increased incidence of type 2 pre-existing diabetes, but also as a risk factor in pregnancy.

SCREENING AND PRE-PREGNANCY CARE

SCREENING FOR GESTATIONAL DIABETES

Gestational diabetes is defined as carbohydrate intolerance of variable severity with onset or first recognition during the current pregnancy[1]. It is a heterogeneous disorder and affects at least 3 percent of pregnancies in the Western World[2, 3]. The metabolic adaptation that occurs during normal pregnancy involves apparent deterioration of glucose tolerance and hyperinsulinism, but only in a minority of women the diagnostic criteria for gestational diabetes are present[4]. Insulin secretion is increased during pregnancy and there is evidence that insulin resistance exists[5, 6]. The morphological basis for this hyperinsulinism is marked B cell hypertrophy and hyperplasia, and hyperactivity of the individual B cell[7].

In the past, gestational diabetes was reported to be associated with increased perinatal mortality[8-10]. More recently, this was not completely confirmed. However, gestational dia-

betic women receive more obstetric attention and there is increased perinatal mortality in undiagnosed gestational diabetes[11]. Perinatal morbidity, in particular fetal macrosomia is increased in gestational diabetes. Fetal macrosomia is associated with an increased number of operative deliveries and with shoulder dystocia[12, 13].

Gestational diabetes remains a risk factor for the mother and the child. It is therefore necessary to screen for this disorder during pregnancy. Universal screening with a 50 g 1 h glucose challenge is recommended. The final diagnosis is made with a 100-g oral glucose challenge test. This clearly means that women with risk factors (obesity, a history of familial diabetes, a personal birth weight of more than 4.500 g, pre-eclampsia, polyhydramnios, fetal macrosomia, perinatal death and congenital anomalies) need a 100 g glucose tolerance test.

PRE-PREGNANCY CARE.

There is growing evidence that tight control of diabetes before pregnancy improves fetal and maternal outcome. Education and management may prevent congenital malformations and early pregnancy loss, and can improve the maternal condition[14]. Many studies have shown that congenital malformations are more numerous in infants of type 1 diabetes. Kucera[15] reviewed the world literature between 1930 and 1964: the incidence of congenital malformations in diabetic pregnancies was 4,8 percent compared with 1,65 percent in normal pregnancies. Anomalies of the central nervous system, heart, skeleton, gastrointestinal tract and genitourinary tract are prominent. The same degree of severity of congenital malformations is seen in type 2 pre-gestational diabetes. Furthermore at the present moment the number of congenital malformations remain high in pre-gestational diabetes[16].

However it has been shown that that optimal treatment with insulin in the critical period of organogenesis reduces the rate of fetal malformations in the rat. Furthermore there is evidence that in the human the strict metabolic control before conception reduces the number of congenital malformations. However a number of women with pre-gestational type 1 diabetes do not attend pre-conceptional counselling, moreover only a few with type 2 pre-gestational diabetes attend[17-19].

MANAGEMENT OF DIABETES IN PREGNANCY

MEDICAL CARE OF THE PREGNANT DIABETIC WOMAN

Normoglycemia from the pre-conceptional period until the time of delivery must be achieved in pregnant diabetic women with pre-existing diabetes. In order to reach this goal, intensive education of the diabetic woman is necessary. The skills, knowledge and experience of medical and non-medical advisers are important. The care of the diabetic pregnant woman needs a multidisciplinary approach with combined clinics even before pregnancy. It is a permanent learning and educational process for the medical and paramedical team and certainly for the woman and the partner.

Self monitoring of capillary blood glucose must be taught before conception and continued during pregnancy.

Optimal blood glucose levels are 4,0 mmol/l (80 mg/100 ml) pre-prandial and 6,0 mmol/l (80 mg/100 ml) post-prandial. Since hypoglycaemia can occur in the first trimester, it is

advisable to use the same dose of insulin as that used before pregnancy. With further progression of gestation the dose of insulin will increase with several injections per day.

Glycosylated haemoglobin is the standard to evaluate good diabetic control, it is important to achieve a low level(optimal 6 percent)[19].

During labour and delivery, blood glucose is controlled by an intravenous infusion of dextrose and insulin.

Gestational diabetes can be treated by diet alone or by diet and insulin, certainly when the blood sugar levels remain high or when blood fasting glucose is elevated. It is the intention to control fetal hyperinsulinismin in order to prevent macrosomia, neonatal complications and effects on long term[20].

The use of oral agents is still controversy, it may be indicated in obese women[21].

OBSTETRICAL CARE OF THE PREGNANT DIABETIC WOMAN

Perinatal mortality in pregnancies of women with pre-existing diabetes has been reduced over the last few decades. Congenital malformations and unexpected stillbirths remain the leading cause if death. The most important obstetric management therefore includes the detection of congenital anomalies, fetal surveillance and the prevention or early detection of complications of pregnancy. Congenital malformations can be detected by ultrasound examination between 16 and 20 weeks. Ultrasound examination is also important for the evaluation of fetal growth[21]. Fetal surveillance can be monitored with the biophysical profile. It is our experience that these tests are more ominous for the fetus of a diabetic woman than for the fetus of a woman with other complications of pregnancy.

Maternal complications are still frequently seen in pregnancies complicated by diabetes. An increased incidence of pre-eclampsia has been demonstrated[22, 23]. When polyhydramnios is found, fetal anomalies must be excluded and re-evaluation of strict metabolic control is advisable. Polyhydramnios can be caused by excessive fetal urine production secondary to hyperglycemia. Premature rupture of the membranes, preterm labour, cord prolapse and abruptio placentae are known complications. The use of tocolytics and corticoids can result in maternal hyperglycemia, hyperinsulinemia, hypocalcemia, ketoacidosis and pulmonary oedema[24].

In the last decades it has been suggested that diabetic pregnancies under tight control and without complications should be allowed to continue to near term. The incidence of abdominal deliveries is high, but with close supervision the caesarean section rate can be reduced without increased perinatal risk[25].

The obstetric management of the mother with gestational diabetes is concentrated on fetal growth and surveillance, depending on the severity. In the absence of any obstetrical complication spontaneous labour can be awaited[26].

EFFECT OF DIABETES

THE EFFECT OF MATERNAL DIABETES ON THE FETUS AND THE OFFSPRING

Alterations in the intrauterine environment affect fetal growth and development. In diabetic pregnancies not complicated by vasculopathy, fetal hyperinsulinism and macrosomia are mostly present. The insulin producing fetal B cells are hyperactive. However,

when vasculopathy and nephropathy are present, intrauterine growth restriction and hypoinsulinism are common findings. At present human and animal data show longterm consequences related to abnormal fetal growth[27].

Indeed it has been clearly demonstrated in the human and in animals that fetal hyperinsulinimn results in a deceased capacity for insulin secretion in later life; if these offspring are also obese, insulin resistance is a complicating factor. These effects are transgenerational[28].

It is therefore crucial that in the care of the diabetic pregnant woman, major attention is given to fetal growth.

OBESITY AND PREGNANCY

Obesity is an important health problem, with even epidemic proportions.

In the EU, 14 million of children are overweight and 3 million are obese.

Moreover the number of children with overweight and obesity increases every year with more than 400.000.

In many EU countries more than half of the (adult) population is overweight, and between 20 and 30 percent are obese[29].

It is well documented that obesity strongly correlates with an abnormal metabolic function and is responsible for an increased incidence of cardiovascular disease. Indeed obesity induces insulin resistance[30].

However not so much attention has been given to women in reproductive age and in particular to obesity and pregnancy. Obesity in pregnancy is responsible for an increased maternal and perinatal morbidity and mortality; there is an elevated risk for hypertensive disorders and gestational diabetes[31, 32]. Furthermore the prevalence of congenital malformations in the offspring is increased in these pregnancies[33]. Obesity plays also an important role in pre-gestational diabetes. Of the group with pre-gestational diabetic women, type 2 pre-gestational diabetes has in some European countries reached nearly 50 percent, meanly due to obesity. Type 2 pre-gestational diabetes has the same deleterious effects for mother, fetus and newborn as type 1 pre-gestational diabetes. Moreover, these obese pre-gestational diabetic women are not frequently attending pre-conceptional counselling[19, 34, 35].

It is therefore evident that obesity in the female takes also into account reproduction and in particular pregnancy.

But even more, an abnormal intra-uterine environment has consequences for diseases in the offspring in later life. Perfect developmental programming needs a normal perinatal period.

Early development is related to fetal growth. Fetal growth and development are determined primarily by the genetic potential of the fetus. However, the genetically predetermined growth and development can be influenced by environmental factors, which can exert stimulatory or inhibitory effects. These changes in fetal growth and development can have consequences for later life.

Developmental programming is a process of an insult in utero and in early postnatal life, inducing a permanent response in the fetus and newborn, leading to enhanced susceptibility to later diseases.

The first evidence of developmental programming came from animal research in 1979, where it was demonstrated that induced diabetes in the pregnant rat has an effect in the offspring until the third generation[36].

Epidemiological data have shown that intra- uterine growth restriction is related to diseases in later life such as cardiovascular diseases and insulin resistance.

Fetal overgrowth, as seen in (gestational) diabetes and in maternal obesity, induces type 2 diabetes and obesity in the offspring, and particular gestational diabetes in the female offspring[28, 37].

It is clear that maternal obesity and gestational diabetes result in fetal over nutrition and have the same deleterious effects on the offspring (obesity, insulin resistance, cardiovascular diseases)[28, 37].

In the human there are a few studies showing that obesity induces metabolic and vascular alterations[38]. Furthermore maternal obesity is linked with cardiovascular and metabolic disorders in the offspring, and maternal overweight results in an increased incidence of type 2 diabetes (insulin resistance) in the offspring[39, 40]. Childhood obesity is correlated with maternal pre-pregnancy weight[37].

In animals different approaches have been made to manipulate the nutritional status during pregnancy and lactation (induced diabetes, starvation, protein deficient diet, reduced blood supply to the pregnant uterus, obesogenic diet)[41].

By inducing obesity in the rat with an obesogenic diet before pregnancy, it has been shown that when pregnant, these animals have insulin resistance and an abnormal glucose tolerance. Offspring of these pregnant obese rats remain obese in their further life and have insulin resistance[42].

Numerous studies in animals have confirmed that maternal over nutrition induces an deleterious effect during perinatal life, leading to a metabolic syndrome in the offspring[37, 41, 42].

Obesity is an increasing health problem in the Western world. Important efforts are underway to reduce overweight and obesity in adults and children. The EU has made special attention on obesity in the women.

However, since the woman is the most important partner in reproduction and the most important responsible person for the health of the next generation, major attention is needed regarding obesity and pregnancy. Obesity in pregnancy has disadvantages for the mother, fetus and newborn. But even more important, maternal obesity is responsible for increased obesity in the offspring, inducing a trans-generational effect.

Pre-conceptional weight loss, if possible starting in adolescence, can therefore reduce obesity in the next generations.

It should be clear that the intra-uterine and immediate postnatal period are crucial for human life. Indeed there are 43 cycles of cell divisions between fertilisation and birth and only 5 from birth to death.

CONCLUSION

About one 100 years ago a large number of diabetic women died before the age of reproduction or were too unwell to ovulate. When pregnancy occurred, maternal morbidity and mortality were very high and only a few children were born alive. The discovery of insulin was beneficial for the mother but perinatal survival was still very rare. With improvement in diabetic care, perinatal mortality improved but remained very high. Clinical and fundamental research indicated that for the treatment of the fetus maternal normoglycemia is obligatory. To protect the fetus at the time of conception, tight control is necessary before

conception. This implies commitment from the physician, obstetrician, neonatologist, non medical personnel, but certainly the diabetic woman and her environment.

The most important goals for the future are the reduction of congenital malformations, the prevention of diabetic complications during pregnancy, the increased problem of obesity and the mechanisms to better understand fetal programming.

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CHAPTER 12

Preeclampsia/Eclampsia

PREGNANCY

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INTRODUCTION

Preeclampsia occurs in approximately 3 to 14 percent of all pregnancies worldwide and is associated with significant maternal and fetal morbidity and mortality. The clinical manifestations of pre-eclampsia consist of maternal hypertension, proteinuria, as well as possible additional life threatening hematological, hepatic, and neurological complications.

Tables 1 and 2 summarize the management and treatment options for pregnancies complicated by arterial hypertension and/or preeclamptic patients.

CLASSIFICATION OF HYPERTENSIVE* DISORDERS IN PREGNANCY

According to the ACOG, the diagnosis of hypertension in pregnancy is made by any one of the following criteria:

1. A rise of 30 mmHg or more in systolic blood pressure.
2. A rise of 15 mmHg or more in diastolic blood pressure.
3. A systolic blood pressure of 140 mmHg or more.
4. A diastolic blood pressure of 90 mmHg or more.

These alterations in blood pressure should be observed on at least two different occasions at least 6 hours apart.

* *Note from Editor:* Some sections of this chapter (*) have been enlarged in order to be adapted to the low and middle-low income countries.

Table 1.

	Pregnancy induced hypertension *(diagnosis: > 20. weeks of gestation)*			***Chronic hypertension*** *(diagnosis: < 20. weeks of gestation)/ chronic nephropathy*		
	Out-patient[1] Check-up		**In-patient**	**Out-patient** Check-up		***In-patient***
Blood pressure (mmHg)[2]	140/90 - ≤155/95	1x/week	>155/95	<110 diastolic. (moderate)	1x/week	>/= 110 diastolic (severe)
Proteinuria[3]	− /+	1x/week	++ or +++	− /+	1x/week	++ or +++
Laboratory parameters[4]	Normal	1x/Wo	Pathologic	Normal	1x/week	Pathologic
Ultrasound/ Doppler[5]	Normal	1x/10-14days	IUWR (<3rd percentile), pathologic Doppler	Normal	1x/10-14days	IUWR (<3rd percentile), pathologic Doppler
Cardiotocogram[6]	Normal	1x/week	Suspicious	Normal	1x/week	Suspicious
Cerebral/abdominal symptoms[7]	No	Every check-up	No	No	Every check-up	Yes
Lung maturation	No[8]		Individually[8]	No		No
Antihypertensive therapy[9]	No		See category: Anti-hypertensive therapy[17]	Yes, if preexistent drugs		See table 2
Consultation by a specialist	Yes		Obstetrical/ anesthesiological team	Yes		Obstetrical/ anesthesiological team
Info Anesthesia/neonatology	No		Yes	Yes		Yes
Interdisciplinary obstetrical-nephrological consultation	Ante partum: no Postpartum: yes		Ante partum: Not routine Postpartum: yes	Yes	Alternate Obstetrical unit/ nephrological consultation	Yes
bed rest/ disability 100 %	Individually		Yes	No		Yes
Info Patientin[10]	Yes		Yes	Yes		Yes
Prophylaxis: low-dose aspirin	+[11]		+	+		+

Table 2.

In-patient treatment	*Mild preeclampsia*		*Severe preeclampsia/imminent eclampsia**		
			Observation phase[12]		
		Check-up		**Conservative approach**** Check-up	**Aggressive approach*****
BD (mmHg)[2]	140/90-160/110	Measurement: 3x/day	>160/110	Measurement: Every 4(-6) hours	**FOCUS ON DELIVERY** >34 weeks of gestation: Induction of labor/c-section. <23 weeks: Individual approach, eventual abort induction. Generous indication for epidural anesthesia. Attention: Thrombocytopenia <60.000/µl Diffuse intravascular coagulation.
Proteinuria[3]	+/++/+++	1x/day	+++/>+++	1x/day	
Laboratory parameters[13]	Normal	1x/d/every 2nd day	Pathologic	1-2x/d	
Weight gain	<2 kg/week	2x/Week	Yes (>2 kg/week)	1x/day at the same time	
Urine catheter	No		Yes[14]	Control 3-4 hours	
Respiratory frequency/auscultation	No		Yes[15]	Control 3-4 hours	
Ultrasound/Doppler[5]	Yes	1x/10-14days	Yes	Individually	
Cardiotocogram[6]	Yes	2x/day	Yes	3-4x/day- continuous cardiotocogram	
Surveillance in the obstetrical unit[1]/ delivery room[2]	1		2		
Emergency set in patient's room (including rubber key)	No		Diazepam as second line therapy available		
Lung maturation[8]	Yes		Yes		
Magnesium infusion[16]	No		Yes		
Antihypertensiva[17]	Yes		Yes		
Diuretics [18]	No		Pulmonal edema (PaO2 <90)		
Information to senior doctor	Yes		Yes		
Information to anesthesia/NICU	Yes		Yes		

Legend for table 1 and 2

1. Out-patient controls (eventually after in-patient clarification and observation of the progress), if stable: **small meshed controls;** in case of one pathologic parameter, discuss in-patient treatment.
2. Repetitive measurements with electronically blood pressure; measurement over 30 minutes in **lateral position.**
3. Urine stick: in case of ++/+++ proteinuria: Confirmation with urine sediment in case of in-patient observation/treatment:

   1x ascertainment

   Total protein in urine, Total protein/Creatinin (>30 mmol/l)

   (Total protein in 24 hours: >300 mg)
4. Laboratory parameters: electrolytes, liver/kidney parameters, hemogram, coagulation status, d-dimers, blood group, type and screen, serologic testing during first consultation.
5. Ultrasound with Doppler regular >22.-24 weeks (if possible).
6. >24 + 0 weeks.
7. visual disturbances, headache, increased reflexes; epigastric pain.
8. >24 + 0 weeks: Betamethasone 12mg i.m. 2x within 24 hours (until 34 weeks).
9. See table:

   Evaluation of high risk patients.

   Preconception: Change therapy in case of ACE-inhibitors and therapy with atenolol: Change drug!
10. Counseling the patient about cerebral/ epigastric symptoms. Check-up in the clinic.
11. In case of a previous early preeclampsia (occurrence in the 2nd trimester): application of aspirin (10 mg) from the 12th week until 37 + 0 weeks of gestation (pause 72 hours before until 48 hours after an elective operation, such as cerclage or amniocentesis).
12. **Observation phase until 33 + 6 weeks.**

    Attention: >34 + 0 weeks: immediate delivery (discuss an individual induction of labor, cesarean section)

    Time frame of the observation phase 12-24 h after admittance with the diagnosis of severe preeclampsia:

    STANDARDIZED PROCEDURE:

    - Fasting patient, bed rest, psychological care, quiet environment.
    - Volume: ringer lactate 100-125 ml/h.
    - Prophylaxis to prevent for eclampsia: Magnesium infusion (see item 16).
    - Antihypertensive therapy if needed: see table.
    - Lung maturation: see item 8.
    - following interdisciplinary decision, together with neonatologists and anesthetists regarding **conservative ** or aggressive approach***.**
13. Laboratory parameters: hemogram, electrolytes, liver/kidney parameters, uric acid, coagulation parameters, d-dimer testing, type and screen, fibrinogen. (In case of **HELLP:** additionally: fragmentocytes, reticulocytes, haptoglobin, factor VIII, antithrombin III).
14. Oliguria <30 ml/h over 3hours: ringer lactate 500 ml i.v.
15. **Attention pulmonal edema:** pulse oximetry, in case of lowered saturation (<92%: moving in of the anesthesia
16. Magnesium infusion see below.
17. **Goal:** Blood pressure 130-160 systolic and 90-100 diastolic.
18. Only in case of pulmonary edema and/or cardiac insufficiency: diuretics (furosemide).

Hypertension in pregnancy is classified into the following groups:

1. Pregnancy-induced hypertension.
   a) Preeclampsia. *b)* Eclampsia.
2. Chronic hypertension of whatever cause, but independent of pregnancy.
3. Preeclampsia or eclampsia superimposed on chronic hypertension.
4. Transient hypertension.
5. Unclassified hypertensive disorders.

Each of these forms of hypertension are definied by ACOG as follows:

Preeclampsia. Hypertension associated with proteinuria, greater than 0,3 g/L in 24-hour urine collection or greater than 1 g/L in a random sample; generalized edema, greater than 1^+ pitting edema after 12 hours or rest in bed or a weight gain of 5 lb or more in 1 week; or both after 20 weeks of gestation.

Eclampsia. Convulsions occurring in a patient with preeclampsia.

Chronic hypertension. The presence of sustained blood pressures of 140/90 mmHg or higher before pregnancy or before 20 weeks.

Preeclampsia or eclampsia superimposed on chronic hypertension. The occurrence of preclampsia or eclampsia in women with chronic hypertension. To make this diagnosis it is necessary to document a rise of 30 mmHg or more in diastolic blood pressure, associated with proteinuria, generalized edema, or both.

Transient hypertension. The development of hypertension during pregnancy or the early puerperium in a previously normotensive woman whose pressure normalizes within 10 days postpartum. There must be no evidence or preeclampsia.

Unclassified hypertensive disorders. Those in whom there is not enough information for classification.

DIAGNOSIS OF PRE-ECLAMPSIA*

Pre-eclampsia is by definition a disease which occurs only during the second half of pregnancy. If the hypertension is detected before the 20th week or persists after the puerperium, some other cause for the hypertension must be considered, such as essential hypertension or renal disease.

Pre-eclampsia is a disease of sings without symptoms, and the patient feels well even when the condition is advanced. She will complain of abdominal pain and headache only when she is on the brink of eclamptic convulsions or abruptio placentae.

The signs of pre-eclampsia are:

- Hypertension (always).
- Proteinuria (nearly always).
- Excessive oedema (sometimes).

HYPERTENSION

Any reading over 140/90 is abnormal and a second recording should be made after rest. Small elevations are common near term, but sustained diastolic levels above 100 are a matter of concern. Hypertension early in pregnancy suggests a non-pregnancy cause, usually essential hypertension or renal disease.

PROTEINURIA

The normal pregnant urine contains up to 20 mg% of protein, and proteinuria means in practice, an excretion rate of over 30 mg%.

The reagent strips which are dipped into the urine and display a colour change, are sufficiently sensitive for obstetric purposes.

		+	++	+++	++++
< 20%	trace	> 30%	> 100%	> 300%	> 1000%
Yellow . . . . . Dark green					

OEDEMA

This occurs in all pregnancies, and even when pretibial pitting on pressure can be demonstrated it is not by itself significant. Pathological oedema is a late sign of acute PE and develops very quickly. Oedema is not consistently present in PE and is the least important sign.

OTHER SIGNS AND SYMPTOMS

Headaches are usually present in moderate-to-severe forms of pre-eclampsia. The pain may be frontal or occipital, pulsatille or dull, and can occur simultaneously with visual symptoms. It may be specially intensive, when preceding the onset of convulsions.

The most common visual symptoms appearing in patients who are going to develop preeclampsia is scotoma, a transient perception of bright or black spots.

Epigastric or right upper quadrant pain is also common in patients with severe forms of the disease but may also occur before the onset of obvious signs or symtoms of preeclampsia.

LABORATORY FINDINGS IN PRE-ECLAMPSIA

The laboratory changes reflect the effects of the disease on the kidney, liver and hematologic elements.

ALTERED RENAL FUNCTIONS

In well developed PE a reduction in renal function can be demonstrated.

Uric acid retention. 80 % of the uric acid in urine is secreted by the distal tubule. As this function is impaired there is a rise in plasma urate from about 230 μmol to above 350.

Plasma urea and creatinine. *Urea:* normal 3 mmol may rise to over 6. *Creatinine:* normal 50 μmol may rise to over 100.

CHANGES IN LIVER FUNCTION TESTS

In severe pre-eclampsia marked increases in ASAT, ALAT, γGT and LDH are commonly found. After delivery SGPT and SGOT levels rapidly decrease.

BLOOD COAGULATION CHANGES

There is an increased activation of the blood clotting system, leading to intravascular fibrin deposition. Serum FDP's are increased (from a normal of about 3 μg/ml to 14), and the platelet count falls from a normal 300.000/mm^3 to as low as 150.000.

SEVERITY CLASSIFICATION OF PRE-ECLAMPSIA*

Usually pre-eclampsia is classified in three degrees of severity: mild, moderate and severe (table 3). The most important criterion for differentiation is the magnitude of the blood pressure elevation.

Increase in the severity of the pre-eclampsia is accompaniel by an increase of the risk for the mother and the fetus.

The maternal risks are sudden onset of eclampsia with death from vaious causes; and the sudden onset of abruptio placentae with the risk of death from haemorrhage or renal failure.

Table 3. Severity classification of preeclampsia-eclampsia

Variable	*Mild*	*Moderate*	*Severe*
Diastolic blood pressure	90-100 mmHg	100-110 mmHg	>110 mmHg
Convulsions	Absent	Absent	Present
Blindness	Absent	Absent	Present
Headaches	Minimal	Mild	Marked, persistent
Visual symptoms	Minimal	Mild	Marked, persistent
Oliguria	Absent	Absent	Present
Upper abdominal pain	Absent	Absent	Present
Fetal distress	Absent	Absent	Present
Fetal growth retardation	Absent	Absent	Present
Intravascular hemolysis	Absent	Absent	Present
Thrombocytopenia	Absent	Absent	Present
Blood urea nitrogen (BUN), creatinine, uric acid levels	Normal	Midly elevated	Markedly elevated
ASAT, ALAT and LDH	Normal	Midly elevated	Markedly elevated

On the other hand the increase in the severity of the PE is accompained by a increase in fetal hypoxia, and the risks are:

1. Sudden death in utero.
2. Pacentae abruptio leading almost certainly to fetal death.
3. Intra-uterine growth retardation.
4. An increased risk on RDS after delivery, either from immaturity or from the prolonged hypoxia.

TREATMENT OF PRE-ECLAMPSIA

The *objectives* of treatment must be:

a) To protect the mother from the dangers of eclampsia cerebral haemorrhage.

b) To deliver the fetus before term if growth restriction is suspected.

The management of *mildly affected* patiens consists of rest and sedation.

The decrease in activity is supposed to reduce blood pressure, and improves the blood flow to the kidneys ant the placenta.

Drugs such as diazepam will allay anxiety and predispose the patient to rest. Sedative drugs should really only be given to anxious patients.

Many patients could very well rest at home, with instructions to report at once any sign of fulminating disease such as headache and blurring of vision, and to test their own urine for protein. Their blood pressure would be recorded daily by the doctor or midwife, and there would be weekly visits to the antenatal clinic. PROTEINURIA is an indication for hospital admission, so that intensive observation may be instituted.

Once a diagnosis of severe pre-eclampsia is established the patient must be admitted to the hospital. In this cases, te management will consist of: 1. Prevention os seizures; 2. Control of hypertension; 3. Delivery.

SEVERE PREECLAMPSIA

CRITERIA

- Blood pressure ≥160 systolic or ≥110 diastolic (measurement 2 times within 6 hours apart.
- Acute renal failure (proteinuria >5 g/ 24 h or >/= +++ in urine stick).
- Oliguria <500 ml/ 24 h.
- Eclampsia.
- Pulmonary edema.
- HELLP-Syndrome (Decrease of haptoglobin, increase of LDH, fragmentocytes; ASAT, ALAT, γGT and increase of bilirubin; thrombocytopenia <100 .000/ µl).
- Symptoms of a significant organ involvement:
  - Headache, hyperreflexia.
  - Visual disturbance (skotomes, blurred vision).
  - Epigastric pain.
- In some cases: additional IUGR and/or oligohydramnios with/without pathologic Doppler.

CONSERVATIVE APPROACH

MATERNAL INDICATIONS

- Blood pressure is controllable with drugs.
- Oliguria (<0,5 ml/kg body weight/h) is remediable with addition of liquid (goal: in case of 60 kg: >30 ml/h.
- ASAT or ALAT >2x over normal values and *without* epigastric pain.

FETAL INDICATIONS

- Amniotic fluid index (AFI) >2 cm.
- Fetal biometry/weight estimation >3 percentile.
- Inconspicuous Doppler, pathologic Doppler, inconspicuous cardiotocogram.

AGGRESSIVE TREATMENT (DELIVERY WITHIN 72 HOURS)

MATERNAL INDICATIONS

- Non controllable hypertension (treated with two different antihypertensive drugs at adequate doses): persistent blood pressure >160 systolic or >110 diastolic.
- Eclampsia (delivery *after* stabilization of the mother).
- Progressive thrombocytopenia <100.000/µl (attention: **HELLP-Syndrome**).
- ASAT or ALAT >2x above normal range *with* epigastric pain.
- Pulmonal edema.
- Persistent oliguria or increase of the serum creatinine.
- Persistent severe headache or visual disturbances.

FETAL INDICATIONS

- Cardiotocogram: fetal distress.

- AFI < 2 cm.
- Intrauterine growth restriction (≤ 3 percentile).
- Pathologic Doppler.

Important: These guidelines constitute the basis for an individual assessment!

HELLP SYNDROME

DEFINITION

Decrease of haptoglobin (<10% of the reference value), elevated indirect bilirubin (>20,5 µmol/l), elevated LDH (>600 IU/l), significant decrease of hemoglobin.

Elevated ASAT (>70 IU/l) and ALAT (>70 IU/l),

Thrombocytopenia (<100.000/µl).

MATERNAL AND FETAL MONITORING: INTRAPARTAL MANAGEMENT

INDICATION FOR A CESAREAN SECTION

HELLP before 30 weeks of gestation without any uterine contractions and a Bishop score <5.

HELLP and IUGR and/or oligohydramnios <32 weeks, taking the dynamic of the disease and the estimated birth weight (<1.500 g) into consideration.

Anesthesiological/maternal indication.

Fulminant HELLP >32 weeks, decompensated preeclampsia >32 weeks.

Important: These guidelines constitute the basis for an individual assessment!

Epidural anesthesia: contraindication in case of thrombocytopenia <50.000/µl or diffuse intravascular coagulation; relatively contraindicated in case of thrombocytopenia <60.000/µl and normal coagulation.

Transfusion of thrombocytes in case of a severe bleeding and/or thrombocytes <20.000 /µl.

INDICATIONS FOR INDUCTION OF LABOR (IOL) WITH PROSTAGLANDINS

>34 weeks of gestation: liberal IOL.

Important: These guidelines constitute the basis for an individual assessment!

MATERNAL SURVEILLANCE: POSTPARTUM MANAGEMENT

Close meshed surveillance for 48 hours postpartum, including blood pressure, pulse, maternal weight (excretion), maternal blood parameters, O_2-oxygenisation.

Magnesium-Sulphate intravenously for (12)-24-48h hours.

Antihypertensive therapy in case of elevated blood pressure (systolic >160 mmHg, diastolic >110 mmHg).

ECLAMPSIA*

Convulsions occurring in the antenatal period, during labour, or post-partum. They are nearly always preceded by pre-eclampsia, but sometimes appear with such unexpectedness as to justify the Greek derivation, eclampein: to flash out.

Pre-eclampia and eclampsia is the third commonest cause of maternal mortality. The fetal mortality is still about 40%.

CLINICAL FEATURES

1. (Usual) signs of fulminating pre-eclampsia very high blood pressure,

heavy proteinuria, acute oedema —with complaints of headache and visual upsets.

2. Twitching of face and hands.
3. Tonic phase with rigidity, apnoea, cyanosis.
4. Clonic phase with spasmodic movements, during which the patient may throw herself out of bed.
5. A period of unconsciousness.

DIFFERENTIAL DIAGNOSIS

1. **Epilepsy.** Epilepsy has no association with hypertension.
2. **Subarachnoid haemorrhage** or **cerebral haemorrhage.** The coma deepens. Lumbar puncture may be necessary.
3. **Brain tumour.** This must be considered if the patient does not respond to anticonvulsive treatment or if coma deepens.
4. **Uraemia** from a cause other than pregnancy.

COMPLICATIONS

1. **Hypertension** causes cerebral haemorrhage or thrombosis.
2. **Repeated fits with periods of anoxia** lead to pulmonary oedema and cardiac failure.
3. **Liver necrosis** may lead to acute liver failure.
4. **Glomerular or tubular necrosis** may lead to anuria.
5. **Placental necrosis** will lead to fetal death.

When the patient develops eclampsia, the pregnancy must be terminated.

MAGNESIUM THERAPY

GOAL

Prevent pregnant women from eclamptic seizures in case of preeclampsia, prevention of recurrent seizures.

First line therapy in case of acute eclampsia.

INDICATION

Severe preeclampsia (>160/110 mmHg [2 measurements 6 hours apart], Proteinuria >5 g/24 h or urine stick: +++, Oliguria <500 mL/24 h).

HELLP syndrome (Decrease of haptoglobin, increase of LDH, fragmentocytes, increase of ASAT, ALAT, γGT, bilirubin; thrombocytopenia <100.000/ μl).

Progress from light to severe preeclampsia.

Eclamptic seizures.

ECLAMPTIC SEIZURE

Do not leave the patient alone.

Call for help (additional obstetricians, anesthestists, neonatologists).

Prevent the patient from additional injuries.

Position the patient on the left side and application of oxygen.

Surveillance of the vital parameters (keep airways open, stabilize blood pressure, and control saturation with pulse oximetry, urinary volume).

APPLICATION OF MAGNESIUM INTRAVENOUSLY

Bolus: 8 mL Mg 5 Sulphate 50% (=4 g) in 100 mL NaCl 0,9% over 15-20 minutes intravenously.

Continuous infusion: 1 g Magnesium/hour = = 12,5 mL/h [50 mL Mg 5 Sulphate 50% (=50 g) in 250 ml NaCl 0,9%].

Continuous cardiotocogram.

ECLAMPTIC SEIZURE UNDER MAGNESIUM INTRAVENOUSLY

Second bolus of 2 g Magnesium intravenously (4 mL Mg 5 Sulphate 50% in 100 mL NaCl 0,9%, respectively, 8 mL Mg 5 Sulphate 50% in 100 mL NaCl 0,9%) over 15 minutes 2 g in case of weight <70 kg, 4 g in case of weight >70 kg.

Alternatively: Increas infusion rate to 1,5-2 g Mg/hour (= 25 mL/h).

In case of repetitive seizures under Mg i.v.: Diazepam 0,02-0,03 mg/kg i.v.

SURVEILLANCE

Check urine excretion (>120 ml / 4 h)

Clinical examination (patient's condition: e.g. headache, visual disturbances).

Respiratory frequency: <12/minutes, pulse oximetry: saturation >94%.

Allocate antidote (Calciumgluconate 10%).

Duration of Magnesium therapy: Taper.

Magnesium infusion after (12)-24 hours.

ANTIHYPERTENSIVE THERAPY

INTRAVENOUS THERAPY

Labetalol

Initially application of 20 mg, in case of missing effect: repetition every 10-15 minutes with increasing dose 40-80 mg (total dose 300 mg).

Maintenance dose: 20-160 mg/hour.

Dihydralazine

Initially application of 5-10 mg.

Maintenance dose: 5-10 mg every 20 minutes.

(Max. 30 mg.)

Urapidil

5-10 mg i.v., max. 24 mg/h.

ORAL THERAPY

Labetalol

3-4 × 100 − 200 (−400) mg /d.

(Max. 2.400 mg/day.)

Metoprolol

2 × 50 up to 100 mg/day.

Methyldopa

2-3 × 250 mg/day.

(Max. 3 g/d.)

Combination

Attention: additive effect.

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Multiple pregnancies

CHAPTER 13

I. Blickstein

INTRODUCTION

Multiple pregnancy (MP) and birth are high-risk situations, and thus a challenge to all disciplines involved in caring for the mother and children. Although a plethora of literature exists about management of these complex cases, there are rather few, evidence-based, recommendations. The reason is that multiple pregnancies were quite rare not more than 20 years ago and few centers gathered significant experience in dealing with complications. Not infrequently, data related to singletons were extrapolated to multiples. However, in the last 2 decades, a significant increase in multiple births was noted in most developed countries, mainly as a result of the widespread implementation of infertility treatment. Consequently, more centers became more experienced, and therefore, most of the evidence-based recommendations are related to modern techniques and methods.

In general, the most important clinical problems are preterm birth and low birth weight. Not only are these problems the greatest contributors to perinatal morbidity and mortality, but their importance is also related to the fact that current management has no effective remedies to avoid them.

In terms of prenatal diagnosis, the most important variable is chorionicity because monochorionic (MC) twins are by far more disadvantaged compared to dichorionic (DC) sets. In addition, MC twinning is associated with extremely complex situations which definitely deserve the attention of experienced tertiary centers.

DIAGNOSIS

1. Ideally, all pregnancies should be screened at the first trimester to exclude the presence of MP.
2. Once a MP is found, the first trimester scan is the best means to establish the number of gestational sacs, the number of embryos, and chorionicity.

3. Dichorionic (DC) placentation is certain if the «twin peak» (Lambda) sign is seen.
4. If a DC placenta is excluded, third level ultrasound is indicated to establish the diagnosis of MC twins and to assess amnionicity (bi- vs. monoamniotic twins).
5. MC twins occur also in triplets or in higher-order sets.

FIRST TRIMESTER COUNSELING

1. The patient should receive information related to the potential risks of her MP, as derived from plurality and chorionicity
2. Zygosity is certain in unlike-sexed twins (dizygotic) or in MC twins (monozygotic). Zygosity cannot be established in the remaining sets (about 45 %, i.e., in like-sexed twins with a DC placenta).
3. Weight gain should be encouraged. Overall, a minimal 14 kg weight gain by 24 weeks was associated with improved outcomes in terms of fetal weight.
4. Each fetus in a MP has a similar risk of chromosomal aberrations as singletons. However, it is believed that the probability of the maternal-age related risk of having at least one affected child is almost doubled in dizygotic twins.
5. The risk of amniocentesis and chorionic villi sampling (CVS) in twins is quite similar.
6. If multifetal pregnancy reduction is contemplated, the risks and benefits should be explained and tailored to the maternal phenotype as well as to her wishes. MFPR should be scheduled at 11-13 weeks' gestation.
7. Pre-MFPR diagnosis can be performed by CVS.
8. If invasive cytogenetic studies are not considered, an estimated risk of aneuploidy by nuchal translucency (NT) measurements should be performed. NT is also advisable in all MC twins to assess the risk of early onset twin-twin transfusion syndrome (TTTS).
9. A late first trimester scan can establish the diagnosis of embryonic death («vanishing» twin syndrome).
10. All MC twins should be evaluated to exclude the presence of unique, but rare, MZ-related complications such as monoamnionicity, twin reversed arterial perfusion (TRAP) sequence, and conjoined twins. If found, expert consultation should be offered.

SECOND TRIMESTER FOLLOW UP

1. Standard of care should be at least as extensive as it is for singletons. Thus, routine follow up as performed in singletons should be performed in MP as well.
2. Iron and folate supplementation should be given, as anemia of pregnancy is likely in MP.
3. Early (15-16) anatomical scan should be routine in all MC twins. This is derived from the increased (X 2-3) risk of structural malformations in MZ twins. Since zygosity cannot be established in a significant proportion of MPs, early anatomical scan is advisable in DC sets as well.

4. Selective reduction of a twin with structural malformations in DC sets is performed by intracardiac injection of KCl. In MC sets, selective umbilical cord occlusion should be performed.
5. If amniocentesis is indicated, it should be performed after careful «mapping» of the fetuses, without installation of dye, and with careful designation of the sampled gestational sac.
6. Growth assessment should be performed at a 2-4 weeks intervals in order diagnose early discordant growth. Cases with severe 2nd trimester growth discordance should be referred to experienced centers.

SECOND TRIMESTER MANAGEMENT OF MC TWINS

1. Since TTTS may occur anytime during the 2nd trimester, one should look for the first (simple) sign of Twin Oligopolyhydramnios Sequence (TOPS).
2. Early growth discordance can be seen by comparing crown-rump lengths.
3. Both TOPS and early discordance should be defined as complicated MC twinning, and these cases should be referred to experienced centers.
4. Current opinion holds that laser photocoagulation of the inter-twin anastomoses is the method of choice for treating TTTS.
5. When laser photocoagulation is not available, amnioreduction and possibly septostomy should be offered. All measures to treat TTTS are buying time to avoid the risk of severe preterm birth. Consequently, treatment is seldom needed if TTTS is diagnosed when viability approaches 100 %.
6. Severe early growth discordance in MC twins increases the risk of fetal death and subsequent damage to the survivor. Doppler studies of umbilical artery blood flow should be performed to assess this risk. Such cases should be referred to experienced centers, and in cases with impending single fetal demise, preventive umbilical cord occlusion should be considered.

MANAGEMENT OF SINGLE FETAL DEATH

1. The risk of maternal DIC is extremely rare. There is no need to test the mother's coagulation system.
2. Single fetal death in DC twins has no consequence to the survivor and no intervention is required.
3. Single fetal death in MC twins may cause death of the co-twin and if not, there is a 30 % risk of end-organ damage. Careful targeted sonography (in particular of the brain and kidneys) should be performed. Some authorities advocate fetal magnetic resonance imaging (MRI) at 31-33 weeks to exclude subtle brain damage.
4. Most authorities hold that immediate (preterm) delivery is not indicated if single demise is seen in MC twins.

PREVENTION OF PRETERM BIRTH

1. There are no proven prophylactic measures that reduce preterm birth in MP.
2. Some authorities suggest that early weight gain, sedentary life style, and progestatives, may increase gestational age. There is no indication for prophylactic cerclage as well as for prophylactic hospitalization.
3. Biweekly measurement of cervical length (24 to 32 weeks) is advisable in order to screen for silent impending preterm birth.
4. No tocolytic agent is superior in MP. However, the side effect profile of several agents (i.e., betamimetics) is increased among MP.
5. The current standard is to administer corticosteroids as in singletons, although data indicate that the dose might be insufficient to significantly reduce the risk of respiratory distress syndrome.
6. Management of preterm rupture of membranes in MP is not different from that in singletons.

THIRD TRIMESTER FOLLOW UP

1. Growth assessment should be performed bi-weekly as growth aberrations usually begin around 28 weeks.
2. Severe (>25%) discordance in estimated fetal weight should be assessed with Doppler studies to exclude genuine growth restriction.
3. Most of the morbidity and mortality related to severe growth discordance is seen in the smaller twin, but mainly if this twin is also small-for-gestational age (SGA). Differentiation between relative (discordant) and genuine growth restriction should be done by using MP-specific growth charts.
4. Severe discordance has no significant implication if the smaller twin is not SGA.
5. Signs of maternal hypertensive disorders should be looked for. This is because preeclampsia is more frequent, occurs earlier, and manifest in a more severe form.
6. Prophylactic preterm birth for uncomplicated MC twins is not indicated.

PERIPARTUM CONSIDERATIONS

1. Most twins and certainly all higher-order multiples will be born before 38 weeks. However, some mother will continue their pregnancy beyond 37 weeks.
2. There is much circumstantial evidence that 'term' occurs earlier in twins —at 38 weeks. Consequently, twin gestations carried beyond this date should be managed as post-term pregnancies.
3. Vaginal delivery is probably safe in the vertex-vertex combination, and is also permissible in vertex-nonvertex sets. However, many cases, in particularly those considered as «premium» pregnancies, those with small fetuses, those following a complica-

ted gestational course, and where manual dexterity is not available, should be offered an elective cesarean section.

4. Because of the a priori increased risk to twin B, combined vaginal and cesarean births should not be an option when counseling patients about the mode of delivery.
5. Labor induction and augmentation appears to be safe when vaginal birth is desirable.
6. It is imperative that fetal heart rate monitoring should be performed during labor. Care should be given to trace each twin separately.
7. Labor and delivery of twins should be carried out in a facility with an operating theatre and blood banking. Anesthesia and bedside ultrasound may help in complex deliveries. The presence of a neonatolgist is mandatory.
8. The placenta should be examined postpartum to establish chorionicity and amnionicity. This should be recorded in the patient's chart.

CHAPTER
14

Infectious disease in pregnancy

PREGNANCY

J. M. Carrera | J. Mallafré | B. Serra

INTRODUCTION

A pregnant woman can be affected by an important number of infections, from the moment of conception itself to delivery. These infections not only can deteriorate her health, to a greater or lesser degree, they can also affect the foetus negatively. Effectively, the infectious agent (virus, bacteria, etc.) can reach the embryo or foetus by different paths: by the transplacenta form, by swallowing contaminated amniotic liquid, through membranes, and so on. In addition, according to the type and aggressiveness of the microorganism, the foetus can be contaminated, become infected and/or have its growth pattern altered. For this reason, it is important for the obstetrician to be well versed in the main infectious diseases and their clinical pictures, to have appropriate information about diagnosis and treatment of these diseases, and to know how to manage the resources we currently have available, so as to evaluate their possible effect on the foetus.

This chapter reviews, with a practical focus, sexually-transmitted infections and the principal viral, bacterial and protozoal infections that can cause problems during pregnancy.

SEXUALLY TRANSMITTED INFECTIONS

SYPHILIS

Infection produced by a spirochete called *Treponema pullidum*, which is impossible to culture. It is transmitted to the foetus via the vertical and horizontal pathways[2, 3]. It evolves in three stages.

- Primary, characterized by the appearance of the first clinical manifestation, from 3 weeks to 3 months following contagion, in the form of a chancre, located at the site of infection, painless, which disappears in 3 to 5 weeks.
- Secondary, which manifests as a cutaneous eruption.

- Tertiary, which —after a period of clinical silence— manifests in the form of late lesions in the skin, bones and cardiovascular and central nervous systems.

DIAGNOSIS

Diagnosis is based on the detection of the chancre and on laboratory tests.

Serology must be performed on all pregnant women in the first trimester or in the first prenatal visit in areas of high incidence. Other types of detection are recommended in the third trimester or before delivery for high-risk women.

Congenital syphilis is considered a fetopathy. Up to the 9th week of gestation, a small quantity of treponema can pass through the placenta, without causing infection. From the 9th to the 18th week, there is a possibility of infection, especially if there are circulatory problems or alterations in placental filtering. After the 18th week, the risk of contagion increases progressively until birth; the more recent and more evolved the maternal syphilis is, the greater the foetal risk.

In the case of **symptomatic early syphilis,** foetal mortality is 50 %. Among the survivors, generally premature infants, 50 % develop asymptomatic congenital syphilis.

In the case of **early latent syphilis,** the rates of mortality, premature birth and congenital syphilis are 20 %, 20 % and 40 %, respectively.

In the case of **late syphilis,** the incidences of premature birth and of syphilis are both 10 %. If maternal syphilis of more than 8 years' evolution exists, the risk is minimal.

TREATMENT

In **primary syphilis:**

1. Benzathine penicillin G (2,4 million units), in a single dose.
2. If there is allergy.
   a) Ceftriaxone 125 mg/day intramuscularly for 10 days.
   b) Erythromycin 500 mg orally every 6 hours for 15 days.

In cases of **secondary syphilis** or when neurological affectation is suspected:

Procaine penicillin G (2,4 million IU) every 2 days, up to a total of 10 injections.

In **children** born to allergic mothers treated with erythromycin, neonatal treatment with penicillin is recommended.

GONORRHOEA

Infection produced by *Neisseria gonorrhoeae.* It is most frequently located in: cervix, urethra, para-urethral glands, Bartholin glands, anorectal channel and pharynge. It runs its course asymptomatically in most women (80 %). Transmission is mainly through sexual contact and asymptomatic carriers are the main source of contagion. The incubation period is from 3-5 days. It is frequently associated other sexually-transmitted diseases (Chlamydia in 50 % of the cases).

CLINICAL PICTURE

It consists of infections of the Bartholin and Skeene glands, purulent cervicitis, greenish-yellow leucorrhoea and dysuria, generally mild. More serious complications: Pelvic inflam-

matory disease (15%) and disseminated gonorrhoea (2%). Complications are rarely produced after the first trimester[3, 4].

DIAGNOSIS

This is based on detection of *Neisseria*.

- Gram tincture in endocervical and/or urethral swabs.
- Endocervical and or urethral culture: This is the most sensitive and specific test.
- Antigenic detection of *Neisseria*.

TREATMENT

Treatment of localised infection (urogenital, anorectal, pharyngeal).

The treatment of election is cephalosporins.

1. Ceftriaxone: 125 mg. intramuscularly, a single dose.
2. Cefixime: 400 mg. orally, a single dose.
3. If intolerance or allergy to cephalosporins exists: Spectinomycin, 2 g. intramuscularly, a single dose.
4. The couple must be treated. Other options are added to the previous ones.
5. Concomitant treatment is recommended in the case of Chlamydia, given its high association (unless its presence has been eliminated through the appropriate tests).

Treatment of disseminated infection. Ceftriaxone 1 g. intramuscularly or intravenously every 24 hours, or cefotaxime/ceftizoxime 1g/8 hours intravenously. If allergy or intolerance to cephalosporins exists: Spectinomycin 2 g/12 hours intramuscularly. Treatment must be maintained until 24-48 hours after improvement begins; after that, it can be substituted by: cefoxim 400 mg/12 h orally, for one week of antimicrobial treatment.

Prevention of ophthalmia neonatorum. Any of the following measures must be applied after delivery, whether vaginal or caesarean.

1. Ophthalmic preparation of erythromycin at 0,5% (a single application).
2. Ophthalmic preparation of tetracycline at 1% (a single application).
3. Aqueous solution of silver nitrate at 1% (a single application).

CHLAMYDIA

Infection caused by *Chlamydia trachomatis*. This is one of the most frequent causes of sexually-transmitted diseases (STD). Infections through *Neisseria gonorrhoeae* are associated in up to 50% of Chlamydia cases.

The most frequent site in women is the cervix. The role of Chlamydia in the increase of premature births, restricted intrauterine growth and/or postpartum endometritis is under discussion[5, 6].

CLINICAL PICTURE

Cases can be asymptomatic, but up to 30-50% of cervicitis cases from Chlamydia present symptoms (vaginal discharge, abdominal discomfort, bleeding following sexual relations and dysuria).

The risk factors for infection during pregnancy are: Multiple partners, age <20, presence of other concomitant STDs, non-gonococcic urethritis in the couple, presence of mucopurulent endocervicitis, sterile pyuria (acute urethral syndrome), low socioeconomic status and late or non-existent obstetrics follow-up. Chlamydia should be suspected in all cases of urethritis or genital infection in which no other specific agent (gonococcus, etc.) can be diagnosed.

TREATMENT

Treatment alternatives.

1. Amoxicillin 500 mg/8 h for 7 days.
2. Base erythromycin 500 mg/6 h for 7 days (tolerated worse by the patient).

The use of doxycycline, ofloxacin and erythromycin estolate is contraindicated during pregnancy.

HERPES SIMPLEX

This is one of the most frequent sexually-transmitted diseases; it is produced by the group of the herpesvirus (DNA virus). It is characterised by being neurotropic viruses. They can be grouped into two serological groups: Type I (HSV-1) and Type II (HSV-2).

Both the primary infection and recurrences are more frequent during pregnancy (triple the frequency). The risk of a herpes outbreak in the moment of birth is 36% if the primary herpes infection is produced during the pregnancy.

Transmission pathways: The majority are intra-delivery, but 5% can be intrauterine. Postnatal transmission (through mouth and hand lesions, from the parents and health staff) also exists.

CLINICAL MANIFESTATIONS

1. **HSV-1.**
   a) Primary infection: gingivostomatitis. This also produces up to 30% of the genital primary infections, although with less frequent relapses than in Type II.
   b) Recurring infection: labial herpes and buccal blisters.
2. **HSV-2:** Primary infection and genital recurrence: pruriginous erythema followed by the appearance of papules, vesicles, ulcerations and scabs. Similar lesions can appear in nearby dermatome (sacral area, gluteus, etc.). The presence of antibodies against HSV-1 can make primary infection through HSV-2 asymptomatic.

In both serological types, primary infection can give rise to a disseminated infection and even mortality: fever, anicteric hepatitis and ulcerative pharyngitis.

The incubation period is 2-7 days.

Neonatal affectation is more serious and more frequent in cases of primary maternal infection than in those of recurrent infection (40-50% against 5%).

DIAGNOSTIC METHODS

Clinical suspicion in the case of orolabial or genital manifestation during pregnancy.

Seroconversion of specific antibodies.

PREVENTION

- Consider high-risk patients to be all those with a history of genital herpes during pregnancy or during the previous 6 months. Included in this group are also those whose sexual partner has this infection.
- Advise sexual abstinence during the pregnancy if the couple present active oral or genital herpes.
- Periodic clinical vigilance, above all during the third trimester.

  Oral treatment with acyclovir (200 mg/6h or 400 mg/8 h) from the 36th week until the moment of birth lessens the rate of herpes outbreaks at delivery by 50 % (especially in cases of primary infection during pregnancy). Such treatment also lowers the rate of asymptomatic excretion of the virus.
- Cesarean section do not prevent the possible appearance of neonatal herpes, given that up to 20-30 % of newborns with herpes infection were born through caesareans. At any rate, this is still the method of choice when faced with active lesions at the moment of birth.
- Postnatal care. Isolating the newborn from the mother is not necessary, but the neonate must be isolated from the other newborns.

TREATMENT

Topical and oral acyclovir (200 mg/6 h for 7-10 days).

Current data suggest that there is no greater incidence of major congenital defects in the population treated with systemic acyclovir during the first trimester, as compared with the general population.

HUMAN PAPILLOMAVIRUS

Infection by the virus of human papilloma (HPV) is a very frequent sexually-transmitted disease.

The majority of the infections are sub-clinical and can often go undetected. The most frequent clinical manifestations are condylomata acuminata (genital warts), generally caused by the low risk types 6 and 11[8].

Although there is a possibility of spontaneous regression, the tendency is to treat clinical lesions (condylomata acuminata) in order to control the disease.

The choice of treatment type depends on a series of factors, such as the number, size and anatomical distribution of the lesions.

Some of the treatments normally used are contraindicated in pregnant women (5-fluorouracyl, interferon, podophyllin, podophyllotoxin).

Treatment can be carried out by: Trichloroacetic acid, diathermic loop, cryotherapy, laser or surgical removal. The advantages of vaporisation with CO_2 laser make this the technique of choice. It presents a cure rate of nearly 95 %.

The existence of HPV infection during pregnancy doe not constitute an indication for cesarean section, except in cases of bulky condylomas that obstruct the birth canal or represent a serious risk of haemorrhage. The risk of laryngeal condylomatosis in the newborn is very low; therefore, it is not a reason for doing caesareans.

VAGINITIS

During gestation, not only physiological vaginal secretions increase, the pathological ones do, as well. The incidence of inflammatory processes of microbial origin of the vagina doubles[9].

DIAGNOSIS

Any excessive vaginal secretion, especially if accompanied by inflammatory symptoms (itching, burning, bad odour, etc.), must be etiologically investigated. In practice, it is particularly important to ascertain if it is a mycosis, trichomoniasis or bacterial vaginosis.

- On many occasions, anamnesis can give an orientation as to the causal agent. Leucorrhoea usually produces burning if a mycosis is involved, or pruritis if it is a trichomoniasis.
- Leucorrhoea type is also very orientative: a cheesy type, in the case of mycosis; a foamy yellow colour, if it is a trichomoniasis; yellowish-white colour, in the case of vaginosis.
- Confirmation must be microscopic, with the help of double fresh examination (potassium hydroxide drop and physiological serum). In the case of mycosis, the hyphas are observed; no mobile protozoa is seen in the case of trichomoniasis.

TREATMENT

Mycotic infection by *Candida*. Only topical therapies should be used; 7 days of treatment are advised. Oral therapy and ketoconazole are contraindicated throughout any pregnancy.

1. Nystatin: 2 applications of cream a day for 7 days, or clotrimazole vaginal tablets (100 mg) for 7 nights (before the 16th week of gestation).
2. Clotrimazole: 1 vaginal tablet (100 mg) for 7 nights. The couple can also be treated together, preferably with fluconazole.

Trichomoniasis infection. It is recommended not to treat this during the first trimester and to do so after that with a single dose of oral metronidazole (2 g), in asymptomatic patients.

The couple must be treated with tinidazole, 2 tablets every 12 h, for a day.

***Chlamydia* infection.** Erythromycin, an oral pill of 500 mg every 6 h for 7 days.

VIRAL INFECTIONS

The repercussions of virosis, especially in the foetus, are varied, depending on the virus itself and on the moment in the gestation: from malformations (German measles, chickenpox, cytomegalovirus, etc.), premature birth from maternal hypoxia (influenza), growth restrictions (poliomyelitis), typical exanthematic cutaneous lesions (measles), etc.

RISK OF VIRAL CONTAGION DURING PREGNANCY

CONCEPT

Exposing a pregnant woman to a viral infection by direct, person-to-person contagion makes specific prophylactic measures advisable, in certain cases.

NORMS ACCORDING TO VIROSIS

Infectious Agent	*Potential Foetus Effects*	*Level of Perinatal Transmission*	
Herpes Simplex: **Primary or recurrent infections**	Primary: – Foetal loss. – Congenital syndrome. Primary and recurrent: – Mucocutaneous lesions. – Disseminated disease. – Encephalitis.	– Birth transmission in 90-95 % of the cases. – Primary form in 41 %; recurrent in 4%. – Neonatal infection rate: 1/5.000 births.	
Human Immunodeficiency Virus (HIV)	Progression during infancy. (practically eradicated with triple antiretroviral therapy.	– With zydovudine, 8 % transmission; with triple antiretroviral therapy, <1%. – Most infected in the 1st trimester or when breast-feeding.	
B19 Parvovirus (5th disease)	– Foetal loss. – Hydropexia. – Anaemia. – Congestive heart failure.	– 17-33 %. – Maternal infection: if <20 weeks of gestation, 17% foetal loss; if >20 weeks, 6 % foetal loss.	
Cytomegalovirus (CMV): **Primary or recurrent**	Congenital syndrome: – Deafness. – Hepatosplenomegaly. – Jaundice. – Microcephaly.	Primary maternal infection: 15 % transmission – Recurrences: 5 %. – About 2,3% of newborns affected if intrauterine infection. – 10-20 % if HBeAg (+).	
Hepatitis B	– Hepatitis. – Cirrhosis and/or hepatic cancer.	– Normally transmitted at delivery.	
Hepatitis C	– Hepatitis. – Cirrhosis and/or hepatic cancer.	– Transmission 10-20 % if DNA-VHC, but <1 % if DNA-VHC (−).	
German Measles (Rubella)	– Foetal loss. Congenital syndrome: – Chorrioretinitis. – Hydrocephaly. – Intracerebral calcifications.	– 67-85 % in the 1st trimester, associated with serious infection. – 25-35 % in the 2nd and 3rd trimesters.	
Varicella-Zoster (VZ)	– Primary. Congenital syndrome: – Limbic hypoplasia. – Ocular abnormalities. – CNS alterations. – Eruption limited to dermatome. Perinatal period: – Chickenpox. – Encephalitis.	– 5-7 % of pregnancies complicated by VZ. – 2 % risk of congenital VZ if the mother develops VZ in the first 20 weeks. – 20-40 % neonatal VZ if the mother gets infected around the delivery period.	

	Maternal Filtering	*Prevention*
	– Determine virus (RCP) if primary infection suspected. – Lesion inspection at delivery (remains can be emitted without lesions).	– If herpes lesions exist at delivery: Caesarean. – Acyclovir in third-trimester infections.
	– CA Anti-HIV as a rule in the 1st trimester. – Repeat in the 3rd trimester if risk factors exist.	– Avoid high-risk behaviours. – If HIV (+), prenatal and perinatal antiretrovirals. – Avoid maternal breast-feeding.
	– Not routinely requested. – If maternal exposure or suspicion of infection, determine IgG and IgM against Parvovirus.	– Avoid contacts. – If serologies (+), series echographs. – If hydropexia foetal in echo: cordocentesis, correction of foetal anaemia and Parvovirus determination.
	– Not recommended as routine.	– Hand-washing (especially when changing nappies) – At-risk staff, teachers, nursery personnel.
	– Routine HBsAg in the 1st trimester. If (+), determine HBeAg and anti-HBeAg.	– At birth, immunoglobulin and vaccine for newborn. – In non-immune and exposed pregnant woman, vaccine and immunoglobulin.
	– Routine HCV CA in the 1st trimester. If positive, determine qualitative DNA-HCV (quantitative has little validity, from discordant values).	– Avoid risk behaviours: Greater control in IVDA and transfusions prior to 1992. – No prophylaxis available.
	– Routine serology in the 1st trimester and preconception determination.	– Vaccine before or after the pregnancy (never during). – Avoid contact.
	– Not recommended as routine. – If the pregnant woman was exposed, determine IgG. – If primary infection is suspected, lesion study and serological analyses (IgG and IgM).	– Non-immunised women: vaccine before or after the pregnancy. – Exposed non-immunised pregnant woman: vaccine within 96 hours. – If the newborn is exposed, vaccine.

PROGNOSIS AND TREATMENT ACCORDING TO CAUSAL AGENT

CYTOMEGALOVIRUS (CMV)

Up to 40 % of pregnant women lack immunity against CMV. Primary infections presents in 1,2 % of them, with a risk of vertical transmission of 40 % before 20 weeks. Vertical transmission rate drops to 0,5-1 % in cases of recurrence. Primary infection cases develop asymptomatically in adults in 90 % of the cases, the most frequent long-term sequela being unilateral or bilateral deafness (5-10 %).

There is no prophylaxis or specific therapy for CMV infection.

FLU (INFLUENZA)

The influenza virus belongs to the group of the *Myxovirus*. Symptoms consist of an upper-chest respiratory picture, fever, myalgia and cephalea. It has a short incubation period (1-4 days) and it lasts approximately 3 days. Special attention should be given to pneumonic risk and bacterial over-infections, which generally require hospital admittance and wide-band antibiotic treatment.

No data as to foetal repercussion exist, but seemingly it can produce fetal hypoxia.

Maternal treatment is symptomatic.

HEPATITIS

Pregnant women run no greater risk of suffering from this. The complications are the same as those in cases outside gestation. It increases the risk of abortion and premature birth.

There is no formal contraindication against breast feeding in hepatitis cases.

If it occurs near the time of delivery, the possible haemorrhagic repercussions from hepatic dysfunction must be taken into consideration.

PAROTIDITIS

No greater incidence of malformations has been associated to this, but miscarriages are more frequent.

Maternal treatment is symptomatic.

PARVOVIRUS B19 (INFECTIOUS ERYTHEMA OR 5TH DISEASE)

This is a DNA virus of the family *Parvoviridae*. Transmission pathway: respiratory. Incubation: 4-14 days. Viremia: at 7-8 days of initial infection, lasting 4 days. After that, a rash appears and the patient stops being contagious and acquires permanent immunity.

Clinical picture: maculopapular rash at 17-21 days following contagion (initially on the cheeks and then spreading to the trunk and extremities). It can be preceded by a non-specific respiratory picture. Symmetrical polyarthralgias. The appearance of pure red cell aplasia or pancytopenia is less frequent (resolution in 2-3 weeks). Up to 25 % of the cases run asymptomatically, but such lack of symptoms is not associated with a better foetal prognosis when infected.

If infection occurs during the first half of the pregnancy, anaemia, along with myocarditis and affectation of the endothelium, can cause an abortion. If infection occurs later than

this, it can set off a non-immune hydropexia from cardiac insufficiency secondary to foetal anaemia.

The infection is confirmed through specific antibodies (IgG and IgM).

Treatment can be conservative, especially in the case of mild hydropexias in which a progressive improvement of the echographic picture is seen, or when a foetal haemoglobin ≥8 g/dl can be observed.

Foetal transfusion: This can be considered with haemoglobin values ≤8 g/dl.

No sequela have been detected in foetuses that survive the infection, whatever the treatment applied.

POLIOMYELITIS

This can provoke some paralysis in the foetus, as well as intrauterine growth restriction.

Isolation measures should be instituted, both for the mother and for the newborn, to avoid dissemination through excreta.

RUBELLA (GERMAN MEASLES)

The risk of congenital German measles is 81 % if the rash is produced between the 12th day and the 12th week with respect to the date of the last menstruation (DLM). If the rash appears before the aforementioned 12th day, there is considered no risk.

Systematic filtering before gestational desire is recommended.

Maternal German measles treatment is symptomatic.

VARICELLA (CHICKENPOX)

Low incidence during pregnancy: 0,1-0,7 %.

Risk of congenital chickenpox: *a)* 0,4 % before week 13. *b)* 2 % between week 13 and week 20. *c)* Minimal risk during the second trimester. *d)* Moderate rate of foetal affectation when the maternal rash is produced between 3 weeks and 7-5 days before delivery. *e)* 10-20 % when the maternal rash is produced between 5-10 days before or after delivery.

Symptomatic maternal treatment and isolation during the contagious period. Attention to chickenpox pneumonia that, although it is not the most frequent, it is the most serious result and generally requires hospital admission.

Using hyper-immune immunoglobulins systematically is not recommended, unless the patient is immuno-depressed.

TOXOPLASMOSIS

This is an anthropozoonosis disease caused by *Toxoplasma gondii*. Foetal infection takes place through the placenta, as a consequence of primary maternal infection during gestation[10].

The risk of foetal transmission increases with gestational age; however, at the same time, the severity of the affectation decreases.

Occasionally, it causes a non-specific picture, with fever, general feeling of illness, lymphadenopathies, photofobia and/or painful cervical adenopathies.

The most frequent congenital foetal pathology is chorrioretinitis, although up to 87 % of congenital toxoplasmosis cases are asymptomatic at birth or present non-specific symptoms.

PREVENTION

a) Measures of **primary prevention** are vital, as they avoid contact with the invasive form of the toxoplasma (cyst or trophozoite):

1. Avoid contact with the transmitting agent of the disease (especially cats) or materials that might be contaminated by their faecal matter.
2. Always cook meat at temperatures above 66 °C, to achieve cyst inactivation.
3. Wash fruit and vegetables properly.

b) **Secondary prevention** consists in serological determination of the maternal immunological state against the toxoplasma, thus establishing the diagnosis of the disease. Diagnosis of seroconversion can be simple, but establishing the chronology of the infection is difficult when the prior immunological situation of the mother is unknown (see Diagnosis).

DIAGNOSIS

A toxoplasmosis must be suspected when faced with the following circumstances:

1. Antecedents of miscarriages, premature births, malformations and perinatal mortality.
2. A pregnant woman with lymphadenopathy, fever and fatigue. The clinical picture sometimes simulates infectious mononucleosis. Every adenopathy during gestation must make the doctor suspect a toxoplasmosis.
3. A pregnant woman who consumes meat that is not well-cooked or who is in contact with animals chronically infested (cats, dogs, pigeons, chicken).

Diagnosis of maternal infection during pregnancy is established by:

Maternal seroconversion through determination of specific antibodies against the toxoplasma.

TREATMENT

- When a maternal infection is diagnosed and while waiting for confirmation of foetal infection, spiramycin 4 g/8 h should be administered for 3 weeks. Following this, the cycle is repeated every 2 weeks or the treatment is continued uninterrupted until delivery.
- When foetal infection is diagnosed (through detection of toxoplasma DNA or the parasite itself in amniotic fluid):
  1. First trimester: spiramycin, 1 g/h continuously.
  2. Second and third trimester: pyrimethamine (Daraprim®), 25mg/day, and sulphadiazine (Flammazine®), 4 g/day in 3-week cycles, alternating with 3 weeks of spiramycin. Supplement with folinic acid, 10 mg/12 h.

LISTERIOSIS

LIsteria monocytogenes is a gram-positive aerobic bacteria and beta haemolytic. It is found particularly in soft cheese, milk, vegetables and seafood.

Asymptomatic carriers exist in the digestive tract and vagina.

The disease is generally benign in the mother, but the foetus can be seriously affected (abortion, intrauterine death).

1. **Infection during pregnancy** is often asymptomatic. Some patients can present a pseudo-flu picture, characterised by chills, fever and lumbar pain; this occasionally mimics a pyelonephritis.

   It can begin as a threat of preterm birth, or as the work of preterm birth founded on brownish liquid that can be confused with meconium.

2. **Foetal infection** can be produced by:

   a) Transplacenta infection. Foetal haematogenic dissemination (foetal septicaemia) is produced from the placenta.

   b) Amniotic infection. Infection produced by swallowing or breathing liquid contaminated with foetal urine.

   c) Ascending infection. From the cervix, where the listerias are lodged, and through the ovular membranes.

   d) Transcervical infection. At the moment of delivery, when the foetus passes through a contaminated cervical canal.

DIAGNOSIS

- Listeriosis **must be suspected** in the following circumstances:

  1. Antecedents of abortions, stillborn foetuses or neonatal sepsis.
  2. Febrile outbreaks of uncertain etiology (pseudo-flu syndromes, pseudopyelitics, etc.).
  3. Women in contact with rodents or birds (rural or professional settings), or who consume unpasteurized milk or raw meat.

- **During pregnancy,** listeriosis is difficult or impossible to identify clinically. Laboratory tests (serological) must therefore be used.

TREATMENT

Ampicillin 1 g/6 h and gentamicin 2 mg/kg/8 h for 7-14 days, intravenously.

Antibiotic prophylaxis during pregnancy is not recommended.

SANITARY-DIETETIC RECOMMENDATIONS TO PREVENT LISTERIOSIS FROM CONTAMINATED FOOD

a) Cook raw meat from calves, pigs and colts thoroughly.

b) Wash raw vegetables carefully before eating them.

c) Keep raw meat separate from vegetables and precooked or cooked foods.

d) Avoid consumption of non-pasteurised milk or dishes prepared with raw milk.

e) Wash your hands, the knives and the cutting boards after having worked with raw foods.

f) Avoid soft cheeses (Mexican style, brie, camembert, etc.) and choose cured cheeses, cream cheese, cottage cheese or yoghurt instead.

g) Precooked food must be reheated.

STREPTOCOCCUS AGALACTIAE

Streptococcus agalactiae or Group B streptococcus (Group B strep or GBS) is a gram-positive coccus that fundamentally causes infections in newborns, pregnant women and adults having other diseases[11].

GBS is at present, in the absence of prevention measures, the most frequent cause of vertically-transmitted perinatal bacterial infection.

The gastrointestinal tract is the reservoir of GBS. Vaginal colonisation is intermittent, and the colonisation rate in pregnant women ranges from 11 % to 18 %.

GBS transmission from the mother to the newborn mainly occurs at the beginning of delivery, or following rupture of the membranes. The frequency of colonisation of newborns from colonised mothers is around 50 %, and 1-2 % of colonised newborns develop infection.

DETECTION OF CARRIERS

- If possible, a vaginal and rectal culture should be performed on all pregnant women between the 35th and 37th week of gestation.
- If the pregnant female has had bacteriuria from GBS during the gestation, or if antecedents of a child with GBS neonatal infection exist, it is not necessary to do the culture and prophylaxis should always be administered.
- The culture must be repeated if more than 5 weeks take place between the samples and the delivery.
- Samples are obtained from the external third of the vagina (a speculum is not required) and from introducing a swab in the rectum. Cervical cultures are not acceptable.
- In a programmed caesarean, even though the culture is positive for GBS, prophylaxis is not given, as long as the delivery has not begun and the membranes are intact.

ANTIBIOTIC RECOMMENDATIONS

- **Drug of choice.** Intravenous penicillin G, 5 million units as an initial dose at the beginning of labour; repeat 2,5 million units every 4 hours until the baby is born.
- **Antibiotic of second choice.** Intravenous ampicillin, 2 g when the labour begins; repeat 1 g every 4 hours until the baby is born.

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CHAPTER 15

Tropical Diseases and Pregnancy

PREGNANCY

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INTRODUCTION

The high proportion of the world population that lives in tropical and subtropical areas leads to serious public health problems, due to the great prevalence of pathologies associated with these environments. Such pathologies are generally responsible for health problems because of urgent public health needs and the limited economic and health resources. These situations are conducive to the development of vectors and the means of transmission of different parasites, bacteria and viruses, which can give rise to pathologies called tropical pathologies.

The fact that a pregnant woman has a tropical pathology may involve alterations in her normal physiology, as well as making the pathology more severe. The profound hormonal and physiological changes that occur in gestation are generally events that lead to a period of immunosuppression, a special characteristic that arises so that the developing foetus is not rejected. These conditions can be negative factors in the presence of an attacking germ, whether it is a parasite, bacteria or virus. Thus, a thorough knowledge of these types of pathologies is required in cases of gestation, particularly to avoid serious complications. This knowledge is doubly important because the presence of the embryo or foetus may impose restrictions on the effective treatments that can be administered. In such situations, specialists must be capable of scientifically evaluating the risks and benefits of the therapy to be administered.

This chapter provides a summary analysis of the most prevalent infectious pathologies in tropical areas.

MALARIA

Paludism or malaria is a widespread disease in tropical areas and constitutes one of the main causes of mortality in the world. It is considered a serious public health problem, especially in the tropical areas of developing countries in Africa, Asia, Oceania, and Cen-

tral and South America, as well as in Caribbean countries. It is estimated that there are between 300 to 500 million cases a year and that 1 to 2 million deaths occur annually due to this tropical pathology. About 40 % of the world population who live in over 100 countries in these geographical areas run the risk of catching the disease[1].

Considered as veritable plague, malaria has a history as ancient as humanity. Innumerable texts written thousands of years before Christ, in countries such as China, Greece and Rome, describe and report on its pathology. Its presence is even described among the soldiers involved in the wars of Spain's ancient civilizations.

ETIOLOGY

Malaria is caused by a parasite in the form of Sporozoea of the Eucoccidiida order, *Plasmodiidae* family and *Plasmodium* genus. Different species can parasitise humans and various animals. There are two main species in humans, which are *P. vivax* and *P. falciparum* (see table 1), although two more species exist on a regional level, called *P. malariae* and *P. ovale.* These species are distinguished morphologically in coloured plaques. However, in humans the initial symptoms do not permit a differentiation by species, which can only be confirmed by laboratory analysis. Nonetheless, the most severe form of malaria is caused by *P. falciparum,* which can bring about diverse clinical manifestations, with the presence of fever, chills, sweating and headaches; the symptoms can evolve to jaundice, coagulation defects, shock, renal and hepatic insufficiency, acute encephalopathy, pulmonary and cerebral oedema, coma and death[2].

Kingdom	Protista
Phylum	Apicomplexa
Class	Aconoidasida
Order	Haemosporida
Genus	Plasmodium
Species	P. falciparum

Table 1.
Categorisation of the *plasmodium falciparum.*

The parasite has two life cycles: one takes place in mosquitoes *Anopheles* (sporogonic cycle, with sexual reproduction), whilst the other occurs in humans (schizogonic cycle, with asexual reproduction). Thus, mosquitoes are the final host and humans are the intermediary host.

INCUBATION PERIOD

The time that lapses between the infectious mosquito bite and the appearance of clinical manifestations is generally 12 days for *P. falciparum,* 14 for *P. vivax* and *P. ovale* and 30 days for *P. malariae.* However, some strains of *P. vivax,* which are widespread in temperate climate zones, have been reported to have a lengthy incubation period; this can reach up to 8 or 10 months, or even more in cases of *P. ovale*.

PHYSIOPATHOLOGY

In general, all the types of *Plasmodium* alter the erythrocytes. Each species has a preference for a specific type of erythrocyte (reticulocytes, young erythrocytes or mature erythrocytes). This results in different levels of haemolysis, which causes anaemia and, there-

fore, anoxia. Haemolysis in turn liberates haemoglobin, parasites, malarial pigment or haemozoin, toxins and antigens. Free haemoglobin increases bilirubin levels (especially indirectly) and causes haemoglobinuria. Toxins and antigens may act on the vascular system and form immune complexes, which lead to a decrease in the complement. Capillary clots may block the capillaries and give rise to anoxia, which can cause tissue damage. There have also been reports of vasodilation and an increase in capillary permeability, which are prominent at the cerebral level (particularly in the case of *P. falciparum)*[3].

Along with these symptoms, alterations in the coagulation process may occur, which may be caused by hepatic insufficiency or disseminated intravascular coagulation. The latter is a manifestation that can be made worse by the retention of platelets in the spleen, which can become enlarged (splenomegaly). The hepatic damage may be progressive, especially if the infection is from *P. falciparum,* and may develop into hepatic insufficiency. There is hepatomegaly in most cases. When there is a problem in the central nervous system, it is almost certain that is due to *P. falciparum,* although isolated cases caused by *P. vivax* have recently been detected. In these cases, diffuse acute encephalopathy appears. In general, each organ in the body may suffer specific alterations. Almost all cases are accompanied by oedema and symptoms of cellular congestion.

CLINICAL MANIFESTATIONS

The signs and symptoms are experienced generally depend on the infecting parasite species, the number of parasites and the host's immune state. However, the clinical picture is characterised by the presence of chills, fever and sweating, which are associated with anaemia, leucopenia and the previously-mentioned splenomegaly. If the disease is not diagnosed and treated in time, it can become chronic, with latent periods and stages of relapse. In acute attacks of the disease, intense shivering, heavy sweating and a notable increase in temperature (over 40 ºC) appear. During the febrile stage, reddish facies, hot dry skin, tachycardia occur and may be accompanied by hypotension. In addition, there may be cephalgia, dorsalgia, nausea, vomiting, abdominal pain, diarrhoea and even alterations in consciousness. The febrile period generally lasts from 3 to 6 hours. Immediately after the fever, intense sweating begins and the temperature drops. Subsequently, there is polydipsia and the patient feels exhausted[3].

MALARIA DURING PREGNANCY

Malaria has shown itself to be frankly unfavourable in the course of gestation, as miscarriages or premature births may occur[4]. In addition, instances of foetal death, placenta infection and even eclampsia have been reported[5].

Malaria caused by *P. falciparum* is the most severe during pregnancy. This pathology increases both maternal and neonatal morbidity and mortality. Non-immune pregnant women, especially primiparas, are the most susceptible; they can present a severe clinical picture, thus entailing miscarriages and stillbirths, depending on the gestational age. The probable state of immunosuppression present in pregnancy is a factor that favours the development and the severity of the disease. Early in gestation, hyperpyrexia can complicate the pregnancy with a clinical picture that may entail a threat or actual miscarriage. If the pregnancy is of greater gestational age, there is a parasites are captured and developed in the placenta. This situation leads to an obstruction of the microcirculation towards the foetus, which alters fetal nutrition and oxygenation in particular. The mother can develop acute pulmonary oedema, as well as hypoglycaemia. Acute fatal suffering may exist, accompanied by intrauterine growth retardation. Under these conditions, the occurrence of premature birth and/or fetal death is frequent[3, 6].

Anaemia is the most common complication. If it is severe and not properly controlled, the risk of foetal and/or maternal death increases. When the species involved is *P. falciparum,* there is a possibility of cerebral malaria and a high-mortality clinical picture. Furthermore, hypoglycaemia in pregnant women causes blurred vision, vertigo and hypotension, while in severe cases convulsions may be an added complication, which can lead to errors in diagnosing gestational pathologies.

The passage of plasmodium (as sporozoites or merozoites) through the placenta has been reported. The bibliography on congenital malaria is extensive, its incidence being from between 0,03 % and 3,6 %, which is the same proportion that is most frequent in patients with elevated parasitemia. It has even been shown that asymptomatic patients can develop neonatal malaria. Fortunately, the maternal antibodies produced by the presence of the infection protect newborn babies, generally over the course of their first six months of life[7].

Finally, it must be pointed out that the effort involved in childbirth may aggravate or reactivate a malarial clinical picture and may give rise to a possible circulatory shock during the postpartum period[5].

DIAGNOSIS

Diagnosis begins by examining susceptible patients who live in endemic areas or who have travelled to these areas. Malaria can be mistaken clinically for other pathologies that are also accompanied by fever (especially in atypical cases). Therefore, the presence of the parasite in blood should always be sought; if detected, the diagnosis may be taken to be positive. These parasites are found inside the red blood cells. The most reliable and most utilised method is called the «thick blood smear». As a large quantity of blood is subjected to analysis, this technique facilitates the observation of a large number of parasites. The analysis consists in destroying the red blood cells and visualising the parasites that are fixed on the slides. However, diagnostic tests based on the detection of antigens derived from the parasites in blood may also be performed by using various alternative methods[8].

TREATMENT

The primary goal of treatment is to eliminate the asexual erythrocytic forms of the parasite, which are responsible for the symptomatology. The drugs used for this purpose are called blood schizonticides. However, during treatment it is also important to eliminate subsequent stages of relapse of *P. vivax* and *ovale,* which can develop in the liver, by administering tissue schizonticides.

Until 1926, quinine (a plant in the tropical areas of America) was the only drug used for the treatment of malaria. Subsequently, advances in pharmacological research gave rise to various alternative treatments, thus improving the availability of pharmacological antimalarials[9].

If pregnant women suffer from malaria, the treatment must be even more careful. Patients should be admitted to hospital and even to an Intensive Care Unit, given that significant complications may appear[3, 6, 9].

In general, the drugs used in the treatment of malaria can be given during pregnancy. However, there are certain restrictions and complications that should be noted:

Malaria produced by *P. vivax* and *ovale* responds well to treatment using chloroquine. This drug can be administered at any gestational age. The maximum dose for chloroquine is 1.500 mg, which should be administered in an initial dose of 600 mg (4 tablets, each

of 150 mg); 450 mg (3 tablets) are then given 24 hours later and a repetition of 450 mg at 48 hours after the start of the treatment. Another method that has been suggested is 600 mg as an initial dose and then 300 mg at 6, 24 and 48 hour[9]. Possible side effects are nausea and vomiting; if these are severe, antiemetics should be added to the treatment. The dosage must not exceed 1.500 mg, as it can cause damage in the foetus's cochlear nerve. Therefore, it is important to ascertain whether or not patients have previously undergone this treatment from their case histories.

If the malaria is produced by *P. falciparum*, which is resistant to chloroquine, quinine is recommended, providing there is a control of maternal glycaemia and uterine contractions. This is because quinine has a contractile effect on the uterine and could set off preterm labour (analyse the gestational age). The drug can be administered in the form of Quinine Sulphate (10 mg/kg for 3-5 days, orally) or Quinine Dichlorhydrate (7-10 mg/kg every 8 hours, dissolved in 300-500 ml of Dextrose, transfused over 30-60 min. The minimum parenteral treatment is 3 days; after that, oral administration for at least 10 days is recommended[10]. A higher dose than those indicated can result in ototoxic effects[9].

Mefloquine (25 mg/kg as a base) can also be used in cases of resistance to chloroquine. Its safety during gestation has been reported, although its use in the first trimester of pregnancy is not recommended[11].

The use of Sulfadoxine (tablets of 500 mg) and Pyrimetamine (tablets of 25 mg) should be avoided if at all possible. If necessary, the single, total dose is 1.500 mg and 75 mg for Sulfadoxine and Pyrimetamine, respectively (3 tablets). Severe reactions of maternal hypersensitivity can occur. The medication crosses the placenta and can alter bilirubin concentrations, which may even give rise to kernicterus in newborn babies. It must not be administered as a preventive drug[11].

Primaquine is an antimalarial drug that cannot be administered to pregnant women. There would be a high risk of haemolysis, which is a very serious complication in pregnancy (due to glucose-6-phosphate dehydrogenase deficiency, a metabolic disorder linked to the X chromosome that is prevalent in black individuals)[11].

Finally, we should point out that proguanil is acceptable as an antimalarial treatment as its administration during pregnancy is safe. In contrast, tetracycline and doxycycline definitely cannot be administered to pregnant patients.

On occasion, if a pregnant woman wishes to travel to malaria-endemic areas, chemoprophylaxis can be carried out through the administration of Chloroquine 300 mg for one week before the trip and then for a period of 6 weeks on returning from this endemic area. Following this procedure has been shown to reduce infant mortality by up to 50 %[12].

CHAGAS DISEASE-AMERICAN TRYPANOSOMIASIS

Carlos *Chagas* was a doctor from Brazil who, while he studied malaria in the Brazilian state of Minas Gerais in 1909, found a trypanosome different from those that had been reported in Africa. A few years later, he described the biological cycle of the disease and called it *Trypanosoma Cruzi* in honour of his Professor (Osvaldo Cruz). Several decades later, *Dr. Chagas's* findings were identified and confirmed in various tropical areas of Latin

America. In addition, several risks involved in the presence of this pathology were extended.

Chagas disease is zoonosis that is widespread in the area stretching from southern United States to southern Argentina. It has been calculated that there are 18 million people infected and over 100 million at risk of catching the disease. There is an incidence of approximately 1 million cases a year, which causes some 45.000 deaths annually, especially from the cardiac complications this pathology causes[13].

ETIOLOGIC AGENT

T. cruzi belongs to the subphylum *Mastigophora*, order *Kinetoplastida*, family *tripanosomatidae.* The flagellate form of *T. cruzi* is found in circulating blood of infected individuals or animals, especially in the initial and/or acute stages of the pathology. This circulating form is known as Trypomastigote; it is elongated and fusiform, and is approximately 20 micras long[13].

TRANSMISSION MECHANISMS

The main way people catch the disease is through contamination with excrement from triatoma insects that have *T. cruzi*. In addition to this entomological infection, blood transfusions represent another mechanism. However, there are reports of other, less important ways the disease is transmitted, which have been described by several authors: through the mother's milk, from urine from infected animals (dogs and cats) and through the placenta[14, 15].

BIOLOGICAL CYCLE

The insect vector of *T. cruzi* is a parasitic protozoan belonging to the family *Reduviid,* subfamily *Triatominae*, genera *Rhodnius*, *Triatoma* and *Panstromgylus*. These agents are popularly known as «*chinches*» (bedbugs), although their name can vary from country to country.

CLINICAL SYMPTOMS

The symptomatology has classically been divided into three stages, which present a different clinical state.

Acute stage: *T. Cruzi* amastigotes reproduce inside the cell (macrophages, fibroblasts, myocytes, Schwan cells), destroying them, which leads to a state of inflammatory reaction. The point of entry (mosquito bite) presents a swelling, called *Chagoma*, which looks furuncular, rarely erysipeloid, similar to anthrax, of different sizes. At times, this is the only manifestation. On the fifth day, the amastigotes transform into trypomastigotes and extend to the regional ganglia (adenopathies), blocking the lymphatic channels and producing a local oedema. (If the wound is located on the eyelid, it is called *Romaña's sign*). After that, the parasites are found in almost all body organs (spleen, spinal cord, bone, heart, digestive system, adrenal glands, adipose cells, glial cells, etc.), producing varied symptomatology. Generalised adenopathy exists, of variable size, hard, non-painful. There can also be intermittent or continuous high fever. Additional symptoms that can occur are chills, anorexia, vomiting, diarrhoea, cephalgia, intense muscle pain and even exanthem. However, mortality is very low in this parasitic invasion. If patients die, it is due to the complications of the clinical picture: myocarditis, meningoencephalitis, bronchial pneumonia[16].

Chronic asymptomatic stage. Following the acute stage, there is an immune response that helps lower parasitemia, keeping the infection to a few selected focuses. It can generally be stated that, from the symptomological point of view, the pathology can remain undetected for a long time after infection (acute stage). The reason is that a high proportion of the individuals infected are healthy carriers. In nearly all the cases (95%), the symptoms are so slight that they can go unnoticed for 10 years or more, before entering into the chronic stage, when clinical symptomatology appears[16].

Chronic stage. This stage is characterised by scant parasitemia, but with the appearance of typical lesions in the heart and gastrointestinal tract. The most important pathology is undoubtedly Chagasic cardiopathy, characterised by dilation of the right cavity and frequently accompanied by endocardial (mural) thrombosis. Multiplication of the parasites in cardiac muscle fibres causes myocarditis (destroying the myocardiac fibre), which leads to the liberation of antigens and toxins that produce interstitial oedema and infiltrate, especially mononuclear. At the same time, antibodies against endocardium, blood vessels and striated muscle interstitium are produced. This inflammation can reach the subendocardial layer, adipose tissue of the endocardium and nerve ganglia[16, 17].

This chronic stage of the disease, characterised by this cardiomyopathy, generally causes sudden death, even without development of a congestive cardiac insufficiency. There can be a slight ventricular hypertrophy with apical aneurysm through necrosis, a standard alteration called Apical Lesion. In the chronic stage, hypertrophic lesions of the digestive system can also exist, there being a notable enlargement of the viscera (megaviscera), particularly at the level of the esophagus and colon (megaesophagus-megacolon). In these cases, intestinal peristalsis is altered and the concommitant neuronal destruction destroys the myenteric plexus, with all the consequences that this anatomical y histological alternation involves[16, 18].

If the myocarditis does not cause sudden death, there will progressively appear congestive cardiac insufficiency, severe cardiomegaly and ventricular hypertrophy (with dilation of the heart cavities, especially on the right side). This cardiac picture generally produces hepatomegaly as a result. With this clinical picture, the patients normally die within an average of 5 years[16, 19].

CHAGAS DISEASE DURING PREGNANCY

Pregnancy does not affect the course of the symptomatology. Gestation can coincide with any of the disease stages and its course, as well as the symptomatology, depends on the phase of the pathology. Naturally, if the Acute Stage coincides with pregnancy, the «*chagoma*» will be present and its accompanying symptoms will be those described above. However, the risks of complications will be greater, especially if it affects the heart, with all the consequences of congestive cardiac insufficiency, a circulatory alteration that will affect foetal development. The presence of damage to digestive system muscle is also a determining factor; the resulting diarrhoea may lead to electrolyte and hydric imbalance in patients. Maternal disorders always affect foetal development and the common denominator can be causing newborn babies to be underweight at birth[16].

Undoubtedly, one of the most serious complications is placental transmission of the parasitemia, producing *Chagas* disease in the newborn and all its consequences. *Dr Chagas* already suspected in 1911 that this form of transmission existed, as he identified the disease in a 17-day-old newborn, without finding the «gateway» for the disease.

In 1949, a Venezuelan researcher, *Dao*, was the first to demonstrate the congenital transmission of *Chagas* disease. He detected amastigotes in the blood of a pregnant woman in her seventh month and in her newborn two days after birth. Likewise, two cases of new-

born babies who died led *De Gavaller* to demonstrate the presence of amastigotes in their tissues. For this reason, it is suggested that specific laboratory tests be given to pregnant women from endemic areas. Over the past several decades, some cases of *Chagas* disease through congenital infection (placental transmission) have been reported for both individuals and animals[15].

In 1977, *Schumuñis* and *Szarfman,* in a study carried out in Argentina, published an incidence of *Chagas* disease in pregnant women, with a rate of 9-20%, depending on the area. In the majority of these cases, the infection was asymptomatic and did not influence the development of the gestation. However, they reported a congenital transmission that ranged from 0,75% to 3,50%. Later, another Argentine study performed in 1983 found that seropositive pregnant patients had double the risk of miscarriages and perinatal mortality[6].

In general, it has been demonstrated that a placenta without alterations (normal chorionic ectoderm) does not allow the passage of the parasite. If the infection occurs, placental alterations also occur, such as large oedematous cotyledons, irregular lesions in various places, necrosis and infiltrates, parasitic pseudocysts and a virtually destroyed chorial epithelium. However, a relationship between parasitism and foetal death has not been demonstrated. Generally, if intrauterine death has not been produced, the newborn has a notably low weight (below 2 kg) and is premature, and hepatomegaly, splenomegaly and poor vitality (low Apgar) are always present[16].

The risk of transplacental infection is greater during the acute stage of the disease. *Bittencourt* has reported congenital infection in 5 out of 8 cases of pregnant women in the acute stage[20]. In cases of chronic infection, transmitting *Chagas* disease through the placenta is less frequent; it has been established that it is usually produced between the gestational age of 19 to 27 weeks, being greater at 22-26 weeks of pregnancy. In addition, it is known that *T. cruzi* does not cause embryopathies, only foetopathies, as all protozoa do[6, 21].

DIAGNOSIS

This depends on the stage of the disease. In the acute stage, it could be mistaken for febrile pathologies, but the presence of the chagoma or *Romaña's sign* make identification easier. In chronic stages, diagnosis may be complicated due to the non-specific clinical signs, given that they are the result of the degree of alteration that the affected organs has suffered. For this reason, if there is any clinical suspicion and especially if the patient comes from endemic areas, the diagnosis should be confirmed by the laboratory[17, 22].

Identification of the parasite in blood is useful in the acute stage, although it is considered that negative results do not eliminate the disease. In the chronic stage, it is unusual to manage to identify the parasites and various special dilutions are needed. A microscopic analysis of fresh blood (from the fingertip) allows the visualisation of the parasite (forma de trypomastigote). This identification is of 90% in the acute stage and only 10% in the chronic stage. If the parasite is observed, doing a blood count (for mm^3 of blood) gives an idea of the degree of parasitemia[17].

Generally speaking, if it has not been possible to identify the parasites, there are other types of exams to which you can turn, such as concentration methods (Strout's method) and even biopsies (which identify tissue forms of *T. Cruzi).* It is also possible to recur to laboratory methods that identify the presence of the parasite indirectly. Among these are xenodiagnosis, polymerase chain reation (PCR: DNA sequences of the parasite), culture *(Liver Infusion Tryptose)* and serological procedures such as indirect immunoflouresence (a method that is highly sensitive to the presence of the disease), ELISA, indirect haemaglutination, Latex and direct agglutination[23].

TREATMENT

Two drugs exist for the treatment of *Chagas* disease: Benznidazol (nitroimidazoles) and Nifurtimox (nitrofurans). These drugs have been shown to be effective in the acute stages of the disease, although no benefits have been found in its chronic stages. Neither drug can be administered during pregnancy (in spite of the fact that no embryotoxic effects have been demonstrated, particularly in the case of nifurtimox). Treatment with these drugs is lengthy (2 to 3 months); in the case of pregnant women in whom the presence of the parasite is established, treatment should be delayed until after birth for foetal safety. If symptoms of cardiac and/or digestive alterations exist, treatment should be aimed at compensating this type of symptomatology, with the goal of avoiding modifications of the normal homeostasis of the organism as much as possible[24].

Therapies based on Ketoconazol and Alopurinol have also been tried. However, results published for several projects have involved different outcomes and their effectiveness has been different for each series. That is why they should not be in fact be administered in pregnancy, especially without being sure they will work. However, it should be pointed out that chagasic infection can persist throughout a patient's life; pregnant women should receive treatment after the birth of their babies, particularly to avoid congenital transmission in any later gestation[16].

LEISHMANIASIS

Leishmaniasis is a disease classified as zoonotic, produced by an obligatory intracellular protozoa, of which there are several species, of the genus *Leishmania sp*. The species *Donvani* has been found in Asia, the Mediterranean and eastern Africa, while the species is called *Chagasi* in Central and South America. It is calculated that there are 61 countries with health problems due to this pathology, with around 12 million patients. This number increases annually by some two million[25].

ETIOLOGIC AGENT

The disease is produced by the protozoa that belong to the family *Trypanosomatidae,* with the genus *Leishmania.* The different species bring about different biological and immunological responses, just as in the case of the clinical picture of the pathology.

TRANSMISSION MECHANISMS

The pathology is transmitted by the vectors of the genera *Phlebotomus* and *Lutzomyia.* The promastigotes are in the invertebrate host (mosquitoes) and are the form of inoculation to the vertebrates. They become oval or round amastigotes, with a size of 2-5 micras of length or diameter.

CLINICAL SYMPTOMS

Three clinical forms are generally produced: cutaneous or diffuse cutaneous, mucocutaneous and visceral:

The cutaneous form is initiated with the mosquito bite, which does not go unnoticed as it is painful. Approximately 2 weeks to 2 months after this event, the lesion appears on the skin; it can be single or multiple. The lesions are most often found on the face and/or the limbs, as they are the most exposed parts of the body. Appearing as a macula with erythema, the lesion then becomes a papula or boil, which is hard but not painful, occasio-

nally with itching; a process of slow growth then ensues. A few days after that, ulceration is produced and a yellowish, sticky liquid appears, which later becomes a scab. The lesion extends below this scab, in both area and depth. The scab border is hyperhemic, dry and lifted. If the scab is removed, the lesion is granulous, clean and without exudate or purulent material. Over the course of various months, the lesion can reach several centimetres in diameter and produce lymphangitis, with the presence of chain regional adenopathies. It can also suffer infection and purulent material can appear. On other occasions, the lesion can grow and affect mucous tissues, especially nasal, oral and bucal, and complicate its evolution even more[26].

Visceral leishmaniasis is generally produced by *L. donovani,* a parasite that has a life cycle similar to that described for skin and mucous lesions. Its entry point is the skin. There is marked adenopahty, with ganglia full of parasites. Its dissemination puts the organism's entire endothelial reticulum system at risk, the organs most affected being the liver (hepatomegaly), spleen (splenomegaly), bone marrow (hyperplasia) and ganglia (hyperplasia). The incubation period is generally prolonged after the mosquito bite (6-10 months). When symptoms exist, a non-specific, infrequent temperature rise presents, which later becomes permanent, with rises and fall. The organic complications of the liver, spleen and bone marrow normally lead to death in a few years[27].

DIAGNOSIS

Differential diagnosis against other pathologies that produce these lesions is necessary, although the lesion is sometimes characteristic, especially if the areas where the patient lived or visited. In general, the most practical way of diagnosing is identifying the presence of the parasite. To do so, various laboratory exams are utilised, such as direct exam, biopsy, electrophoresis, cultures (the *Novy-MacNeat-Nicolle* medium, known as *NNN),* PCR test, the Montenegro reaction. Serological methods are also used, especially in cases of difficult differential diagnosis or visceral lesions from an initial cutaneous leishmaniasis[28].

LEISHMANIASIS DURING PREGNANCY

The disease can be transmitted during pregnancy or be present before gestation. If it is transmitted during pregnancy, all the signs and symptoms described with respect to the mosquito bite will exist; treatment can be given with the local measures described in the following paragraph. However, if present since before the pregnancy, the infection might have produced various ulcerations, even at mucous level; treatment should be delayed until after the gestation finalises. The same is true of a visceral leishmaniasis, which should receive effective treatment after pregnancy, due to the wide dissemination of the infection in the organism.

TREATMENT

The medicine of choice for all the forms of Leishmaniasis is pentavalent antimoniate (N–methyl Glutamine Antimoniate or meglumine), administered parenterally. It is normally expensive and relapses are frequent. This, added to the fact that it is poorly tolerated, has made its administration limited. In consequence, there has been a search for alternative oral drugs such as the imidazoles, paromomycin and even mefloquine, with all the considerations expressed about this drug in relation to pregnancy. Generally speaking, if the lesions are limited to dermis ones, local topical treatment is recommended. However, if the lesions are not extensive, they can often be cured spontaneously[29].

Local treatment does not necessarily have to involve drugs. If the lesions are isolated, curettage is normally performed (applying the respective norms of asepsia and antisepsia).

Cryotherapy (dry ice or liquid nitrogen) applied twice a week for at least three months can also give good results. Thermotherapy (local heat, 39-42 °C) has likewise been reported to be effective. Reports of local administration of imidazoles (clotrimazole, miconazole, ketoconazole) are contradictory. While there are reports of their effectiveness, other researchers have found a complete cure in only 15% of the cases, and even found it ineffective in others[29].

At any rate, isolated local lesions can receive local treatment during pregnancy. However, in the case of generalised leishmaniasis, oral and parenteral treatments must be administered over a long period of time and have undesirable side effects and toxic effect (particularly the antimoniates); these facts make such treatment inadvisable during pregnancy.

AMEBIASIS

Entamoeba histolytica is a parasitic species that is frequently found in humans and is a habitual guest in the large intestine. However, there can also be clinical pictures that reveal its presence outside the intestine.

Intestinal amebiasis was identified in the 19th century (1875) in a patient who presented a clinical picture of dysentery. These mobile microorganisms were observed with the presence of ectoplasm and endoplasm, there being erythrocytes inside them. Almost a decade later, while patients from a cholera epidemic were being studied, amoeba were observed placed in the mucosa of the intestinal wall in the capillaries next to the hepatic vessels and even in the exudate from hepatic lesions. It was at the beginning of the 20th century that the pathogenicity of *E. Histolytica* was demonstrated, leaving *E. coli* free from aggressiveness. Years later, several researchers completed diverse culture media, antigen presence and serological reactions, plus analysing the immunological, biochemical and genetic effects.

ETIOLOGIC AGENT

The agent is *E. histolytica,* capable of invading tissues and producing serious clinical and pathological effects. The trophozoite (vegative form) varies in size from 20 to 40 micras; its motile stage is carried out through a pseudopod, which is easily identified. In aggressive trophozoites, red blood cells are found inside the cytoplasm.

LIFE CYCLE

The trophozoite, which replicates through binary division, is found inside the colon or invading its tissues. The parasite eliminates its food vacuoles there and becomes precysts, which in turn transform into cysts thanks to the covering they acquire and the provision of four nuclei. This process always occurs in the lumen of the large intestine. They are eliminated in human faeces in the form of trophozoites, swim cells or cysts. The cyst is the only form that can produce infection orally. The effects of gastric juice transform the cysts into trophozoites and the pathological cycle begins again[30].

EPIDEMIOLOGY

Due to the faecal origin of human transmission, amebiasis presence is usually extensive in poor populations and countries. The infection has humans as their source, who eliminate them in the form of cysts and who are normally asymptomatic. These cysts resist in water and earth up to several months at normal environmental conditions and then return to the

organism through water and food not prepared with requisite asepsia measures. Generally speaking, lack of hygiene and improper elimination of excrement (environmental sanitation and sewer system) are the fundamental causes of dissemination of the pathology.

CLINICAL SYMPTOMS

In 90% of the cases, intestinal amebiasis can be asymptomatic, while a clinical picture of colitis without dysentery exists in 9%. Only in 1% of the cases is the infection accompanied by dysentery. The latter two are considered invasive intestinal amibiasis and present when the trophozoites invade the wall of the large intestine[30].

In amebiasis without dysentery, there is abdominal pain of a colic type, change in the frequency of deposits (increases and decreases) and possibly diarrhoea accompanied by mucous and haemorrhagic spotting. Slight straining at stool or tenesmus can also appear; pain is usually more intense before and after the deposits, there being relief between these physiological events. If there are stages of constipation, they are generally due to the presence of cysts; in contrast, the presence of trophozoites characterises the stages of diarrhoea. There can be a sensation of fullness, abdominal distension, flatulence, increased bloating, etc.[30].

In amebiasis with dysentery, the clinical picture described above is more intense and, of course, the presence of diarrhoea is typical: very frequent diarrhoea, which becomes more and more liquid, with the presence of greater mucous and blood. In addition, it is very painful at the abdominal level, accompanied by straining and very painful tenesmus. This clinical picture can regress (with or without treatment) and become chronic amebiasis, without dysentery. On other occasions, particularly in the face of lack of treatment, amebiasis evolves towards a fulminating form, due to gangrenous amibiasis, hyperacute, with very intense abdominal pain, straining, tenesmus and anorexia. On deep abdominal palpation, the pain is extreme and particularly located within the colonic frame. Diarrhoea can lead to hypovolemic shock, with serious changes in blood pH that require immediate correction. The intestinal lesions induce perforation and the patient can die from acute peritonitis.

AMEBIAN HEPATIC ABSCESS

This is the most frequent complication in colonic amebiasis. When the colon has been invaded, the amoeba enter the liver through portal access; thrombi are produced in the small vessels there, causing necrosis and microabscesses. When the abscesses rupture, a multiple inflammatory clinical picture ensues; this can evolve to form an amebian abscess. The content of this abscess is not purulent material; it is normally a thick chocolate-colour liquid full of lumps, with the presence of coagulant material. The abscess is most frequently single and is usually located in the right lobule or in its upper region. Its size ranges considerably, from a few millimetres up to even various centimetres. The abscess can rupture (in 2-7% of the cases) and drain into the peritoneum, pleura and even the lung and pericardium. In some cases, this rupture can produce fatal consequences[31].

Patients with this complication have a clinical picture characteristic of intestinal amebiasis (with or without dysentery). In addition, they add pain in the right hypochondrium (sometimes radiating to the back, right shoulder or epigastrium), rise in temperature, anorexia and general weakness to their symptoms[31].

DIAGNOSIS

The presence of symptomatology with a clinical picture of abdominal pain, accompanied by the dysentery typical of amebiasis is confirmed by the presence of the amoeba cysts in patient faeces. In the case of hepatic abscess, in addition to the symptomatology de-

scribed previously, an ultrasonography or hepatic tomography can confirm the diagnosis[31]. However, examinations of greater technical complexity (which are not justified, in our opinion) have also been described[32].

AMEBIASIS DURING PREGNANCY

There is a divergence of criteria with respect to treatment of amebiasis during pregnancy. If the patient presents evident symptoms, especially with dysentery, treatment is obligatory as the clinical picture could seriously damage the patient's general state. Asymptomatic patients can wait until the end of the pregnancy to receive treatment. However, we must always consider that in amebiasis, because hemitropic parasites are involved, hemoglobulin levels can drop and produce or increase anaemia, which is a pathological state with a negative influence on the development of foetal and maternal couplet[33].

TREATMENT

Intestinal amebiasis tends to be frequent in the general population, particularly in areas with deficient environmental sanitation and even more so in poor tropical areas. However, in the majority of cases, treatment is only given when the symptomatology leading the patient to consult presents. In the case of extraintestinal amebiasis, the symptoms even require patient hospitalisation.

In asymptomatic amebiasis, location of the parasites in the lumen of the large intestine is characteristic; if they are in the wall of the intestine, symptomatology is present. These considerations are crucial in choosing the type of treatment and the drug involved. This is even truer if the patient is pregnant.

Several drugs for the treatment of luminal amoeba location have been tried, such as diloxanide, quinfamide, teclozan, etc. However, given that the treatment for the condition is not urgent and the patient generally has no symptomatology, such drug therapy is not justified[30].

When symptomatology presents, especially in the face of amebian dysentery, treatment in the pregnant woman is necessary and indispensable. For these cases, the drugs administered must have tissue effects at the level of the intestine wall. In most cases, it is accepted that treatment will be based on the derivatives of the Nitroimidazoles: Metronidazole 750 mg is given three times a day for 10 days; Tinidazole 2 grams a day in a single dose or Secnidazole 2 grams, also in a single dose, are other alternatives. In general, these drugs are used with safety during pregnancy and no negative effects have been demonstrated. In severe cases, even parenteral metronidazole can be used[30].

For amebian hepatic abscess, the patient must be hospitalised and treated with parenteral metronidazole. The dose to be given in gestation is 15 mg/kg diluted in 500 ml of dextrose, slowly over the course of an hour. Following that, 7,5 mg/kg should be given every 6 hours for 6 days. A possible alternative that could be used is Tinidazole 2 g/day for 5-7 days[30].

CHOLERA

This is a severe intestinal bacterial pathology accompanied by acute, very profuse diarrhoea. Therefore, it can produce serious dehydration quickly, involving fatal consequences due to acidosis and circulatory collapse. The cause is *Vibrion Cholerae,* a curved *gram* negative bacillus; it is highly motile, a facultative anaerobic, responsible for a few world pandemics and considered a serious Public Health problem.

V*ibrion cholerae* live in salty costal water, as well as in briny rivers, in a tight relationship with plankton. The human being is its reservoir, in spite of the fact that laboratory tests have shown that the environment can also be a reservoir. Transmission takes place by ingestion of contaminated water or foods also directly or indirectly contaminated with faeces or vomit of patients who have the disease. The incubation period normally ranges from just a few hours up to five days, the average being from two to three days. The period of transmission by faeces lasts a few days after the recovery of the patient once the disease symptomatology has withdrawn[34].

Following the infection and incubation period, cholera comes on abruptly, with profuse diarrhoea, which leads to a serious hydroelectrolyte imbalance. It is accompanied by vomiting, but a rise in temperature in not normally present. Cramps, particularly abdominal, are very frequent and painful. The liquid faeces have a non-bilious aspect, with mucous but no blood, and are not fetid. They are called faeces «in rice water» because of the macroscopic similarities. The symptoms are directly related to the magnitude of liquid and electrolyte loss: intense thirst, low blood pressure, tachycardia, weak pulse, and oliguria, presence of folds in the skin, sinking of the eyeballs, somnolence and even coma. A non-compensated clinical picture can easily become complicated with renal insufficiency secondary to a tubular necrosis process[34].

Cholera is a pathology mediated by toxins. Thus, diarrhoea is produced by a protein enterotoxin synthesised by *V. cholerae.* The bacterium can be identified in the faeces, normally by using a dark-field microscope.

CHOLERA DURING PREGNANCY

If a pregnant woman presents a clinical picture compatible with this pathology, it is important to give correct, effective treatment because the liquid and electrolyte losses can involve alterations in the uterine muscle fibres (presence of contractions). This is especially true if the clinical picture is accompanied by cramps and vomiting, which are unfavourable conditions for every pregnant woman, regardless of the gestational age. Lack of proper attention can lead to severe hypotension, a negative situation for the patient, but particularly so for the foetus; it can even cause intrauterine foetal death.

Specific treatment is aimed at intensive hydration, specific antibiotics and avoiding or treating complications. Hydration depends on volume of the losses, as well as the need for electrolytes (in particular, sodium, potassium and chlorine).

The antibiotics administered to eradicate the *V. cholerae* bacillus is usually limited in use in pregnancy. The antibiotic most often used is tetracycline, which is not permitted in gestation. Indiscriminate use of sulphas is likewise restricted. Pregnant women can be given Erythromycin 250 mg every 6 hours for at least 5-7 days. In addition, there is the possibility of administering derivatives of the quinolons, naturally in doses specific for each one[35].

DENGUE INFECTION

Most of the tropical and subtropical areas of the world are regions endemic for this pathology. It has been calculated that about 100 million people are infected each year in populations distributed in the topical areas of the world; according to OMS data, the figure is approximately 2 billion people. The disease in usually more manifest in winter and it is transmitted house by house, as the mosquito does not have the capability of flying long distances[36].

Dengue is a febrile pathology of viral origin, produced by an arbovirus of the family *Flaviviridae* and transmitted by the bite of the mosquito *Aedes aegypti.* The mosquito is present in homes, infecting containers or collections of water (natural or artificial) in particular. The female mosquito feeds on human blood and also that of animals. Once the bite has occurred, the incubation period varies from 3-14 days, with an average of 5-7. It is important to point out that no person-to-person transmission exists. It is the patients with Dengue who transmit to other mosquitoes, again by their bites, which become infective 8-12 days after their infection from biting a human being.

As this pathology usually presents in the form of an epidemic and its complications are so serious (particularly in dengue haemorrhagic fever), it has been considered as a public health problem. The number of patients easily increases and the infections has a market geographic propagation[36].

The symptomatology is characterised by the presence of sudden fever, generally biphasic and lasting 3-5 days. There are also chills, cephalgia, pain in the eyeballs, generalised muscular and osteoarticular pain and presence of exanthem; leucopenia is observed in the blood count, normally with relative lymphocytosis. Patients habitually present adenopathies and petechias on the skin. The pathology lasts a week on average and patients need a recovery period of 2-3 weeks.

If it is a case of dengue haemorrhagic fever, there are very high fever, haemorrhage (epistaxis, bleeding of the gums, hematuria, hypermenorrhea, digestive bleeding), hepatomegaly and circulatory failure due to hypovolemic shock, as the plasma leaks into extravascular space. This complication can lead to the individual's death. In the laboratory, thrombocytopenia and transaminases are found, in addition to leucopenia. Exceptionally, signs of meningitis, alterations in consciousness, shock and coma can be observed.

The virus is present in blood from the beginning of the febrile clinical picture and can remain there for several days. The histopathological lesions are found in the endothelium of the small vessels, there being perivascular oedema and infiltrate with mononuclear cells.

Diagnosis can be performed by several laboratory methods: hemagglutination, complement setting, G or M (antibody) immunoglobulins processed by Enzyme-Linked Immunosorbent Assay (ELISA). These are equal to or greater than 1.280 of Immunoglobulin G or by the positive test of Immunoglobulin M in a serum received in the late acute stage or during the recovery period. IgG positivity indicates current or recent infection and can already be detected from 6-7 days after the infection begins.

DENGUE DURING PREGNANCY

Infection by Dengue virus in pregnant women is increasing due to the presence of greater and more severe epidemics in all the tropical areas. A pregnant woman who lives in endemic zones is not free from this pathology. The clinical picture can be made worse by the conditions of the gestation. These are basically related to a significant rise in temperature, loss of liquids and electrolytes and the accompanying symptoms (articular, muscular, ocular pain, etc.), which are very uncomfortable for pregnant patients. If the clinical picture evolves toward Dengue haemorrhagic fever, the prognosis is frankly unfavourable, depending on the gestational age.

Dengue infection can occur through transplacenta transmission, as has been shown in children from mothers who had the disease at the end of pregnancy[37]. In these cases, the children can develop a clinical picture characteristic of Dengue haemorrhagic fever. In addition, an increase in the number of premature infants and of those having low weight

when born have been demonstrated[38]. A probable association between Dengue infection and increase in neural tube anomalies has even been reported in India[30].

TREATMENT

This is based on general measures to control the patient's signs and symptoms. Proper maintenance of liquids and electrolytes is crucial, as are antipyretic medicine and administrations of analgesics necessary. In the case of a pregnant woman, acetaminophen 500 mg every 6-8 hours to relieve pyrexia and pain has been recommended. Adequate hydration and electrolyte management for each case must not be neglected.

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CHAPTER 16

Acquired immunodeficiency syndrome (AIDS) in pregnancy

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THE AIDS EPIDEMIC

The number of people living with HIV (38,6 million with a range from 33,4 to 46,0) and the number of deaths due to AIDS (2.6 million more than in 2004) are still increasing[1]. The estimated number of adults and children newly infected in 2006 is 4,1 million (range: 3,4 million-6,2 million) which is about 400.000 more than in 2004. Two thirds (63 %) of all adults and children with HIV globally live in sub-Saharan Africa and almost three quarters (72 %) of all adult and child deaths due to AIDS in 2006. In the past two years, the number of people living with HIV increased in every region in the world but the greatest increases have occurred in East Asia, Eastern Europe and Central Asia. In these areas, the number of people living with HIV in 2006 was over 21 % higher than in 2004.

Among children under the age of 15, 2,3 million are infected and over 1.400 children continue to become infected with HIV every day. Children still account for more than 12 % of all new infections[2].

ABBREVIATIONS

3TC: lamivudine.
ABC: abacavir.
AIDS: acquired immunodeficiency syndrome.
ARV: antiretroviral.
ARVT: antiretroviral treatment.
d4T: stavudine.
ddI: didanosine.
EFV: efavirenz.
FTC: emtricitabine.
HIV: human immunodeficiency virus.
LPV/r: lopinavir with a low-dose ritonavir boost.
MTCT: mother-to-child transmission of HIV.
NFV: nelfinavir.
NRTI: nucleoside analogue reverse transcriptase inhibitor.
NNRTI: non-nucleoside reverse transcriptase inhibitor.
NVP: nevirapine.
PI: protease inhibitor.
Sd-NVP: single dose nevirapine.
SQV: saquinavir.
TDF: tenofovir.
ZDV: zidovudine.

LATEST DEVELOPMENTS AND RESOURCES

In the last few years there have been many promising efforts and developments to properly address the AIDS epidemic[1]. The access to effective treatment and prevention programs has increased dramatically. There have been significant advances in recent years in the global fight against AIDS financing. A total of 8,3 billion US$ in funds have been dedicated to responding to AIDS in low- and middle-income countries in 2005 which is well within the 2001 target range of 7 to 10 US$ billion for 2005. Between 2001 and 2005, the number of people on antiretroviral therapy in low- and middle-income countries increased from 240.000 to approximately 1,3 million (20%, with a country range: 1%-100% coverage), (n =116). Although the global target of 50% has not been achieved, 21countries have achieved it.

The percentage of HIV-positive pregnant women receiving antiretroviral prophylaxis is 9% (country range coverage in 41 countries: 1%-59% coverage). No country has achieved the goal of 80% coverage.

In 2001 approximately 30% of infants born to HIV-infected mothers became infected. Te transmission rate has been reduced approximately a 10% between 2001 an 2005, with a transmission rate of 26%. The goal was a 20% reduction and 11 of the most affected countries have achieved this goal.

MOTHER-TO CHILD TRANSMISSION (MTCT) AND PREVENTIVE MEASURES

The majority of HIV-infected children have acquired the infection through MTCT. Such transmission may occur during pregnancy (labor and delivery) or during breastfeeding. If no preventive measures are applied, MTCT rate in non-breastfeeding women is 15-30%. Breastfeeding increases the risk by 5-20% to a total of 20-45%[3]. If the infected pregnant woman is identified and preventive measures are applied, the risk of MTCT can be reduced below 2%[4].

Infected children have now become rare in high-income countries. Interestingly such measure that where unfeasible in many countries with limited resources, can now be done. Nevertheless some limitations appear: an elective caesarean delivery is seldom feasible or culturally accepted and bottle feeding may be impossible or risky. The most effective measure is then the use of ARV prophylaxis in the third trimester of pregnancy. A reduction ot MTCT to 2-4% may be obtained[5]. In such settings, research on the efficacy of preventive ARV prophylaxis during breastfeeding is underway and required. Many ARV regimens (even with a one or two drugs) reduce the risk of MTCT by decreasing viral replication in the mother and through prophylaxis for the fetus and infant during and after exposure to the virus. Despite limitations on comparing studies directly we can conclude that: longer regimens starting earlier in pregnancy are more efficacious than shorter regimens and that combination regimens, are more efficacious than single-drug regimens.

Currently several programs have shown to be feasible, acceptable and cost-effective in setting with limited resources but have to be implemented in more areas. Such programs have to include prenatal care and testing to all women. WHO's goal is to achieve to universal access to treatment for all those who need it by 2010.

WHO recommendations for the use of ARV drugs for PMTCT have been reviewed and simplified (WHO 2006[6]). Several factors have contributed to make recommendations more clear and effective. More drugs and more potent and with less side effects are now available. More is known on the effectiveness of ART in preventing MTCT, on their safety during pregnancy and the implication of the appearance of resistances following ARV prophylaxis.

Current recommendations are in accordance with the WHO guidelines for the treatment of the adult and the infant (table 1). Such recommendations have to be based on evidence from randomized controlled trials, high-quality scientific studies for non-treatment-related options, observational cohort data, or expert opinion when data are not available.

Preventive measures are detailed in table 2.

Table 1. Criteria for initiating ART for pregnant women (general recommendations for adults).

Treatment required if:
• Clinical stage 4 irrespective of the CD4 cell count.
• Clinical stage 3: If no CD4 counts available: always. If available: if CD4 $<$ 350 cells/mm^3 c.
• Clinical stage I and 2 with a cell count of CD4 $<$ 200 cells/mm^3.

Based on WHO clinical staging criteria alone and weight loss during pregnancy in limited resources settings or plus CD4 count in other settings.

Table 2. Preventive measures to reduce mother-to-child HIV vertical transmission.

• Prenatal screening of all pregnant women during pregnancy. If no test is available during labor or shortly after childbirth. Identification in the early postpartum period should be done. If infected: screening for TB and reinforcement of prevention or treatment of malaria if high risk area.
• Prevention of infection of the non-infected women.
• Antiretroviral prophylaxis given to: The women during pregnancy and labor. The infant in the first weeks. Symptomatic women or women with low CD4 counts (if available) (table 2) always treated with ARVT during pregnancy and cotrimoxazole for PCP prophylaxis if indicated. Asymptomatic or high CD4 counts if available: delay prophylaxis.
• Elective cesarean section in selected cases (especially prior to the onset of labor and rupture of membranes).
• Avoidance of breastfeeding.

The objective of antiretropviral treatment (ARVT) is to treat HIV-infected women, to reduce the risk of MTCT, and to minimize the consequences of resistance to NVP from the use of Sd-NVP-containing ARV prophylactic regimens for the prevention of MTCT. The most effective method of preventing MTCT and eliminating the risk of resistance to NVP is to start fully suppressive ART.

National programs on the use of ARVT to prevent MTCT have to be put in place. If the women does not meet treatment criteria or treatment is not available, ARV prophylaxis should be given. Regimen recommended to all infected women is detailed in table 3. A

widespread implementation of this regimen will dramatically reduce the number of infected infants with simultaneously low levels of HIV viral resistance.

Table 3. Prophylaxis to prevent MTCT (a).

Mothers	*Infants*
• Antepartum: ZDV from 28 weeks of pregnancy (or as soon as possible thereafter). • Intrapartum: ZDV and lamivudine (3TC) plus a single dose of nevirapine (NVP). • Postpartum: ZDV and 3TC for on week (b).	• Single dose NVP and ZDV for one week.

WHO 2006[6].

(a) For alternative regimens see the 2006 revised WHO adult guidelines (WHO 2006).

(b) If the mother receives less than four weeks of ART during pregnancy, then four weeks, instead of one week, of infant ZDV is recommended.

Antiretroviral therapy for HIV infection in adults and adolescents: towards universal access. Geneva, World Health Organization, 2006 (http://www.who.int/hiv/pub/guidelines/adult/en/index.html, accessed 4 August 2006).

GROUPS OF DRUGS MAY BE USED TO TREAT HIV INFECTION

Overall benefits of therapy to the mother outweigh the theoretical risks of an adverse pregnancy outcome. Treated mothers have to be monitored to rule out associated toxic effects. The use of HAART is associated with an increased risk of pre-eclampsia. All women under HAART have to be closely monitored[7]. There are very few data on risks associated with the use of ART during pregnancy in resource constrained settings.

NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITOR-BASED TREATMENTS (NRTIs)

Both ZDV and 3TC have extensively been used for pregnant women and infants. When ART is started during pregnancy ZDV should be included in the regimen whenever possible but several drugs may be used as an alternative.

NON-NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITOR-BASED TREATMENTS (NNRTI)

Although NVP is the NNRTI drug of choice for ART in pregnancy, there are concerns about toxicity (specially hepatitis) in women starting NVP-containing ART with a CD4 cell count >250 cells/mm^3. If used, the patient should be closely monitored the first 12th weeks. EFV should be avoided if possible during pregnancy, especially during the first trimester due to the increased risk of fetal anomalies.

PROTEASE-INHIBITOR DRUGS (PI)

There is a great experience in the use of PI during pregnancy. It is unclear whether its use is associated with preterm delivery and with gestational diabetes

SCENARIOS

Prevention and treatment options in resource-constrained settings will depend on whether the following are available, feasible, sustainable and affordable:

– ARV drugs in each setting may have different costs and availabilities.
– Diagnostic tests (CD4 counts, viral load and other blood test to determine drug toxicity).
– Caesarean section.
– Replacement feeding.

In the last few years, HIV antenatal testing and to ARV has rapidly become available in may resource-constrained settings and will probably be better in the next years. Access to other diagnostic tests such as CD4 counts is as well increasing but will be insufficient in the near future. Elective caesarean delivery and formula feeding will be seldom available and/or safe. Each country/setting will have to develop a different strategy according to availability of each one of them.

Several large scale international prevention MTCT initiatives are currently being implemented including «The President's Emergency Plan for AIDS Relief (PEPFAR)», the «Call to Action Project», the «UN Interagency Task Team on MTCT», MTCT-Plus, the Global Fund etc.

WOMEN PREVIOUSLY TREATED

If a woman becomes pregnant while receiving ARVT, she should continue treatment.

During labor, therefore, women receiving ART should continue to adhere to their ART regimen, whenever possible.

WOMEN PREVIOUSLY UNTREATED BUT WITH AN INDICATION FOR ARVT

The current policy is to administer full suppressive therapy to avoid the appearance of resistances to NVP. Therapy should be initiated as soon as possible. If the women is not severely ill, ARVT should be delayed till the second trimester. Regarding the drugs to be used, factors to be taken into consideration are the potential side-effects and toxicity. The currently recommended regimen for pregnant women is ZDV + 3TC + NVP or a PI (Saquinavir (SQV), Nelfinavir (NFV) or Lopinavir/Ritonavir (LPV/r).

WOMEN UNTREATED AT THE TIME OF DELIVERY REGARDLESS OF CLINICAL OR IMMUNOLOGICAL STATUS

Several ARV regimens given during labor and postpartum have been shown to have an impact in reducing MTCT[8]. See the recommended regimen in table 4.

Table 4. Intra and postpartum ARV recommended regimen.

Intrapartum	*Postpartum*
ZDV + 3TC + Sd-NVP	ZDV+ 3TC one week, plus for the infant Sd-NVP immediately after delivery and ZDV for 4 weeks.

- If delivery is expected imminently, the NVP dose for the mother should be omitted, and the same recommendations and considerations apply as for infants born to women living with HIV who do not receive antenatal or intrapartum ARV prophylaxis.
- When delivery occurs within two hours of the woman taking NVP, the infant should receive Sd-NVP immediately after delivery and ZDV for four weeks.

INFANT PROPHYLAXIS

If the mother was adequately treated, the newborn should receive in the first 8 hours after delivery ZDV × 7 days.

If treatment was incomplete, 3TC should be given in the first 12 hours (2 mg/kg/12 h) for 7 days.

If their risk factor for MTCT are present (prematurely, long delivery etc.) one dose of NVP should be given during the first 12 hours and an extra dose at 48-72 hours. Prophylaxis may even be administered >48 h tours after delivery but should be given as soon as possible[9].

Table 5 summarizes different rug regimens and alternatives or prophylaxis of MTCT in resource-limited settings

Table 5. WHO guidelines for PMTCT drug regimens in resource-limited settings.

	Pregnancy	*Labour*	*Mother After birth*	*Infant After birth*
Recommended	ZDV >28 weeks	Sd-NVP ZDV + 3TC	ZDV + 3TC 7 days	Sd-NVP ZDV 7 days
Alternative (higher risk of DR)	ZDV >28 weeks	Sd-NVP	None	Sd-NVP ZDV 7 days
Minimum (less effective)	None	Sd-NVP ZDV + 3TC	ZDV + 3TC 7 days	Sd-NVP
Minimum (less effective, higher risk of DR)	None	Sd-NVP	None	Sd-NVP

DR drug resistance. WHO 2006[6].

SAFETY OF ANTIRETROVIRAL DRUGS FOR PREGNANT WOMEN AND THEIR INFANTS

All ARV drugs are associated with some transient or longer-term toxicity, for mother and child. Nevertheless the benefits of the drugs (reducing the risk of progression and preventing MTCT) clearly outweigh the risks.

Such risk will depend on timing and duration of exposure and the number of drugs used.

In general no dose adjustment have to be made during pregnancy.

NUCLEOSIDE AND NUCLEOTIDE ANALOGUE REVERSE TRANSCRIPTASE INHIBITORS

First line drugs: the NRTI drugs with which the most extensive clinical experience has been gained in pregnant women are ZDV and 3TC. Alternative drugs are abacavir (ABC), d4T and emtricitabine (FTC). The most common toxicity of ZDV is anaemia and neutropenia. TDF should not be used. Second line drugs: didanosine (ddl). Thos drug should be never used in combination with d4T (risk of lactic acidosis)

NON-NUCLEOSIDE ANALOGUE REVERSE TRANSCRIPTASE INHIBITORS

NVP is the NNRTI drug of choice for ART in pregnancy because of substantial clinical experience. Although uncommon, the most frequent adverse effects of NVP are hepatotoxicity and cutaneous rash. NVP should not be used if CD4 cell count exceeds 250 cells/mm^3. Studies in resource-constrained settings among pregnant women suggest that the risk of NVP-related hepatic toxicity is lower than reported in high-income countries.

PROTEASE INHIBITORS

As previously mentioned, PI where suspected to increase glucose intolerance and insulin resistance in pregnancy. A recent prospective study has not shown such association[10].

ARV DRUGS AND BIRTH DEFECTS

The Antiretroviral Pregnancy Registry is a prospectively registry of pregnancies exposed to ARV drugs (alone or in combination) and assesses the risk of birth defects. The incidence of birth defects does not seem to be higher among exposed women to ARVT than in the general population[11]. Nevertheless concerns remain about efavirenz (EFV) and Tenofovir (TDF). Their use should be limited during pregnancy.

EFV increases the risk of birth defects (anencephaly, anophthalmia, cleft palate) in infant monkeys and in humans, four retrospective cases have been reported of central nervous system defects (WHO[6]). Larger studies are required to evaluate the real risk. But currently EFV is not recommended for women with childbearing potential. EFV should only be used during the first trimester of pregnancy if the potential benefit t justifies the potential risk to the fetus. TDF may increase the incidence of bone abnormalities. Current data do no support should not be viewed as an indication for abortion.

LONG-TERM EFFECTS OF EXPOSURE OF THE INFANT TO ARV DRUGS IN UTERO

The long-term effects of exposure of the infant in utero to combination ARV regimens require further

study. Thera are conflicting data on mitochondrial dysfunction caused by ARVT (symptomatic and asymptomatic). Long-term follow-up of uninfected infants born to women living with HIV who had received ART during pregnancy is ongoing.

Safety data are missing for longer ZDV regimens in Africa where anaemia is common.

RESISTANCE TO DRUGS FOLLOWING ARV PROPHYLAXIS FOR PREVENTION OF HIV MTCT

Resistance to HIV drugs occurs more frequently with single and dual drug regimens but may emerge in women receiving triple-combination regimens but. Short-term exposure to ARV drug regimens to prevent MTCT Viral resistance is a potential problem specially for NVP and 3TC, drugs for which a single mutation leads to high-level resistance, whereas multiple sequential mutations are needed to confer resistance to ZDV. This should be taken into consideration when choosing a ARV regimen if more than 2 drugs are available.

MODE OF DELIVERY AND MANAGEMENT OF DELIVERY

The primary objective of in the strategies to prevent MTCT is to reduce viral load at the time of delivery. In settings where caesarean section is available and safe, a vaginal delivery would be envisaged if

- HAART and good adherence.
- Viral load $<$1.000 copies/mL around delivery.
- Singleton pregnancy.
- Cephalic presentation.
- Term ($\geq$36 weeks).

In such cases, caesarean section does not appear to offer a further reduction of the risk of MTCT. If such criteria are not met, an elective caesarean section should be performed around 38-39 weeks. A higher morbidity has been reported in HIV-infected women than among non-infected. Antibiotic prophylaxis should always be administered. The patient should understand the risk and benefits of a caesarean section

If a vaginal delivery is planned, obstetrical interventions should be contraindicated (fetal scalp blob sampling, placement of fetal scalp electrodes for fetal heart rate monitoring). Length of ruptured membranes is associated with MTCT, and therefore, it is recommended to maintain intact membranes as long as possible. Episiotomies and instrumental deliveries should be avoided if possible (MSC 140). HCV infection status did not influence the mode of delivery.

In setting where cesarean delivery is not available or unsafe, some precautions should be taken into consideration.

In any case, all strategies to prevent MTCT are only effective if the women is identified as HIV-infected. Therefore, all women should be tested antenatally and if the result is not available, a rapid test should be performed.

BREASTFEEDING

In developed countries, breastfeeding should always be contraindicated. New evidence now confirms that artificial feeding also presents serious risks for infants of HIV-infected mothers. Breastfeeding actually carries a lower risk of HIV transmission than breastfeeding combined with other fluids or foods.

A consensus statement on HIV and infant feeding has recently been adopted by all relevant UN departments and agencies[2] (CAH, five other WHO departments (NHD, HIV/AIDS, RHR, MPS, and FOS), the WHO Regional Office for Africa, and representatives of UNFPA, UNICEF and UNAIDS. Key recommendations are:

- The most appropriate infant feeding option for an HIV-infected mother should continue to depend on her individual circumstances, including her health status and the local situation, but should take greater consideration of the health services available and the counselling and support she is likely to receive.

- Exclusive breastfeeding is recommended for HIV-infected women for the first six months of life unless replacement feeding is acceptable, feasible, affordable, sustainable and safe for them and their infants before that time.
- When replacement feeding is acceptable, feasible, affordable, sustainable and safe, avoidance of all breastfeeding by HIV-infected women is recommended.

DIAGNOSTIC INVASIVE PROCEDURES

Most invasive procedures such as amniocentesis (for chariotype or fetal lung maturity assessment), chorionic villous sampming, cord blood sampling etc. may increase the risk of MTCT in untreated women. All women undergoing an invasive procedure should have a diagnostic HIV test previously done. If positive, the procedure if clearly indicated should be performed under HAART and minimizing risk factors such as tranplacental passage[12].

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CHAPTER 17

Congenital deffects: screening and diagnosis

PREGNANCY

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INTRODUCTION

Ultrasonography allows for a detailed morphological, functional, behavioral and developmental analysis of the fetus. Advances in technology, including Doppler, 3D, 3DPD and 4D, and as well magnetic resonance imaging have surfaced all expectations. With these advances and improvements, clinicians now have the tool to contend with many significant diagnostic challenges. All of those improvements particularly in the resolution have allowed for greater detection of anomalies in first and second trimester as well as identification of ultrasound markers for aneuploidy. Indeed, with the advent and evolution of 3D (three-dimensional) ultrasound technology during the past 10 years, we now stand at a threshold in non-invasive diagnosis. It is clear that the progression from two to three dimensions has brought with it a variety of new options for storing and processing image data and displaying anatomical structures. Nowadays, this technology provides ultrasound with multiplanar capabilities that were previously reserved for computed tomography and magnetic resonance imaging. In order to reduce the number of unnecessary invasive diagnostic procedures and to increase detection rate of chromosomal abnormalities, several markers have been recommended.

ULTRASOUND SCREENING FOR FETAL MALFORMATIONS

Fetal malformations are diagnosed in about 4-5% of infants during the first year of life. The reduction of other common factors as cause of perinatal mortality explains that congenital defects are now the first cause of perinatal mortality in many parts of the world.

There are three types of **prevention of congenital defects.** The **primary** prevention tries to avoid the production of the defect. This is the case of the prophylactic administration of folic acid to reduce the appearance of neural tube defects. The aim of the **secondary** prevention is the early prenatal detection of defect, making possible the early termination of pregnancy. Naturally it is there in that kind of prevention, where the ultrasonography has a fundamental role. Finally in the **tertiary** prevention, the objective is only the treatment and social adaptation of the malformed child.

In the case of secondary prevention it is important to distinguish between screening test, whose main objective is the identification of pregnancies at risk, through first level test or **detection test,** from the **diagnostic methods** that achieve prenatal diagmosis of the congenital defects using second level tests. In the case of congenital defects for chromosomopathies, the first level will be the biochemical and sonographic test, meaning diagnostic test will be the amniocentesis o villus sampling. But in the case of malformations, the ultrasonography is at the same time the detection test and the diagnostic test. The level of the exploration is the only thing that diferentiates both tests.

If possible, it is advisable to make three sonographic examinations during pregnancy: at 10-14 weeks (for detection of gross malformations and markers of aneuploidies), at 20-22 weeks (for detailed study of fetal anatomy, and detection of the majority of malformations), and at 34-36 weeks (for study of fetal growth).

The 20-22 weeks'examination is specially important because in this moment up to 75% of fetal malformations can be observed.

In pregnancies of high risk for congenital defects the number of malformations is three times the registered in the low risk. But in the low risk there is accumulated the 85% of malformations, in front of the 15% in the high risk. It is due to the fact the vast majority of the pregnant women are in the low risk group.

RECOMMENDATIONS

— If the Health Center disposes of ultrasonography all pregnant women schould be examined by means of this procedure at least to 20-22 weeks.

— The experience and training of the sonographer is very important. The result obtained depends also of the quality of the equipment used and the working conditions.

— The sonographer must know quite well the embriology, dismorphology and the pathology of development.

— Sonographers to should not remain satisfied with merely having detected a malformation. It is necessary look for other anomalies and carry out complementary test (cytogenetic, immunological or biochemical studies).

— If is possible the ultrasound scan at week 20, should be performed at level 2. The level system is the best way to get the highest standards of quality.

— Sonographers should always bear in mind the feelings and the psychological state of the parents as well as the ethical an legal aspects of each case.

— No decisions should be made without having first clearly defined the disorder of the fetus.

— A detailed postmortem examination should be carried out. The purpose is to provide appropiate counselling and the control of the quality.

GENETIC ULTRASOUND

Ultrasound technique is simple, non invasive and effective in the screening for chromosomal abnormalities. As most of the fetuses with chromosomal abnormalities have structural malformations, the so called genetic ultrasound is used for first and second trimester scanning for special markers, which are used in calculation alone or with maternal biochemical screening, for detection of chromosomal abnormalities. When the risk is higher, karyotyping is recommended.

RECOMMENDATIONS

— Severe fetal structural malformations are found to be closely related to fetal chromosomal abnormalities.

— Structural malformations that strongly suggest fetal chromosomal abnormalities are: nuchal edema, cystic hygroma, ventriculomegaly, hydrocephalus, Dandy-Walker complex, holoprosencephaly, fetal hydrops, duodenal atresia, some cardiac anomalies, some urinary tract abnormalities, etc.

— Structural malformations suggesting low risk for fetal chromosomal anomalies: isolated cleft lip and clef palate, gastrochisis, jejunal atresia, large bowel obstruction, unilateral polycystic renal hypoplasia, mesenteric cyst, ovarian cyst, isolated cross-foot, etc.

— Each type of chromosomal abnormality has its own variety of structural malformation.

— More fetal structural malformations suggest higher risk for fetal chromosomal abnormalities.

NUCHAL TRANSLUCENCY

Nuchal translucency is subcutaneous accumulation of fluid in the fetal neck. This echolucent zone is observed by ultrasound during first trimester (nuchal translucency) and second trimester (nuchal fold) of pregnancy. Normally it resolves in the second trimester, and if not nuchal fold or cystic hygroma develops. Both, nuchal translucency and nuchal fold are suggestive of chromosomal defects, whereas cystic hygroma is considered a congenital malformation of variable expression in terms of both morphology and chronology.

From a psychopathological point of view, nuchal fluid comes from the paracervical lymphatic system, which drains into the internal jugular vein. Enlarged NT occurs due to the cardiac failure in association with cardiac abnormalities, venous congestion, abnormal development of the lymphatic system, failure of lymphatic drainage, fetal anemia or hypoproteinemia or congenital infection. Spontaneous resolution of the nuchal fluid is more likely to occur in euploid fetuses, although it has also been described in aneuploid ones.

Benaceraf et al in the year 1995 were the first to describe the increase of the nuchal fold as a second trimester marker of T21. The first who suggested its value as an early marker was Szabó. Value of NT $\geq$ 3 mm in the first trimester implies a detection rate between 28 to 100% of T21, with a specificity of 48-99%. Those results have proven that NT is not only effective in the global screening of the main autosomal trisomies (T18, T21 and T13), but also in less frequent ones (T10), sexual chromosomal abnormalities and polyploidies. In addition, it has a prognostic value in perinatal evolution, with an increased incidence of perinatal morbidity and mortality, and is often associated with structural defects.

RECOMMENDATIONS

— One should obtain mid-sagittal plane with the fetus in neutral position.

— Only the fetal head and upper thorax should be included in the image, and the magnification should be as large as possible.

— The maximum thickness of the subcutaneous translucency between the skin and the soft tissue of the cervical spine should be measured.

— At least three measurements must be taken.

— Measurement should be performed between 11 weeks and 13 weeks and 6 days, when CRL is about 45 to 84 mm. It can be measured both transvaginally and transabdominally.

— Fetal NT normally increases with gestational age.

— Increased NT is associated with T21 and other chromosomal abnormalities. NT screening can identify more than 75% of fetuses with T21 and when combined with maternal serum free βhCG and PAPP-A, about 85-90% can be identified, with false-positive rate of 5%.

— Increased NT, increased NF and cystic hygroma are indications for chromosome karyotyping.

— Strong association between NT and congenital heart defects was found; therefore NT is accepted as a marker for CHD.

NUCHAL FOLD

Nuchal fold is measured between 16 and 22 weeks of gestation, at the transverse plane of fetal cerebellum. The calipers should be placed at the outer edger of the fetal calvarium and the outer edger of the skin. When the measurement is >5 mm, it is considered to be abnormal.

In 1985 Benaceraf et al were the first who reported that NF could be used for trisomy 21 screening. Nuchal fold has a sensitivity of 4 to 75% for trisomy 21with false positive rate of $\leq 2\%$. Nyberg et al recommended NF ≥ 5 mm as a cut-off value; its sensitivity of screening trisomy 21 is 23,2% with a false-positive rate of about 0,6%.

RECOMMENDATIONS

— NF should be measured between 16 and 22 weeks of gestation.

— NF $\geq$ 5 mm is considered to be abnormal.

— It is used for trisomy 21 screening.

CYSTIC HYGROMA

Fetal cystic hygroma is a congenital malformation characterized by distended fluid-filled spaces in the region of the fetal neck. It results from misconnection of jugular lymph sacs to the jugular vein, which is causing accumulation of lymph fluid at the back of the neck instead of appropriate drainage into the venous system. Cystic hygroma can be diagnosed early or late in the pregnancy. Considering prognosis, implications are different depending on the moment when the diagnosis was made; the earlier the diagnosis, the better the prognosis.

In the first trimester cystic hygroma is associated with chromosomal defects in 50% of cases, particularly autosomal trisomies, but with low incidence of adverse perinatal outcome or dysmorphological sequels.

When diagnosed in the second trimester of pregnancy, in about 80% of the cases are associated with aneuploidy; in particular with monosomy X and trisomy 21 or other structural malformations. Prenatal diagnosis always requires very careful assessment meaning kayotyping and ultrasound.

RECOMMENDATIONS

— In about 42% of cases it is associated with monosomy X (Turner Syndrome).

— Careful assessment by ultrasound and karyotyping.

NASAL BONE

It is known that fetuses with trisomy 21 have skeletal abnormalities, including: brachycephaly, long bones with reduced growth velocity, short femur, hypoplasia of the middle phalanx of the fifth digit and absence of ossification of the nasal bones. One physical feature of trisomy 21 is a flat facial profile with a small nose, due in large part to hypoplasia of the nasal cartilage.

Ossification of the nasal bones can be detected in normal fetuses and was found to be absent in one-quarter of trisomic fetuses, regardless of gestational age. Kjaer and Keeling have conducted a postmortem radiographic study of the fetal axial skeleton. Results showed malformation or agenesis of the nasal bones in 19/31 (61%) of trisomy 21 and in 8/10 (80%) of trisomy 18 fetuses. In most of the cases necropsy of trisomy 21 fetuses showed absence or hypoplasia of nasal bones. This is identified as a screening marker and reported by Cicero et al in 2001. In order to detect nasal bone abnormality sonographer should obtain precise screening technique; mid-sagital view (nasal bones normally appear as echogenic linear structures that project slightly outward along the bridge of the nose), separation between nose skin, cartilaginous tip of the nose and bone itself. It is important to mention, that this optimal view differs from that used for measurements of nuchal translucency. Another relevant issue is the insonation angle, if it is less than 45° or greater that 135° it can be mistaken, and suspicious of absence of the nasal bones. Cicero et al have in three different studies reported about 67 to 73% of trisomy 21 fetuses with an absent nasal bone compared with only 0,5 to 2,8% of euploid fetuses. Other authors have found an association between nasal bone anomaly and trisomy 18, Turner's syndrome and partial trisomy 9. Absent nasal bone is not an absolute marker for aneuploidy, because it as well occurs in chromosomally normal fetuses in about 2,2% of Caucasians, 9,0% of Afro-Caribbean's and 5,0% of Asians.

The 89% detection rate for trisomy 21 achieved by the combined screening strategy (NT, free βhCG, PAPP-A), is increased to 97% when detection of the nasal bone is included. Quite opposite, FASTER (First and Second Trimester Evaluation of Risk) trial failed to find any significant connection between the absence and presence of nasal bone and trisomy 21; suggesting that first trimester nasal bone sonography does not have a role in general population screening for fetal aneuploidy. Poor results of this trial may result from differences in image resolution, maternal obesity and suboptimal fetal position.

RECOMMENDATIONS

— One should obtain mid-sagittal view of the fetal profile, and magnify the image that only the head and the upper thorax are included in the screen.

— In the image there should be three distinct lines. The top one represents the skin, ant the bottom one is thicker and more echogenic representing nasal bone. The third line is almost in continuity with the skin, but at a higher level. It is the tip of a nose.

— Hypoplasia or absence of the nasal bone when scanning one should obtain mid-sagittal view of the fetal profile and only echogenic skin could be seen in nasal area.

— Perform scanning between 11w and 13 w6d of gestation.

— When scanning CRL (crown-rump length) should be 45-84 mm, at this stage fetal profile can be successfully examined in more than 95% of cases.

— In chromosomally normal fetuses the incidence of absent nasal bone is less than 1% in Caucasian population and about 10% in Afro-Caribbean.

— The nasal bone is absent in 65 to 70% of trisomy 21 fetuses, in more than 50% of trisomy 18, and 30% of trisomy 13 fetuses.

— Combination screening of sonographic measurement of NT and nasal bone, and maternal serum biochemistry (free βhCG, PAPP-A) can potentially identify more than 95% of trisomy 21 fetuses, with a false-positive rate of 5%.

CHOROID PLEXUS CYST

Choroid plexus are situated in the lateral ventricles, the 3rd and 4th ventricle, and are the places of production of cerebrospinal fluid. The thin wall cysts in choroid plexus are called choroid plexus cysts (CPC), well-known ultrasound aneuploidy marker, easily detectable in second trimester of pregnancy. CPC may vary in size, shape and number, but are mostly less than 1 cm in diameter. They may appear at any age, in one or both sides of the choroid plexus. Simple CPC normally resolves by itself by 24 to 28 weeks of gestation, without special management needed.

CPC in euploid fetuses has incidence of about 1%, and a positive predictive value of 1 to 6%. Occasionally, CPC may be found in fetuses with chromosomal abnormalities. Gray DL et al published an important paper in 1997. about association of unilateral and bilateral cyst with chromosomal abnormalities, where they did not find any significant association, but when CPC diameter was greater than 1 cm, trisomy 18 was confirmed.

In the cases when their association with fetal anomalies is found, bilateral location, diameter is larger than 1 cm, persistence after 22 to 24 weeks of gestation, cytogenetic analysis is indicated. But, their predictive value in other situations remains questionable and limited.

Considering that the miscarriage rate of amniocentesis is about 0,5 to 1%, most experts do not advise amniocentesis for choroid plexus cyst in women less than 35 years of age. Follow-up is advised by 28 weeks and after the delivery.

RECOMMENDATIONS

— CPC may resolve by 24 to 28 weeks of gestation.

— If CPC is diagnosed in the case when maternal age is > 35 years, or maternal serum hCG < 0,3 MoM- genetic counseling is advised.

— CPC in cases with previous history of fetal chromosomal abnormalities- genetic counseling is advised.

— CPC with face abnormalities, skeletal anomalies, heart, CNS, gastrointestinal and urinary anomalies- genetic counseling is advised.

— CPC with ultrasound markers like nuchal fold ≥6 mm, echogenic bowel, intracardiac foci, hydronephrosis, etc. —genetic counseling is advised.

ECHOGENIC INTRACARDIAC FOCUS

This soft marker has the incidence of about 0,5 to 20% in the second trimester of pregnancy. It could be seen in left, right or both ventricles, and is usually referred as «golf ball». Echogenic intracardiac focus is caused by variation in the development of the papillary muscles and chordae tendinae. Incidence of echogenic intracardiac focus is 90% in the left ventricle. Most of them decrease in size with gestational age and about 95% of them disappear before the term. Incidence varies in different ethnic groups. Although, Bromley et al have found that echogenic intracardiac foci could be diagnosed in 18% of fetuses with trisomy 21 and that the risk for trisomy 21 is four times higher in fetuses with this soft marker, other researchers showed that in low risk population (maternal age <35, biochemical screening showing low risk) it is not associated with chromosomal abnormalities, and in that case amniocentesis is not advised. On the other hand, in high risk population (maternal age >35, biochemical screening showing high risk, other ultrasonographic markers) amniocentesis is advised. This finding can be as well associated with cardiac tumors.

RECOMMENDATIONS

— Echogenic intracardiac foci are found in 18% of trisomy 21.

— When combined with other soft markers karyotyping is recommended.

ECHOGENIC BOWEL

It was first diagnosed in 1985. by Lince, and is characterized by bowel as echogenic as the bone. The echogenic bowel usually disappears by the end of second trimester or third trimester of pregnancy. It could be seen in about 0,6% of normal pregnancies. Most fetuses with diagnosed echogenic bowel are normal during follow-up. In some cases strong association between trisomy 21 and echogenic bowel is found, and sometimes (in $^1/_3$ to $^1/_2$ of cases) it is the only abnormality that can be detected antenataly. Some authors like Bromley and Thomas reviewed their data and reported that echogenic bowel could be an ultrasonographic marker for trisomy 21 and trisomy 13. According to their findings, for isolated echogenic bowel with no other soft markers the risk for trisomy 21 is 4,2 times that of the background risk. Therefore, it is recommended that if echogenic bowel is diagnosed in low risk population careful examination should be performed, in order to exclude other structural malformations. Echogenic bowel can be a sign of meconium ileus or intrauterine infection like CMV (cytomegalovirus), cystic fibrosis, etc.

RECOMMENDATIONS

— Usually disappears by the end of second or third trimester.

— Association with trisomy 21 and trisomy 13.

— TORCH is recommended.

— Careful anomaly scans examination.

HYDRONEPHROSIS

Hydronephrosis is used as an additional sign in ultrasound screening of trisomy 21, although its value is very limited in first trimester of pregnancy. Mild hydronephrosis was defined by Benaceraf et al as a dilatation of renal pelvis ≥4 mm at 16 to 20 weeks of gestation, ≥5 mm at 20 to 30 weeks, and ≥7 mm at 30 to 40 weeks of gestation.

It is known that 15% of fetuses with trisomy 21 have mild hydronephrosis. The severity of renal pelvis dilatation does not affect the risk for aneuploidy, but as the severity of renal pelvis dilatation increases, the incidence of required neonatal treatment increases. Mild hydronephrosis in most of the cases (74% in one study) resolve spontaneously. Almost all of them do not need neonatal intervention.

In the case of mild hydronephrosis in low risk population there is not enough evidence to advice chromosome analysis. But, if it is accompanied with other abnormalities, it is strongly recommended.

RECOMMENDATIONS

— Increased association with trisomy 21.

— Comprehensive ultrasound examination to assess the presence of other abnormalities.

— Ultrasound should be repeated in the third trimester.

— If renal pelvis dilatation <7 mm persists after 33rd week of gestation, no further evaluation is needed.

— If renal pelvis dilatation >7 mm persists after 33rd week of gestation, neonatal evaluation is advised.

SHORT FEMUR AND HUMERUS

Short stature is one of the prominent features of trisomy 21. Therefore length of femur (FL) and humerus (HL) has also been proposed as a marker in screening for aneuploidies in the second trimester of pregnancy. When measured in the second trimester of pregnancy femur is short, and humerus even shorter. FL is considered to be shortened when it is lagging more than 1,5 weeks behind gestational age.

Its effectiveness has not been proven in the first trimester.

Although short femur is associated with increased likelihood of trisomy 21, some studies showed that it can not be used as an independent risk factor to screen trisomy 21. According to her studies, Benaceraff concluded that short humerus might be a better marker for trisomy 21. Using measured HL/expected HL < 0,90 as a cut-off value, 50% of trisomy 21 could be diagnosed, with the false-positive rate of about 6,25%. When combination of FL and HL is used, specificity is improved. Nyberg et al reported that when FL and HL are shortened at the same time, the risk for T21 is 11 times of the background risk.

RECOMMENDATIONS

— FL and HL are second trimester markers for aneuploidies.

— Short FL is associated with trisomy 21.

— Use combination of FL and HL, higher specificity.

— Slightly shortened femur length varies widely upon ethnicity.

VENTRICULOMEGALY

The term hydrocephaly refers to different pathological conditions causing dilatation of the ventricles with increasing pressure of the cerebrospinal fluid. Hydrocephaly can be the consequence of an obstruction of the cerebrospinal fluid flow or a hyper production of fluid. Antenatal diagnosis relies on the recognition of dilatated lateral ventricles. Diagnosis relies on the measurement of the atrial width which is normally 7,6 ± 0,6 independently from gestational age. The cut-off value is 10 mm, measurements below 10 mm are considered to be normal, those between 11 and 14 mm are defined as borderline or mild ventriculomegaly, and measurements above 15 mm refer to frank ventriculomegaly. Mild ventriculomegaly is usually isolated (absence of CNS and other anomalies), and often present as a normal variant at gestational age >20 weeks, male fetuses, and LGA fetuses. It is caused by increase of cerebrospinal fluid, hypoplasia, dysplasia or atrophy of the brain tissue, craniosynostosis, etc.

Isolated mild ventriculomegaly may resolve *in utero* in about 29% of cases, remains stable in 57%, progresses in 14%. It has been reported that overall outcome of isolated mild ventriculomegaly in early childhood appears to be good with approximately 90% of cases being normal. Unfortunately, reported outcomes are at short terms and unclear and further studies and long terms follow-ups are needed.

On the other hand, mild or borderline ventriculomegaly is commonly associated with agenesis of corpus callosum, spina bifida and fetal infections.

According to Nyberg et al, when mild ventriculomegaly is diagnosed aneuploidy is present in 3,8% of cases, in 4% there are some undiagnosed CNS anomalies *in utero*, or 8,6% other undiagnosed malformations *in utero*, perinatal death occurs with incidence of 3,7%, abnormal development with 11,5% and overall abnormal outcome in 19,6% of cases. Management of borderline ventriculomegaly includes comprehensive ultrasound to search for other anomalies, serial ultrasound evaluation is needed, and MRI should be considered. It is very important to exclude fetal infection and to offer the parents genetic counseling and testing.

RECOMMENDATIONS

— Mild ventriculomegaly is commonly associated with agenesis of corpus callosum, spina bifida and infection.

— Mild ventriculomegaly is not a pathological finding in about 80% of cases (normal), but in 4% associated with aneuploidy.

— Isolated mild ventriculomegaly (no evidence of CNS or any other abnormality) may resolve in utero, progress or remain stable.

— When mild ventriculomegaly is diagnosed detailed and comprehensive anomaly scan should be performed, MRI if needed, TORCH and genetic testing.

— In cases of isolated mild ventriculomegaly serial ultrasound, possibly good short term prognosis.

DUCTUS VENOSUS

Ductus venosus is a tiny fetal vessel that plays a central role in the distribution of oxygenated blood during fetal life, shunting umbilical vein flow into the left ventricle, through foramen ovale. Consequently, in several conditions, DV blood velocity may reflect hemo-

dynamic alteration such as in hydrops, anemia, placental complications, twin-to-twin transfusion syndrome, cardiac disease, diaphragmatic hernia, liver disease, etc.

Reverse blood flow in DV is a sign of hemodynamic compromise.

Moreover, abnormal ductus venosus flow is associated with significant neonatal morbidity and perinatal mortality. Early detection of an increased resistance of ductus venosus has been associated with a higher risk of chromosomal anomalies and congenital heart defects. Its effectiveness is greater for autosomal trisomies, especially in terms of its high specificity and positive predictive value. High incidence of cardiac defects in chromosomally abnormal fetuses has been documented.

Cardial defects, with or without structural defects have been proposed as a possible cause of the development of NT. Changes in DV parameters may be explained by an underlying cardiac defects. Recent data are suggesting that its use in combination with nuchal translucency increases the specificity. Therefore, it could be considered as a secondary screening parameter. Many authors believe that DV blood flow assessment may provide a useful method in reducing the false-positive rate in screening for chromosomal abnormalities by combining maternal age and NT.

RECOMMENDATIONS

— According to many studies NT should be used as a first-line screening test, and DV as a second line test.

— If abnormal DV wave form is detected, congenital heart defect is suspected.

— If abnormal DV wave form is detected, chromosomal abnormality is suspected.

— In cases with increased NT and abnormal DV karyotyping is suggested.

— In chromosomally normal fetuses with abnormal DV waveform, fetal echocardiography should be mandatory, and careful follow up is suggested.

— Some authors suggest that fetuses with absent or reversal DV wave karyotyping should be offered even if NT measurement is normal.

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CHAPTER 18

Premature rupture of the membranes

PREGNANCY

V. Cararach | M. Palacio | F. Botet

INTRODUCTION

Premature Rupture of Membranes (PROM) consists in the rupture of fetal membranes ***before the onset of the labor.*** If PROM occurs before term (37 weeks of gestation) then is called **Pre-Term PROM** and if occurs at term **Term-PROM.**

The frequency of PROM is between 6-16 % depending on the time required to consider that the PROM is produced by the beginning contractions of labor, or before being in labor. Usually, to consider a PROM at term a three hours period without uterine contractions is demanded. In these conditions our rate of PROM is 9,8[1], and in recent ACOG PRACTICE BULLETIN on PROM[2] the quoted figure is 12 %. The importance is that although 75 %-80 % occurs at term[3, 4] it is one of the main causes of Prematurity accounting for the 30-40 % of preterm before 32 weeks[1] (table 1), and is one of the first causes of Perinatal Mortality.

Table 1. % of Pregnant Patients with PROM in the Clinic University Hospital of Barcelona (Spain).

Groups of weeks	< 28	28,0 - < 32	32,0 - < 34	34.0 - < 37	≥ 37	Total
Patients with PROM	22	63	59	193	791	1.128
Total deliveries	101	190	187	788	10.232	11.498
%	21,8	33,2	31,6	24,4	7,7	9,8

Data from 11.498 deliveries / PROM 1.128 (9,8 %); PT-PROM: 337 (2,93 %) / PTB:1.266 (11,01 %); Preterm PROM = 26,6 % of PTB.

ETHIOLOGY

The membranes, that are formed by the apposition of chorion and amnion, are broken when the intrauterine pressure is bigger than the resistance of the membranes, which during pregnancy, are back supported by the uterine wall. During labor, as uterine cervix is getting more open the back support is lacking and usually in the middle of the labor, at

4-7 cm of dilatation, membranes are spontaneously broken during a uterine contraction. When that occurs before labor, it is because its resistance is diminished (except in some cases in which it is caused by direct aggression as amniocentesis, amnioscopy, or other traumatic circumstances). Their weakness sometimes is caused by an asymptomatic and sub clinical infection, as was published by Romero[5], and in other cases by congenital weakness (Elhers-Danlos Syndrome), or acquired by Vitamin C deficit, or by smoking. But during pregnancy in the majority of cases the etiology is not known.

CONSEQUENCES

At **Term PROM** complicates approximately 8 % of pregnancies, and usually is followed by spontaneous onset of labor. With an expectant management near half of the cases are deliveries without problems within the 5-6 hours of PROM, and 95 % within 28 hours[6]. The main risks are maternal and fetal ascending *infection,* which increases with duration of PROM and with digital vaginal explorations, the increase in obstetric interventions, and the increase in fetal distress because of cord compression as a complication of the oligohydramnios, or less frequently by cord prolapse or *abruptio placentae.*

In **Pre Term PROM,** the main risk is the *prematurity* especially before 32 weeks of gestation, as the in the majority of cases delivery spontaneously starts within one week of PROM. But luckily enough the earlier in gestation that PROM occurs, the greater is the latency period (period between PROM and delivery)[2]. Our experience[1] confirms these data as described in table 2, and it is also confirmed in developing countries by Stewart at al[7]. The second risk for the fetus and the mother is infection, that forces to terminate the gestation in interest of both: in the mother produces a *chorioamnionitis* (25-60 %) that will be described in the next guideline, and in the fetus the fetal infection increases the risk of Fetal Inflammatory Response Syndrome (FIRS) as was described by Yoon et al[8], which is linked with *periventricular leukomalacia* and its consequences[9]. Other important consequences of prematurity and infection are the intraventricular hemorrhage, the necrotizing enterocolitis, and also in the fetus, and linked to the oligohydramnios, the limb position defects, the facial anomalies, and especially the risk of pulmonary hypoplasia that occurs only in cases with «severe oligohydramnios» (no amniotic liquid pocket $>$ 1-2 cm)[10].

Groups of weeks	23-27	28-31	32-33
Latency time in weeks	3,4 $\pm$ 1,8	1,2 $\pm$ 0,7	0,4 $\pm$ 0,2
Chorioamnionitis %	22,8	30,0	13,4

Table 2. Latency time, and % of chorioamnionitis with conservative management by groups of weeks of gestation.

In some cases, and more frequently in PROM after amniocentesis, the leakage of amniotic fluid (AF) is spontaneously stopped[11], the membranes reseal and pregnancy follows normally, although there remains a certain risk of another episode of PROM during the rest of pregnancy.

DIAGNOSIS

The diagnosis is obvious in more than 90 % of cases by the clinical symptoms (leakage of transparent and inodorous liquid), and by clinical exploration: observation of the watery liquid in the sterile speculum introduced in the vagina. But in some cases the pregnant

women explain the leakage of the liquid compatible with AF; nevertheless this is stopped and it is not possible to observe liquid on the vaginal speculum. In these cases is necessary to check if the explained leakage was or not AF. A sterile swab of fluid should be obtained from the posterior fornix of the vagina and placed on a clean glass slide, and on a piece of nitrazine paper. If the pH is higher the 6,5 it is quite probable that the liquid was AF as its pH level usually is higher than 7, and the vaginal pH without AF is lower than 5 except in cases of presence of urine, semen, bacterial vaginosis or *Trichomonas* infections, or in cases with plenty of blood. With the observation of the glass slide at the microscope at low magnification after waiting 10 minutes, in case of AF (PROM) it is possible to see images of arborization («ferning»). In both cases the rate of false positive is about 10 %, and the accuracy between 93-96 %. Also the observation by ultrasound (US) of oligohydramnios not existing previously, accompanied by the antecedent of leakage of liquid is very suggestive of PROM, but in rare cases in which the diagnosis is no clear and it could be important we may use the instillation of a dye (Evan's blue, indigo carmine or fluorescein) into the amniotic cavity. Methylene blue should not be used because it may cause fetal metahemoglobinemia. A tampon in the vagina can document a subsequent leakage in case of PROM.

This invasive procedure could be also necessary in cases in which we need to exclude the presence of sub clinical intraamniotic infection (IAI) or to check the lung maturity trough L/S, or other tests for fetal lung maturity (shake test, FLM…).

In some cases the verification of the absence of fibronectine or IGFBP-1 into the vagina through a quick but a more expensive test than the one previously quoted can help to exclude a PROM as their concentration in AF is near 100 times, that of other organic fluids, but not for confirmation of PROM as both can be present in vagina in cases of preterm labour without PROM[12].

MANAGEMENT

The management of PROM is clearly *depending of the gestational age,* as are the main risks: prematurity, infection, fetal distress, and fetal lung hypoplasia. Due to these reasons it is very important to be sure about the:

- Confirmation of PROM.
- Gestational age (it is better if calculated by US before 20 weeks).
- Exclusion at admission of intraamniotic infection, fetal malformations, and fetal distress.
- Depending of gestational age its could be very important to find out if fetus lung is mature or not.

At any gestational age a patient with evident intrauterine infection (clinical Chorioamnionitis), fetal distress or *abruptio placentae,* is best cared with by expeditious delivery.

A general exploration (including temperature, pulse and arterial pressure) and cervical cultures, vaginal/rectal specific cultures for *Streptococcus agalactiae,* and vaginal Gram need to be performed in all cases.

Also at admission maternal blood analysis (Hemograma, PCR and coagulation status), screening analysis for general infections if, they have not been performed before, and coagulation status need to be performed to exclude signs of current maternal infection, and the presence of other general infections.

Table 3. Management of PROM.

I. In all cases:

- In any moment if signs of Chorioamnionitis (CA) proceed to deliver.
- At admission:
  - Confirmation of PROM.
  - To exclude CA signs.
  - Confirmation of gestational age (better by US before 20 weeks).
  - To perform blood analysis (Hemograma, PCR, and coagulation).
  - To take samples for vagina/rectum exclusion of carrying S. *agalactiae,* to cervical culture and Gram stain of vaginal extension.
- To programme:
  - Periodic blood analysis.
  - Periodic NST.
  - Weekly US.
- To avoid digital vaginal exploration.

II. According to gestational age

- **< 24 weeks:**
  - Patient counseling[1] to decide expectant management or induction.
  - In both cases antibiotic treatment.
- **24-31 weeks:**
  - Expectant management[2] *(level A of recommendation).*
  - Antibiotic treatment[3] *(level A of recommendation).*
  - Corticosteroid therapy[4] *(level A of recommendation).*
  - Tocolytic therapy if uterine contractions *(no agreement)*[5].
- **32-34 weeks:**
  - Expectant management[2] unless fetal lung maturity.
  - Antibiotic treatment[3] *(level A of recommendation).*
  - Corticosteroid therapy[4] if no documented lung maturity *(level B of recommendation).*
  - Tocolytic therapy if uterine contractions *(no agreement)*[5].
- **34-36 weeks:**
  - Antibiotic treatment[3] *(level A of recommendation if S. agalactiae carrier or not documented, level B in other cases).*
  - Induce the labour if documented lung maturity.
  - Not to use tocolytic therapy if uterine contractions.
- **≥ 37 weeks of gestation:**
  - Antibiotic treatment[3] *(level A of recommendation if S. agalactiae carrier or not documented, level B in other cases).*
  - Proceed to inducing labour *(level A of recommendation)* within the 6 hours of admission unless labour was spontaneously started:
  - With perfusion of Oxitocina if Bishop Index ≥ 6.
  - With local prostaglandin if Bishop Index < 6.

1. **Patient counselling.** To give all information available about prognostic (mortality and handicap), bearing in mine risk factors involved and if possible of our Unit or our reference Centre.
2. **Expectant management.** Unless signs of IAI, or signs of fetal or maternal distress.
3. **Antibiotic treatment.** It may cover the *S. agalactiae* from the admission. There is no agreement about which antibiotic to use but is also convenient to cover Gram negative nitrobacteria. The combination amoxicillin-clavulanic acid may be not used before 36 weeks of gestation (see text).
4. **Corticosteroid therapy.** One course of Bethametasone 12 mg/day × 2 days. Could be repeated if before 34 weeks labour is imminent with documented absence of lung maturity.
5. **Tocolytic therapy.** There is no agreement on its use, but could be useful to delay delivery at least for 48 hours to allow for effect of corticosteroids. When used with corticosteroids care must be taken to control the liquid balance to avoid or decrease the risk of acute pulmonary oedema.

To exclude a Non Reassuring fetal condition is necessary to perform a NST, bearing in mind that before 32 weeks the value of NST is limited, and it is possible to obtain non reactive but non pathologic result. After PROM, in some cases NST becomes reactive when before it was not. After becoming reactive, a Non Reassuring Fetal Test is suspicious of sub clinical intraamniotic infection (IAI), that could be confirmed by a low figure obtained in the Biophysical Profile (< 6), and in any case before taking important decisions (as is finalization of pregnancy before 34, and especially before 32 weeks), needs to be confirmed by amniocentesis, except in cases of clinical chorioamnionitis.

Often this diagnostic is not clear as we will describe in the next guideline (maternal fever, fetal tachycardia, malodorous secretion by vagina, and uterine tenderness) but there are indirect signs as onset of uterine contractions, temperature between 37,0 and 37,5 ºC, or fetal

tachycardia less than 180, or white blood cells figures between 15.000 and 25.000/mm^3 without or less than 5% of bands (not segmented) leukocytes, or the reverse situation leucocytes less than 15.000/mm^3 but with 6-10% of bands. In all this cases without established clinical picture of chorioamnionitis, it is necessary to confirm of our suspicion of intraamniotic infection (IAI) obtaining AF through amniocentesis controlled by US that usually is possible even with oligohydramnios in more than 90% of cases. A sample of amniotic fluid (AF) is sent to laboratory to be cultured, but a quicker information can be obtained by the level of glucose ($<$13 mg/dL is suspicious of bacterial infection), as well as the presence of more than 50 leukocytes/mm^3, or by the presence of germs in the Gram stained extension of centrifuged AF. As there are false positive results in all these tests, and the decision is especially important before 32 weeks it is necessary to be very sure about the diagnosis to take the decision of finishing the gestation, and by this reason the coincidence in the results of all these tests is required to take this decision.

Once the diagnose has been established and excluded a sub clinical infection and non-reassuring fetus status it is necessary to maintain the *systematic monitoring* of all these parameters to ensure that in case to became suspicious we will detect it. By this reason we need to monitor fetal wellbeing by periodic NST, and to exclude intrauterine infection with maternal temperature/ 6 hours, and periodic blood analysis.

In pre term PROM nowadays there is agreement that *antibiotic treatment* is mandatory, as it prolongs the latency time, and decreases the incidence of IAI neonatal sepsis, and puerperal endometritis[13] (level A of recommendation).

At term antibiotics (penicillin, amoxicillin, or erythromycin in cases of allergy to penicillin) need to be started at admission after performing endocervical cultures, in cases of known *Streptococcus agalactiae* carrier women or in cases that it is unknown.

Although the vagina is a septic cavity with big quantity of germs including anaerobic germs there are two germs responsible of more than 60% of chorioamnionitis and neonatal sepsis: *Streptococcus agalactiae* and gram negative enterobacteria, especially *Escherichia coli*. This is the rationale for using Penicillin, Ampicillin or Amoxicillin (or Erythromycin or Clindamycin in case of allergy to penicillin) and an antibiotic active against this last germ, as Gentamycin, Cefoxytin or the association Amoxicillin-Clavulanic acid. The use of antibiotics at or near term PROM, reduces significantly neonatal sepsis in circumstances or in countries where there is no policy of systematic *Streptococcus agalactiae* screening[14]. The amoxicillin-clavulanic acid may be a good and less toxic option at all gestational ages, but nowadays it has been restricted to a PROM after 35 weeks because after the paper of Kenyon et al[13] it has been linked to an increase of Necrotizing Enterocolitis.

Corticosteroids must be used without doubt systematically between 24 and 32 weeks (level A of recommendation), and probably to 34 and after these weeks if the study of fetal lung maturation indicates a non mature lung. The corticosteroids not only increase the lung maturation, and the production of surfactant, but also decreases intra and periventricular hemorrhage, and intestinal immaturity.

TERM PROM

At tem there is consensus that it is *better to finish* the pregnancy (level A of recommendation). With an expectant management for a short period of time near half of cases will deliver within the 5-6 hours of PROM, and 95% within 28 hours[6]. But since the longer the latency period is more frequent the fetal infection is, if after 6 hours labor has not begun, there is agreement to start with intravenous oxytocin infusion if Bishop test is $\geq$6, or with local prostaglandins E_2 (especially through a vaginal device better than in gel, as devices

do not need to be introduced into the cervix), or with locally application of misoprostol. Although this drug has some administrative problems in many countries, and has the same level of risk of hyper stimulation as other prostaglandins, safely used can be a good option because is very cheap and does not need to be maintained in a cold temperature.

Antibiotics against *Streptococcus agalactiae* (Penicillin, Amoxicillin or Erithromycin in case of allergy to penicillin) need to be started at admission after taking cultures in cases of unknown or positive carrier women. After 6 hours if it has not delivered, it is convenient to add antibiotics active against gram negatives germs[14].

PRE-TERM PROM

In pre-term PROM *it is necessary to group cases according their gestational age:*

- **After 34 weeks**[2, 15], or in cases **after 32 weeks with checked lung maturity**[2], (in these last cases according to results obtained by the Neonatologic Unit) *PROM cases are managed as at term,* bearing in mind that there are cases in which we don't know if they are *Streptococcus agalactiae* carriers or not, and then prophylactic antibiotics may be used at admission after cervical cultures. According to Bishop Index, if it is ≥ 6 we shall with intravenous perfusion of oxytocin, or with vaginal administration of prostaglandins if is ≤ 5.

- **PROM from 24 to 32 weeks**[2, 15], there is agreement to recommend *expectant management* (level A of recommendation), with prophylaxis against *Streptococcus agalactiae,* corticosteroid treatment, antibiotic treatment to prolong latency time and decrease feto-maternal infections, and tocolytic treatment if there are contractions (there is no general agreement about this point). Close monitoring of the suspicious infection and fetal well-being, is necessary but it is possible to send these women home if there are good conditions for it, returning to hospital after reaching the viability limit of their respective center. Even in some regions of Africa[7] it is possible to obtain more than 43 % of survival in PROM before 28 weeks of gestation, as latency time could be more than three weeks at this gestational age[1, 7] although with a 20-30 % of chorioamnionitis that need to be treated expeditiously (see the correspondent chapter).

- **PROM before 24 weeks**[2, 4, 15]: *Patient counseling* with information on results by weeks of gestation and especial circumstances of each center and the available neonatologic unit (usually 30 % survival but variable % of handicaps), to decide for the patient expectant or induction (there is no consensus about antibiotic therapy but we usually use it).

  In all PROM patients and especially in all groups treated with conservative treatment, it is necessary to avoiding digital vaginal explorations if they are not absolutely necessary since they increase the risk of intrauterine infection. A strict control for infections, and an expeditious termination under antibiotic therapy (different to that used before) in case of clinical chorioamnionitis, are the main recommendations.

  No corticosteroids are used in this period, but **the treatment will be adapted to the correspondent period at which the pregnancy is arriving.**

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CHAPTER 19

Rh-Alloimmunization in pregnancy*

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INTRODUCTION

Maternal alloimmunization occurs when a woman's immune system is sensitized to foreign fetal blood group factors (inherited from the father), thereby stimulating the production of antibodies. It includes Rh alloimmunization, a sensitization caused by other erythrocyte surface antigens, and platelet alloimmunization; among more than 50 different antigens capable of causing maternal alloimmunization and fetal hemolytic disease, the ABO and the Rhesus (Rh) blood groups are the most common, and, in particular, the D antigen of the Rh blood group system (Rh D) causes the most severe hemolytic disease of the fetus and the newborn (HDFN). Less frequent causes include Kell, Kidd and Duffy systems.

Table 1. Red blood cell antigens involved in maternal alloimmunization.

Blood group system	*Antigens*	*Hemolytic disease severity*
ABO	A B	only neonatal disease
Rh	C c D E e	moderate-severe
Kell	K k	moderate-severe
Kidd	Jk^a Jk^b	moderate-severe
Duffy	Fy^a Fy^b	moderate-severe

ABO incompatibility is the most important cause of neonatal hemolytic disease (HDFN), affecting 5% of newborn infants.

Characteristics of ABO alloimmunization:

- The disease affects the first and probably the second pregnancy.
- It is a slight disease (anemia with associated hyperbilirubinemia).
- The reaction consists in IgM production, pentameric antibodies that can't cross the placenta; so, pregnancy is not at risk of HDFN.
- The disease does not worsened with each additional incompatible pregnancy.

To the contrary, Rh incompatibility is the most important cause of severe HDFN which does not affect the first pregnancy and probably the second, but with increasing frequency the third, fourth and so on pregnancy. Thus, previous Rh sensitization in the occurrence of an undiagnosed, and so not adequately treated, abortion or blood transfusion, can be the reason of an eventual HDFN at the first pregnancy.

RH INCOMPATIBLE PREGNANCY

Diamond et al, in 1932, recognized that anemia of the fetus and the newborn, icterus gravis neonatorum and hydrops fetalis are probably different aspects of the same disease, which they named «erythroblastosis fetalis»[1]. The discovery of the pathogenesis of that condition by Levine et al. was in 1941[2], and the discovery of the Rh-factor by Landsteiner and Wiener was in 1940; they performed the landmark experiments wherein Rhesus monkey erythrocytes were injected into rabbits and guinea pigs[3].

In 1945 Coombs et al. introduced into clinical medicine the antiglobulin test and, one year later, the same authors described the direct antiglobulin test that they used to detect in vivo sensitization of red cells in the Rh hemolytic disease of the fetus and the newborn (HDFN)[4, 5].

In 1961 Liley defined the natural history of the disease and introduced the spectrophotometric measurement of bilirubin in AF as an index of fetal hemolysis that correlated with its severity[6], and he, two years later, introduced the technique of intraperitoneal fetal transfusion[7].

In 1964, Freda et al. demonstrated that the administration of anti Rh(D) prophylaxis to Rh-negative women within 72 hours of delivery was successful to reduce the incidence of HDFN[8]; thereafter several clinical trials demonstrated that the incidence of the disease had decreased dramatically since the institution of routine Rho γ globulin prophylaxis in Rh-negative women.

The writer (Cosmi EV) is happy to recall that, in 1966, he injected the prisoners of Sing Sing penitentiary with incompatible blood to produce Rho γ globulin under the supervision of Vincent J. Freda. The routine administration of anti-Rho γ prophylaxis has reduced the incidence of Rh-alloimmunization from 7-16% to 1-2 %. The introduction of antenatal Rh IgG prophylaxis has further reduced the incidence of Rh (D) alloimmunization to below 1%. Therefore the disease has practically disappeared with the routine use of Rho γ globulin after possible alloimmunization procedures, e.g., abortion, delivery. However, recently Rh alloimmunization has reappeared for different reasons including: the lack of prophylaxis in certain countries, particularly the developing ones; the delay in prophylaxis to more then 72 hours; variant antigens, known as «minor», «atypical» or «irregular» ones, i.e., Kell, Lewis and Duffy, relatively more frequent in pregnancy, and frequent fetomaternal hemorrhage not identified and therefore not treated.

In 1973 Zimmerman in the preface of his book —*Rh The Intimate History of a Disease and Its Conquest*— wrote: «this book is about creativity in medical research. My aim is to unfold, from the partecipants' viewpoints, a strikingly productive series of observations, intuitions, and deluctions that have led —within the career span of a single scientific generation— from the elucidation to the defeat of one extremely lethal disease. Rarely is a disease dealt with so effectively in so little time»[9].

It should be recall that the **incidence of Rh incompatibility** varies by race and ethnicity. Approximately 15% of whites are Rh-negative, compared with only 5-8% of African Americans, 1-2% of Asians and Native Americans. Among whites, an Rh-negative woman has an approximate 85% chance of mating with an Rh-positive man, 60% of whom are

heterozygous and 40% of whom are homozygous at the D locus[10]. The genetic locus for the Rh antigen complex is on the short arm of chromosome 1; three pairs of antigens, Cc D and Ee, very much alike, exist and are inherited from every parent as two locus of three alleles. Every person can be homozygous or heterozygous for every allele. A person is Rh-positive if he has the antigen D, Rh-negative if he has not the antigen D.

The precise function of Rh antigens is unknown, although they probably have a role in maintaining red cell membrane integrity; the high immunogenicity of Rh (D), in comparison to the hundreds of other blood group antigens, is explainable because:

a) The antigen D is highly immunogenic.

b) It is developed early in pregnancy.

c) A significant proportion of Caucasian population is Rh (D)-negative.

d) The specific antibody is capable of causing fetal hemolysis.

Rh alloimmunization occurs in pregnancy if four circumstances exist:

1. The fetus must have Rh (D)-positive erythrocytes.
2. The mother must have Rh (D)-negative erythrocytes.
3. A sufficient number of fetal red cells must gain access into maternal circulation.
4. The mother must have the immunogenic capability to produce antibodies directed against the D antigen.

PROBABILITY OF ALLOIMMUNIZATION

The probability of alloimmunization of a pregnant Rh-negative woman against Rh-positive fetal red cells depends on several factors[11]:

- *Volume of Rh (D)-positive fetal red cells*: during an uncomplicated vaginal delivery, an episode of fetomaternal hemorrhage is common (about *15 to 50 %* of births), and during normal pregnancy spontaneous transplacenta hemorrhage occurs with increasing frequency with advancing gestational age *(1-2%* of alloimmunizations are caused by antepartum fetomaternal hemorrhage).

  The volume of red cells considerated adequate to induce primary immunization is 1 mL, but this value varies from patient to patient, probably with the immunogenic capacity of the Rh-positive fetal erithrocytes and the immune responsiveness of the mother. As many as 30 percent of Rh-negative individuals appear to be immunologically «nonresponders» even when challenged with large volumes of Rh-positive blood.

- **Rh (D) phenotype of the fetal blood:** the density of Rh(D) antigens on the red cells may influence immunogenicity.

- **ABO incompatibility:** this condition has a protective effect against the development of Rh alloimmunization, because Rh(D) antibodies are less likely to occur while HDFN occurs with lower severity.

- ***Maternal* human leukocyte antigen *(HLA) haplotype:*** the presence of HLA-DQB1*0201 allele is associated with the ability to form high levels of anti-Rh(D); the molecular mechanism responsible for this association is unknown but we know that the immune response is under genetic control.

- **Fetal gender:** the Rh-positive fetus that induce alloimmunization is more frequently male; the ratio male/female being about 1,5.

THE CAUSES OF MATERNAL ALLOIMMUNIZATION ARE:

- Fetomaternal hemorrhage (ante-intrapartum; cesarean section, multiple gestation, placenta-previa or abruption; manual removal of the placenta or intrauterine manipulation, may increase the possibility of substantial hemorrhage).
- Blood transfusion.
- Abortion (therapeutic or spontaneous).
- Obstetric procedures (amniocentesis, chorionic villus sampling, external cephalic version, manual removal of the placenta).
- Ectopic pregnancy.
- Abdominal trauma.

Primary immune response to antigen D takes place from six weeks to twelve months after the contact, and it is a weak reaction that consists in IgM production, pentameric antibodies that can't cross the placenta. So, the first pregnancy is not at high risk of HDFN. Instead, during subsequent pregnancies, if the fetus is Rh-positive, the mother produces IgG, monomeric antibodies, able to cross the placenta causing destruction of fetal red blood cells. Generally Rhesus disease becomes worse with each additional Rhesus incompatible pregnancy.

The rate of transfer of IgG across the placenta may be the rate-limiting step in the immune reaction against fetal erythrocytes, and probably the main factor determining the severity of HDFN; afterwards, maternal IgG anti-Rh bind to their target, fetal red cells, and cause their destruction by the cells of the phagocyte mononuclear system, mainly in the spleen.

CLINICAL ASPECTS

IgG antibody–mediated hemolysis of fetal erythrocytes varies in severity and can have a variety of manifestations:

- Anemia (from mild to severe) with associated hyperbilirubinemia and jaundice.
- In severe cases, hemolysis may lead to extramedullary hematopoiesis and reticuloendothelial clearance of fetal erythrocytes; this may result in hepatosplenomegaly, decreased liver function and ensuing hypoproteinemia, ascites, and anasarca; when accompanied by high-output cardiac failure and pericardial effusion ensue, this condition is known as hydrops fetalis.
- Severe hyperbilirubinemia can still lead to kernicterus, a neurologic pathology observed in infants with deposition of unconjugated bilirubin in the brain: the absence of placental clearance and immature fetal bilirubin-conjugating capability can lead to symptoms that manifest several days after delivery and include poor feeding, inactivity, loss of the Moro reflex, bulging fontanelle, and seizures. If undiagnosed and untreated, this syndrome is often fatal; intensive neonatal care, including immediate exchange transfusion, is required. Infants who survive may develop spastic choreoathetosis, deafness, and mental retardation[12, 13].

CLINICAL MANAGEMENT

All pregnant women should be tested at the time of the first prenatal visit for ABO blood group and Rh-D type and screened for the presence of erythrocyte antibodies and irregular antibodies. These laboratory assessments should be repeated in each subsequent pregnancy[10].

Maternal serum antibody titer is determined with indirect Coomb's test; whereas the fetus and newborn are evaluated with direct Coomb's test. If a woman is Rh(D)-negative and no anti- Rh(D) or other clinically relevant antibodies are detected in the first screening, no further examination is necessary at that time and maternal blood sample are investigated for the presence of irregular antibodies every one/two months till the end of pregnancy.

If a woman is Rh-negative and she has a positive result of the indirect Coomb's test, the initial management is determination of the paternal erythrocyte antigen status. If the father is Rh negative, further assessment and intervention are unnecessary. If the father is Rh-positive, it is advisable to assess if the father is homozygous or heterozygous for the Rh (D) antigen. If the father is homozygous for the D antigen, all his children will be Rh-positive; if he is heterozygous, there is a 50% likelihood that each pregnancy will have an Rh-negative fetus who is at no risk of HDFN and does not require further assessment or treatment. One has to be sure that he is the real father. Because the risk of HDFN is 50%, when the paternal genotype is heterozygous it is necessary the determination of fetal genotype.

Amniocentesis is used to determine fetal blood type through the polymerase chain reaction (PCR) that allows determination of fetal Rh status from the uncultured amniocytes in 2 ml of amniotic fluid. The sensitivity and specificity of PCR typing are reported as 98,7% and 100%, respectively, with positive and negative predictive values of 100% and 96,9%.

Moreover, maternal serum antibody titer must be determined:

- If titer is 1:16 or less, the patient may be monitored with titer assessment every 4 weeks.
- If titer is 1:16 or greater, it is considered to be an indication for further examinations, i.e., transabdominal amniocentesis and Doppler ultrasonography.

Spectral Analysis of Amniotic Fluid (AF): assessment of AF in Rh immunization is based on the original observations of Bevis, subsequently confirmed by Liley, that spectrophotometric determinations of AF bilirubin is correlated with the severity of hemolytic disease. The bilirubin in AF originates from fetal hemolysis, reaches the AF by excretion into fetal pulmonary and tracheal secretions and across diffusion from the fetal membranes and the umbilical cord. AF is promptly centrifuged and then filtered and the filtrates are scanned in a spectrophotometer. Using a semilogarithmic plot, a normal tracing of optical density is a smooth curved line upward in the lower wavelengths of 525 and 375 nm. When the concentration of the bilirubin in the AF increases, it causes a peak at a wavelength of 450 nm. The amount of shift in optical density from linearity at 450 nm (the ΔOD_{450}) is used to estimate the degree of fetal red cell hemolysis (figure 1).

Liley analyzed the correlation of AF ΔOD_{450} with newborn outcome and divided a logarithmic graph into three zones (figure 2):

- Zone I: the ΔOD_{450} value is in the lowest zone and the fetuses are unaffected or with mild anemia.
- Zone II: the ΔOD_{450} value is in the middle zone and the fetuses had disease ranging from mild to severe.
- Zone III: the ΔOD_{450} value is in the highest zone and the fetuses are severely affected.

A single measurement of ΔOD_{450} is poorly predictive of fetal condition unless it is very high or very low. Thus, the clinical management included serial amniocentesis to determinate the trend of ΔOD_{450} values over time.

In 1965, Freda proposed another classification of the tracings depending on the amplitude and on the shift of the abnormal hump (the optical density difference at 450 mμ as mea-

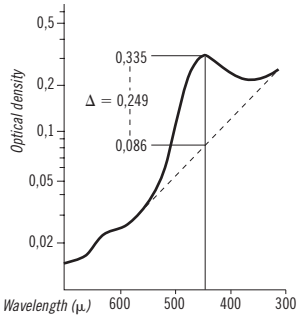

Figure 1. Graph of spectrophotometric analysis of AF from an Rh-Alloimmunization pregnancy[16].

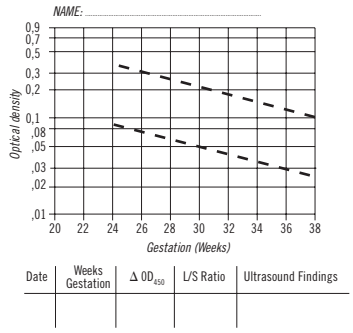

Figure 2. Liley's graph[16].

sured on a linear scale) and, with four curved classified as one-plus to four-plus (figure 3 and figure 4).

- 1+: this is very similar to a normal tracing in clinical significance.
- 2+: it means that the fetus is undoubtedly Rh positive and affected but it also means that the fetus is in no immediate jeopardy from Rh.
- 3+: this tracing indicates fetal distress; therefore the fetus has probably some degree of circulatory failure. Once this tracing appears, it does not regress, but inevitably progresses to a 4+ tracing and then fetal death.
- 4+: this is an indication of impending fetal death, occurring within one week. Although not always hydropic at delivery, these infants invariably show some evidence of congestive heart failure, and, if alive (following induction) they appear depressed and listless, have poor tone and a weak cry, and often require resuscitation. The pick effect at 28 weeks is 450 mμ whereas at 33 weeks it has shifted to 420 mμ (figure 4). This shift from 450 to 420 mμ and increase in amplitude invariably precedes the onset of impending fetal death. The sharp peak at 415 mμ can derive from a contamination with blood and subsequent lysis of a few red cells incurred during the amniocentesis[14, 16].

Ultrasonographic examination: it has become an extremely important adjunct in the management of the Rh-sensitized pregnancy.

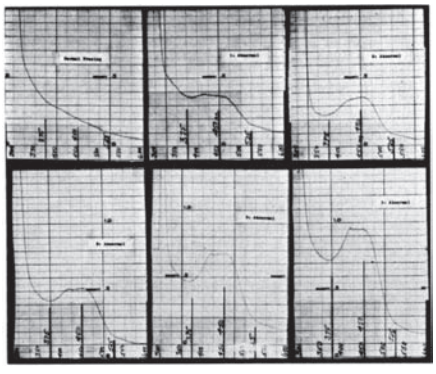

Figure 3. Serial tracings on AF specimens demonstrating the progressive development of the «abnormal curve» from «beginning to end»[16].

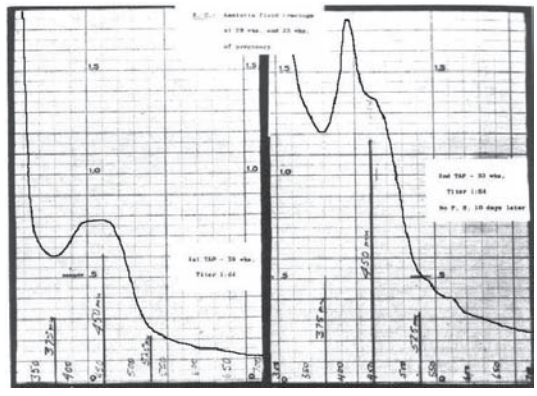

Figure 4. AF tracings at 28 and 33 weeks in presence of a maternal serum antibody titer at 1: 64[16].

Ultrasounds permit to identify sonographic findings that might predict the severity of erythroblastosis fetalis and reduce the need for invasive assessments; various parameters as polyhydramnios, placental thickness greater than 4 cm, pericardial effusion, dilation of the cardiac chambers, chronic enlargement of the spleen and liver, dilation of the umbilical vein have all been proposed as indicators of significant prehydropic fetal anemia.

Another non invasive predictive test for fetal anemia, that is most promising, is the middle cerebral artery peak systolic velocity (MCA-PSV). In 2002 and 2005, Mari G, Cosmi E et al. reported that MCA-PSV had a strong correlation with fetal anemia in Rh hemolytic disease[17-19]. The positive and negative predictive values for combined moderate/severe anemia were of 65 and 100%, respectively.

If the MCA-PSV remains constant at low risk level, ultrasound examinations is performed every 2 to 4 weeks from 20 weeks' gestation until delivery. Alternately, AF ΔOD_{450} determination could be used for the initial management, when the fetus shows no sign of hydrops, performing the first amniocentesis at 24 to 28 weeks' gestation and defining the timing to repeat amniocentesis on the ΔOD_{450} values and trend. To contrary, when the MCA-PSV or ΔOD_{450} values rise, a severe anemia must be suspected and an immediate intervention is required:

- If the gestational age is >32-34 weeks, with lung maturity, delivery is the goal.
- If the gestational age is <32-34 weeks in absence of lung maturity, cordocentesis to sample fetal blood and determine the fetal hematocrit is performed. Intravascular transfusion should be arranged immediately.

Soon after birth, in every pregnancy in which the mother produced Rh(D) IgG, it is necessary to carry out a draft using umbilical cord blood for:

1. Determination of ABO blood group and Rh(D) type of the child.
2. Direct antiglobulin test (Coomb's test) on the child's erythrocytes to determine whether the child's erythrocytes are sensitized with maternal IgG antibodies.
3. Determination of the concentration of neonatal hemoglobin.

If the neonate is Rh(D) positive and the Coombs test is positive, it is need to define the degree of anemia and eventually perform a transfusion (figure 5).

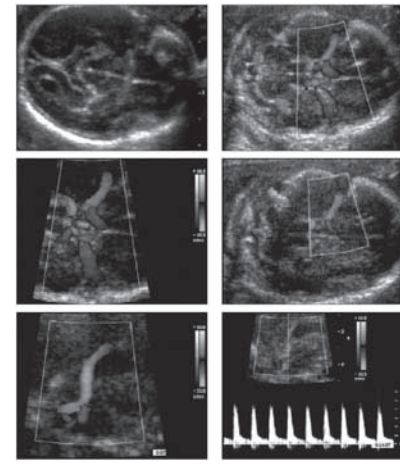

Figure. 5. Steps for correct MCA sampling. Top left, Axial section of the head at the level of the sphenoid bones; top right, color Doppler evidence of the circle of Willis; center left, the circle of Willis is enlarged; center right, the color box is placed around the MCA; bottom left, the MCA is zoomed; bottom right, the MCA flow velocity waveforms are displayed, and the highest point of the waveform (PSV) is measured. Note that the waveforms are similar to each other. The above sequence was repeated at least 3 times in each fetus[19].

PREVENTION OF ALLOIMMUNIZATION WITH RHO γ GLOBULIN

The primary goal of caring for a pregnant Rh-negative nonimmunized, with negative antibody screen during all pregnancy in presence of an Rh-positive fetus, is prevention of alloimmunization with anti-D prophylaxis.

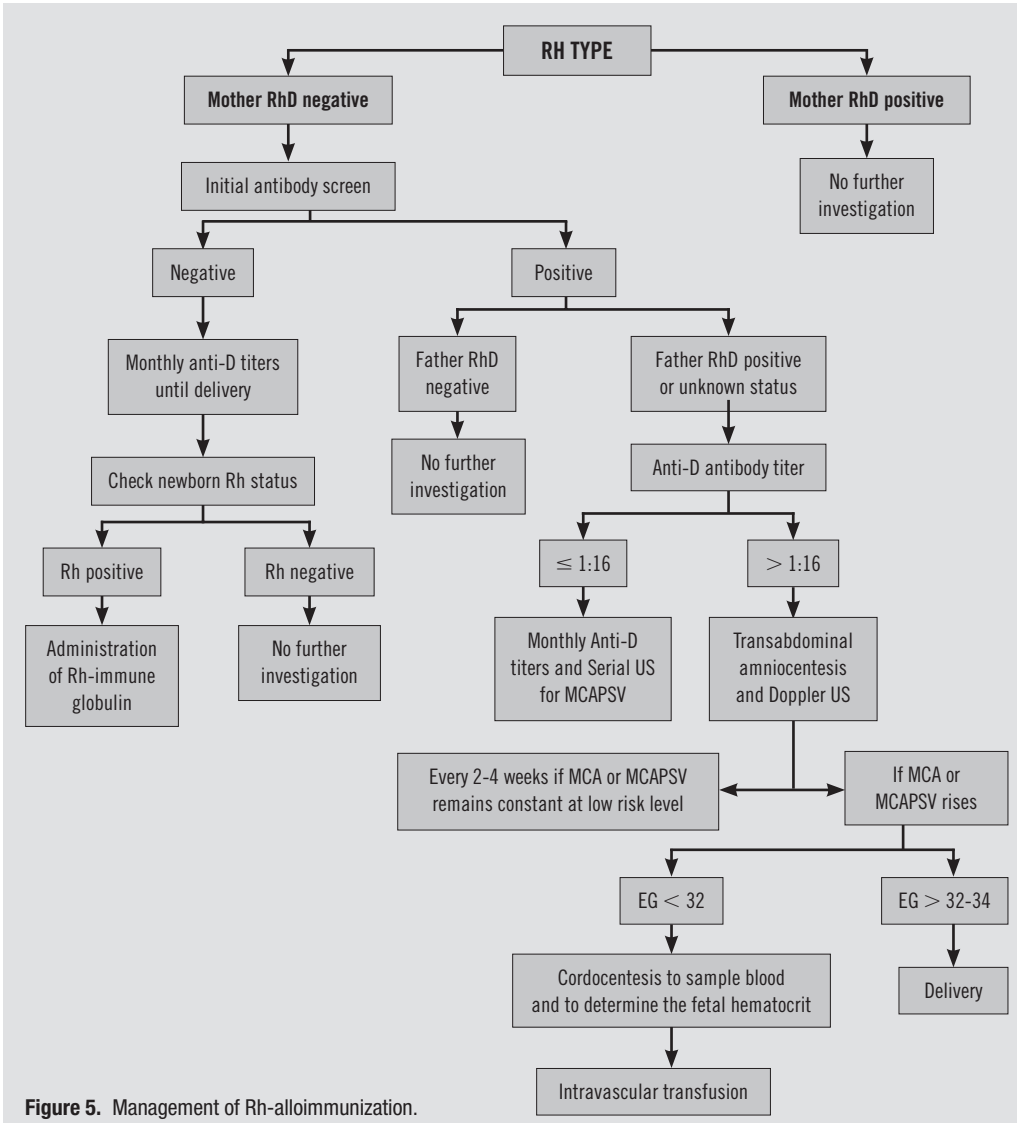

Figure 5. Management of Rh-alloimmunization.

The standard is the intramuscular administration of 300 mcg of Rho γ globulin at both 28 weeks' gestation and at most within 72 hours of delivery, preferably before. Exogenous administration of IgG suppresses the maternal primary immune response because fetal erythrocytes are coated by antibodies which interrupt the commitment of B cells to plasmacell clones. Additionally, these antigen-antibody complexes stimulate the release of cytokines that inhibit the proliferation of antigen-specific B cells.

Although an enormous decrease in the prevalence of alloimmunization, 1-2 % of women continued to become sensitized, probably because of an antepartum feto-maternal hemorrhage.

Anti-D IgG is absolutely contraindicated in women with documented hypersensitivity to anti-D IgG.

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CHAPTER 20

Late pregnancy vaginal bleeding (LPB)

A. Antsaklis

INTRODUCTION

Vaginal bleeding in late pregnancy (LPB) is defined by hemorrhage after 20th week of gestation. It complicates 3% of all pregnancies and potentially leads in hospitalization, increased maternal morbidity, operative intervention and increased fetal mortality and morbidity. Placenta previa and placental abruption are the most common causes of LPB (approximately half of LPB), and as they are both serious and connected to a higher rate of prematurity and perinatal death, they demand accurate diagnosis and optimal management. In table 1 are listed the major and the minor causes of vaginal bleeding in late pregnancy and table 2 presents the differential diagnosis of LPB .

Table 1. Causes of Vaginal Bleeding in Late Pregnancy.

Major causes		*Minor causes*	
• Placenta Previa. • Placenta Abruption.	• Ruptured Vasa Previa. • Uterine Scar Disruption.	• Cervicitis. • Cervical Polyp.	• Cervical Cancer. • Vaginal Trauma.

Table 2. Differential Diagnosis of LPB.

Main Category	*Diagnosis*	
Placental Causes	• Placenta Previa. • Placental Abruption.	• Marginal Bleed.
Fetal Causes	• Vasa Previa.	
Uterine/Cervical Causes	• Uterine Rupture. • Cervical Carcinoma.	• Cervical Polyp.
Miscellaneous	• Vulval Varices.	• Trauma.

PLACENTA PREVIA

Placenta previa is the type of placenta that is implanted wholly or partly over the internal cervical os. It is usually classified into three grades:

1. Low-lying placenta: the placenta is lying close to the internal os.
2. Marginal placenta: the placenta extends to the edge of the internal os but does not cover it.
3. Complete previa: the placenta completely covers the internal os.

EPIDEMIOLOGY

Placenta previa occurs in approximately 0,5% of all pregnancies in the third trimester.

RISK FACTORS

Table 3 presents the risk factors for placenta previa.

Maternal		*Fetal*
• Advanced maternal age. • Multiparity.	• Smoking. • Previous uterine surgery or instrumentation.	• Multiple pregnancy.

PATHOPHYSIOLOGY

The pathophysiology of placenta previa is not clearly understood. The placenta is preferably implanted at the uterine fundus where there is the richest blood supply. Anatomical or scar lesions on the uterine cavity may contribute to the implantation of the placenta on the lower uterine segment.

CLINICAL PRESENTATION

Pregnant women with recurrent, painless maternal spotting or blood loss during late pregnancy should be suspected for placenta previa. The complete previa may present clinical signs during 26th to 28th week of gestation.

Fetal malpresentation is also accompanied with placenta previa due to the difficulty of the fetus to possess a cephalic presentation as the placenta mass occupies the pelvis.

DIAGNOSIS

The diagnosis of placenta previa is based on pregnancy clinical features but is confirmed by transvaginal ultrasound scanning (TVS). The visualization of the placental edge, with a partially full and consequently empty bladder, rule out the localization of the placenta. Table 4 summarizes the diagnosis of placenta previa.

Table 4. Diagnosis of Placenta Previa.

History	Recurrent, painless bleeding or spotting.
Examination	Abnormal fetal lie/presentation.
Confirmation	Transvaginal ultrasound scanning (TVS).

MORBIDITY AND MORTALITY

Placenta previa is followed by operative delivery and the risk concern of bleeding, anesthesia, and postoperative complications. Transfusion may be necessary when placenta accrete and postpartum hemorrhage initiates.

The placenta previa increases the risk in subsequent pregnancy for placenta accreta, increta, or percreta especially when cesarean delivery history exists. It increases also dramatically the risk for fetal mortality and morbidity due to maternal hemorrhage and prematurity. In developed countries the perinatal mortality rate is still 50-60 per 1.000 deliveries.

Transvaginal ultrasound should be employed for women suspected for placenta previa, near term. The outcome of this procedure will determine the exact placenta implantation and the type of delivery. Once the condition is diagnosed the preparative measures should include also the possibility of hysterectomy (category C).

TREATMENT

Pregnant women with placenta previa should avoid sexual intercourse during pregnancy and be prepared for a premature delivery by the use of steroid administration to enhance fetal lung maturity and arrange for antepartum transfer to a tertiary care hospital if indicated. Every Rh negative woman should be treated with the administration of full dose Rh immunoglobulin when antepartum bleeding occurs (category B).

The goal of treatment is the supportive care until fetal maturity is acquired without inducing any harm on maternal and fetal health.

Home care for placenta previa is preferred since it reduces the length of antenatal hospital stay and has no disadvantages (category C). Cervical cerclage for symptomatic placenta previa may reduce the risk of premature delivery (category C).

Routine diagnostic tests for patients with significant vaginal bleeding should include maternal complete blood counts, maternal blood type and Rh factor, and coagulation studies. Transfusion is to be considered depending on maternal circulatory stability, duration of bleeding, and maternal hematocrit. Four units of blood should be cross-matched and be constantly available until delivery.

Maternal hospital admission must be individualized according to symptomatic placenta previa, gestational age, number and severity of bleeding episodes, and other factors, such as patient reliability and distance from the hospital.

Tocolytic therapy is indicated when fetal prematurity is significant, but the pregnant should be hospitalized in a tertiary care unit. This statement can not be supported as there are no randomized controlled studies to bring out its benefits (category B).

Vaginal delivery is not indicated because of the risks of hemorrhage, dystocia and premature placental separation. One exception maybe and that is a dead or abnormal fetus with a low grade placenta previa. Indications for operative delivery with available blood and all surgical anesthesia personnel in place is recommended when lifethreatening bleeding occurs or when bleeding persists or when the fetus is distressed. The possibility of placenta accrete in these case is increased and the woman should be advised —before surgical intervention— about possible hysterectomy, if bleeding is otherwise uncontrollable. General anesthesia has been associated with increased intraoperative blood loss and need for blood transfusion. Regional anesthesia appears to be a safe alternative (category C).

PLACENTAL ABRUPTION

Placental abruption is the premature separation of the placenta from the uterine wall. It is associated with retro-placental or peripheral margin bleeding when the blood tracks down between the membranes.

EPIDEMIOLOGY

Placental abruption occurs in approximately 1-2 % of all pregnancies.

RISK FACTORS

The risk factors are shown in table 5.

Table 5. Risk Factors of placental abruption.

Maternal	*Fetal*
• Hypertension (50% of cases). • Trauma. • Sudden decompression of an overdistended uterus. • Multiparity. • Cigarette smoking, cocaine use. • Antiphospholipid antibody syndrome. • Folate deficiency. • Unexplained elevation of maternal plasma AFP.	• Multiple pregnancy. • Polyhydroamnios.

AFP: Alfa-Feto-Protein.

PATHOPHYSIOLOGY

Following placenta separation, bleeding through the vagina or in the amniotic cavity, or in the retroplacental area leads to clots formation. About 20 % of abruptions are occult. When the blood invades the myometrium then the so-called «Couvelaire» uterus is formed, which may result in postpartum hemorrhage. The consumption of clotting factors may lead to disseminated intravascular coagulopathy.

MORBIDITY AND MORTALITY

Placental abruption with severe hemorrhage is a potentially life-threatening complication. Furthermore, it increases the risk of prematurity, intrauterine growth restriction (IUGR), stillbirth and intrauterine demise. The perinatal mortality is as high as 300 per 1.000 complicated pregnancies and more than half of the perinatal losses are due to death before mother arrival at the hospital.

CLINICAL PRESENTATION

The main symptom of placental abruption is the pain. The abruption is often occult and resolves without any complications. If the separation is more extensive then results to vaginal bleeding that varies from a lifethreatening situation to fetal distress or demise. Concealed hemorrhage is accompanied with back pain, uterus irritability and tetanic contractions, Disseminated Intravascular Coagulation (DIC) and hypovolemic shock. Signs of shock start when blood loss exceeds 30 % of the total blood volume.

DIAGNOSIS

The use of fetal heart monitoring and uterine activity may allow emergency cesarean section and decrease fetal mortality (category C).

Ultrasound scanning is useful only in retroplacental clot or hemorrhage, and should not delay surgical intervention.

Complete blood counts, blood type and Rh factor, and coagulation studies and fibrinogen levels must be performed. Fibrinogen levels less than 150 mg/dl are diagnostic for coagulopathy. PT and aPTT may be prolonged, and platelets levels may be decreased. Four units of blood should be cross-matched and be constantly available until delivery. Table 6 presents the diagnostic signs of placenta abruption.

Table 6. Diagnosis placental abruption.

History	Painful bleeding.
Examination	Uterus tenderness and irritability.
Investigation	Fetal heart monitoring. Coagulation studies.

TREATMENT

The management of placenta abruption depends on the severity of the abruption and on fetal well being. Rh immunoglobulin should be offered in Rh negative patients. Small abruptions are often self-limited. Women with small abruption who are stable and have premature fetus in a good condition should be treated conservatively. Delivery at term may be succeeded.

For more severe abruptions maternal circulation stability and analgesia are priorities. If premature delivery is expected, the fetus should be treated by administration of steroid, to enhance fetal lung maturity and the pregnant woman should be transferred to a tertiary care hospital if indicated. Oxytocin augmentation is not contraindicated. Vaginal delivery is appropriate when an active rapid labor progress and satisfactory fetal heart monitoring exist. Amniotomy is recommended to prevent amniotic fluid embolus and accelerate labor.

Vaginal delivery is indicated for women presenting with severe abruption and fetal demise or alive fetus, as long as adequate progress is made and maternal status can be supported. (category C). Low segment cesarean section is required for obstetric indications, e.g., transverse lie etc, fetal distress, failure of labor progression or when hemorrhage is uncontrollable.

DIC should be managed with the under hematologist monitoring. Most of women with placental abruption and dead fetus will develop coagulopathy in contrast to women with live fetus. After fetus delivery fresh frozen plasma and platelet transfusion should be administrated to the woman.

UTERINE SCAR DISRUPTION

Uterine scar disruption is the discontinuation of uterine wall that can vary from a thinning of the uterine wall to a complete rupture with partial or complete appearance of fetal parts or placenta into the abdominal cavity or without fetal appearance.

EPIDEMIOLOGY

Uterine rupture is reported to count for 0,3-1,7% among women with a history of a uterine scar.

CAUSES

The causes of uterine rupture are shown in table 7.

Table 7. Causes of uterine rupture.

• Cesarean delivery.	• Congenital uterine anomaly.
• Uterine curettage or perforation.	• Uterine overdistension.
• Trauma.	• Vigorous uterine pressure.
• Inappropriate oxytocin usage.	• Trophoblastic neoplasia.
• Previous uterine surgery.	• Placenta, or placenta increta or percreta.

CLINICAL PRESENTATION

Uterine scar disruption may be obscure without clinical signs or it is presented with vaginal bleeding, abdominal pain and cessation of contractions. When the bleeding is severe, it may lead to fetal demise and when the rupture is complete, fetal parts may be palpable.

MANAGEMENT

Operative delivery is necessary for uterine scar disruption. Cesarean delivery is acceptable if during the progression of a vaginal delivery on a previously scarred uterus, clinical setting of sudden uterine rupture appears (category C).

SUMMARY

Vaginal bleeding in late pregnancy is the clinical sign for many pregnancy complications that can be life threatening for the mother and the fetus. The timely and correct diagnosis and appropriate management may reduce maternal and perinatal morbidity and mortality.

SUMMARY TABLE OF RECOMMENDATIONS

Category A

- Routine late pregnancy ultrasound, should be maintained for women suspected for placenta previa and not for low risk pregnancies.

Category B

- Tocolytic therapy in a tertiary hospital, in cases of third trimester bleeding, appears to be a rather safe procedure, although no clear benefits have been so far documented.
- Full dose of Rh immunoglobin, in Rh negative women, should be administrated following every antepartum bleeding episode.

Category C

- Home care for symptomatic placenta previa seems to be an important parameter for its outcome.
- Cervical cerclage can lead to a term delivery with a near normal neonate.
- In cases of placenta accrete, early consultation, intervention and management, should be considered.
- Fetal heart monitoring decreases fetal mortality caused by placental abruption.
- Vaginal delivery can be advised for cases of placenta abruption without maternal shock or fetal distress or in dead fetus.
- Color flow Doppler ultrasound may be useful modality for diagnosis of vasa previa.

LATE PREGNANCY VAGINAL BLEEDING ALGORITHMS

A. EMERGENCY ASSESSMENT

On admition, assess maternal circulation stability and prepare for resuscitation:

- Oxygen.
- Two large-bore intravenous access.
- Cross-match blood and intravenous fluids.
- Coagulation profile.
- Ready for emergency cesarean section.
- Fetal heart monitoring.
- Exam maternal abdomen/Vaginal examination is absolutely contraindicated.

B. STABLE MATERNAL CONDITION

MAIN COMPLAINT

- **Bleeding -** estimate the volume.
- **Repeated bleeding** is associated most with placenta previa.
- **Painful bleeding** is associated most with placenta abruption.
- **Post-coital bleeding** is associated most with placenta previa cervical ectropion or cervical polyp, or carcinoma.

HISTORY

Index Pregnancy

- Fetal maturity.
- Ultrasound scan information.
- History of intervention or injury.

Obstetric history

- Parity.
- Previous LPB episode.

Gynecological history

- Recent Pap-smear.
- Uterine surgery.

Medical history

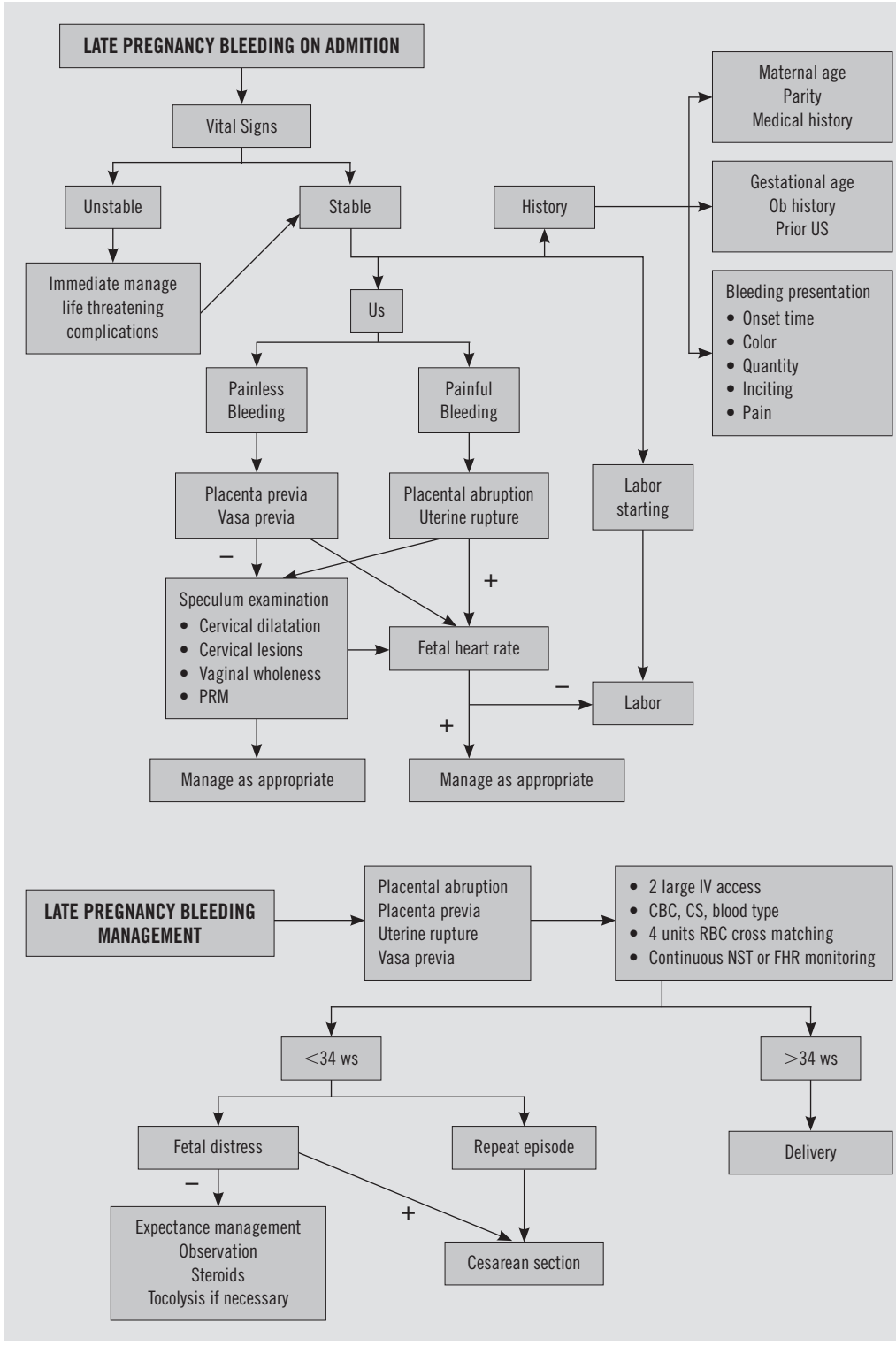
- Increased risk of abruption with hypertension.
- Increased risk of abruption with antiphospholipid antibody syndrome.

Drug history

- Crack cocaine can increase the risk of an abruption.
- Cigarettes increase the risk of both abruption and previa.

Social history

- High parity and poor nutrition increase the risk for abruption.


LATE PREGNANCY BLEEDING ON ADMITION
Vital Signs
Unstable
Stable
Immediate manage life threatening complications
Us
History
Maternal age
Parity
Medical history
Gestational age
Ob history
Prior US
Bleeding presentation
• Onset time
• Color
• Quantity
• Inciting
• Pain
Painless Bleeding
Painful Bleeding
Placenta previa
Vasa previa
Placental abruption
Uterine rupture
Labor starting
–
+
Speculum examination
• Cervical dilatation
• Cervical lesions
• Vaginal wholeness
• PRM
Fetal heart rate
–
+
Labor
Manage as appropriate
Manage as appropriate
LATE PREGNANCY BLEEDING MANAGEMENT
Placental abruption
Placenta previa
Uterine rupture
Vasa previa
• 2 large IV access
• CBC, CS, blood type
• 4 units RBC cross matching
• Continuous NST or FHR monitoring
<34 ws
>34 ws
Fetal distress
Repeat episode
Delivery
–
+
Expectance management
Observation
Steroids
Tocolysis if necessary
Cesarean section

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Prevention of premature birth

CHAPTER 21

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INTRODUCTION

Preterm labor (PTL) is together with premature rupture of membranes (PROM) the main cause for late abortions and premature birth (particularly for the early preterm births). Infants who are born prematurely, that means before 37 gestational weeks (gw) and/or have a low birthweight (< 2.500 g) suffer a higher risk of mortality and morbidity than infants born at term. Despite progress in perinatal medicine, the rate of prematures is increasing in developed countries, e.g. in Germany it has increased from 7,1 % in 2001 to 9,4 % in 2004 and in the USA from 11,9 % in 2001 to 12,3 % in 2003. This may be due to various reasons, e.g. increasing age of the mothers and more pregnancies after infertility treatment.

Mortality and morbidity increases rapidly with decreasing birthweight. Serious complications caused by prematurity are respiratory distress syndrome, intraventricular hemorrhage, leucomalacia and necrotising enterocolitis. Late sequelae include cerebral palsy, hearing and visual deficits, epilepsy and lack of intelligence. A further problem, which is particularly relevant for the developing countries, is the increased susceptibility to infections. The prevention of prematurity and low birthweight infants is therefore an important task for obstetricians both in the developing and in the industrial countries.

CAUSES AND PATHOPHYSIOLOGY

A number of reasons are known to cause preterm labor (see table 1). Lockwood and Kuczynski (1999) divided most of the known causes for preterm labor and/or PROM into four pathogenetic processes:

- Activation of the maternal or fetal hypothalamic-pituitary-adrenal (HPA) axis.
- Decidual-chorioamniotic or systemic inflammation.
- Decidual hemorrhage.
- Pathological distension of the uterus.

The various patho-mechanisms initially follow different pathways —transmitted by substances such as hormones (e.g. CRH), interleukines and prostaglandines— merge later on and cause changes in the cervix, leading to premature contractions and/or premature rupture of the membranes and finally to premature birth.

As far as effective preventive measures are concerned, most of the avoidable causes, particularly before 32 gestational weeks, are to be found among patients with ascending genital infections, patients with urinary tract infection and sometimes with other infections (e.g. systemic infection such as Malaria end even Parodontitis). Therefore we suggest to have the main emphasis on prevention of infections, while if necessary and possible not neglecting other causes (e.g. psychco-social stress). In this way we have great chances to reduce particularly early prematurity at the presently highest possible extent.

Table 1. Anamnestic or other signs of increased risk of late abortion or premature birth.

1. Previous pregnancies and/or operations	• One or more premature deliveries (less than 37 + 0 gw). • One or more late abortions (more than12 + 0 gw). • Two or more artificial abortions. • Multipara with more than 4 deliveries. • Conisation.
2. Present pregnancy	• Poor social status. • Excessive professional stress and/or family demands. • Patients' age is under 18 or over 34. • Multiple pregnancy. • After infertility treatment. • Smoking. • Regular alcohol consumption or use of other drugs (also excessive consumption of stimulants, such as coffee). • Parodontitis.
3. Findings during the course of the pregnancy	• Vaginal-cervical-infection. • Uterine bleeding. • Placenta praevia. • Urinary tract infection, also asymptomatic. • Polyhydramnion. • Premature labor. • Critical cervix state. • Diabetes mellitus (severe form). • Serious organic disease or fever of the mother.

RISK ASSESSMENT

In addition to the prenatal care as customary in the individual country, we recommend as measures for the prevention of premature birth applicable on a broad scale:

- The **estimation of the potential risk factor** (see table 2) and appropriate therapy with emphasis on prophylaxis or early detection of infections by the physician or midwife (see below).

Table 2. Risk and symptoms of prematurity, prophylactic and therapeutic measures and prognosis

Kind of risk	*Symptoms and findings*	*Prophylactic and therapeutic measures*			*Chances of success*
1. Anamnestic risk	≥ 1 miscarriages or very small prematures	Early Total Cervix Occlusion			Best prognosis.
2. Risks in present pregnancy *a)* Disturbance of vaginal milieu	**pH↑ and/or «dysbiosis» in native preparation, but:** – No evidence of Bacterial Vaginosis. – No indication of ascension of bacteria. – No increased contractions. – Normal cervical state.	Only here treatment with Lactobacillus acidophilus alone is recommended (maybe combined with direct acidifying therapy).			
b) Other risks	– Multiples (twins, triplets, etc.). – Organic disorders, parodontitis, etc. – Certain pressure situations (professional or private, physical or emotional).	– Possibly Early Total Cervix Occlusion[1]. – Appropriate medical treatment. – Supportive measures (if necessary and possible).			In most cases good prognosis, according to the situation.
3. Infection: genital or urinary tract infection	Microscopically or culturally proved vaginal infection (such as Bacterial Vaginosis, Trichomoniasis, Candidiasis).	Local therapy: • Antiseptics. • Antibiotics. • Other chemotherapeutics (such as Metronidazole).	Recommendation of rest and measures for relaxation (among others, for improving immunological conditions).	«after treatment» with lactobacillus preparation in case pH↑ (maybe combined with direct acidifying therapy).	Still good prognosis.
	– Evidence of Chlamydia in cervix or urethra. – Evidence of bacteria at the lower egg-pole (extra-amniotic isthmical space). – Significant bacteriuria.	Systemic antibiotic therapy + local acidifying therapy			
4. Symptoms of prematurity	– **Preterm labor and/or critical cervical state.** – Local infection in vagina, cervix or at lower egg-pole (extra-amniotic isthmical space). – Signs of inflammation (e.g. CRP↑, leucocytosis).				Increasingly unsuccessful.

1. Schulze (publication in preparation) achieved very good results with the ETCO, when performed in all pregnancies with multiples; therefore an ETCO might be considered.

- **Plus** if possible the Self-Care-Program for pregnant women (including information about risk factors and regular self measurement of the vaginal pH by the pregnant woman herself) after Saling (see below).
- **If necessary and possible** measures regarding the other risk factors mentioned in table 1 should also be undertaken.

SCREENING MEASURES

Every pregnant woman should be asked about and screened for:

- Signs of pre-infection (disturbance of the vaginal milieu) or infection of the genital tract.
- Signs of urinary tract infections (already asymptomatic UTI increase the risk).
- Signs of other infection (systemic or local).

It is not necessary to make a full examination each time, in particular it is not necessary to have regular microbiological examinations. In most cases the anamnestic history plus vaginal examination (discharge, reddening, etc.) plus measurement of the pH and, if possible, examination of the native preparation provide sufficient information.

The **measurement of the vaginal pH-value** is particularly important. An increase in the pH-value ($\geq$4,2 if measured with pH-meter, $>$4,4 if measured with indicator paper) can point to:

- A **disturbance in the vaginal milieu**, the so-called «dysbiosis», which indicates a disturbance of the «protective lactobacilli-system» (Saling et al. 2006a) and therefore an increased susceptibility for ascending genital infections.
- A **bacterial vaginosis.** Diagnostic clinical criteria (Amsel criteria) in addition to an increased pH-value ($>$4,5) in vaginal secretion are: homogenous (grey-white, not flocky) discharge, fishy odor of the vaginal fluid (especially after the addition of 10% potassium hydroxide solution) and evidence of cluecells. 3 of these 4 criteria must be present to ensure the diagnosis.
- More rarely to another infection. If other infections are suspected, an appropriate examination should be carried out.

OTHER SCREENING MEASURES

- **Risk estimation by vaginal ultrasound.** Transvaginal sonographic measurement of cervical length is an effective way of identifying pregnancies at high risk of preterm delivery (PTD). A cervical length of more than 30 mm is rather reassuring, whereas a length of less than 20 mm constitutes a high risk.
- **Monitoring of uterine contractions and CTG.** The likelihood of preterm delivery is higher with an increased frequency of uterine contractions, but tocography has not been useful for reduction of preterm births in randomised trials. Also an increased uterine activity would rather be a «late marker» than a screening measure for prevention.
- Elevated **fetal Fibronectin (fFN)** has been shown to be a predictor of PTD, and an increased risk of subsequent diagnosed maternal and fetal infection. However, meta-analyses did not show a benefit of treating generally women with elevated fFN (Varma

et al. 2006), only in a subgroup that had both, either bacterial vaginosis or trichomonas vaginalis and a positive fFN.

- **CRP** as unspecific marker for infections is often measured, but it is not so much a screening measure, but rather a «late» marker, e.g. for an already ascended infection.

CONSERVATIVE THERAPEUTIC MEASURES

GENERAL MEASURES

- As **smoking** may lead to both small-for-gestational-age infants and prematurity, patients who smoke should be informed about these risks, encouraged and supported in their efforts to stop smoking.
- Both **physical strain** (e.g. hard manual work) or **psychosocial strain** may increase the risk of prematurity. Many countries have implementing guidelines that protect pregnant women at work. It is not that easy to reduce psychosocial strain, but if necessary and possible, measures to give the pregnant woman support should be undertaken.

TREATMENT OF DISTURBANCES OF THE VAGINAL MILIEU AND INFECTIONS

The treatment will be performed according to the situation. Here are just the most common indications:

- **Disturbances of the vaginal milieu** without concrete signs of bacterial vaginosis or specific infection: lactobacillus preparations provide the best treatment in these cases (If available, preparations that contain only H_2O_2 producing lactobacilli, should be preferred).
- **Bacterial vaginosis** should be treated either locally or systemically with Metronidazol or Clindamycin.
- **Specific urogenital infections** should be treated accordingly.
- Cases with apparent urogenital infection or positive inflammation parameters (e.g. CRP) **and already present symptoms of threatened premature birth** such as premature uterine contractions and/or critical ultrasonic findings of the cervix: Here a systemic antibiotic therapy is often the method of choice. In addition other measures such as tocolysis, rest, etc. will be indicated according to the situation.
- **Systemic infections:** specific therapy.
- **Infection and fever:** If higher fever is present, usage of indometacine should be considered to prevent prostaglandine related effects on the uterus (triggering of labor and softening/ripening of the cervix). This treatment might have serious side effects, though (closure of the ductus arteriosus, oligohydramnion). Therefore indometacine must be limited for women before 28-30 gw, without intrauterine growth restriction and normal amniotic fluid volume. It should not be administred longer than 48 (-72) h. (please compare Di Renzo et al. 2006) E.g. acetylsalicylic acid is also possible, but has a higher risk of bleeding. Please note: Paracetamol hardly inhibits the prostaglandine synthesis.
- **Parodontitis:** dental therapy should be performed, if possible before the pregnancy.

OTHER CONSERVATIVE MEASURES

- **Application of progesterone:** Meta-analyses have shown a beneficial role for prophylactic progesterone supplementation in high-risk pregnancies (previous PTD). But still more research is necessary, before one can recommend it generally for high-risk asymptomatic pregnancies. (Varma et al. 2006.)
- **Prophylactic tocolysis:** Meta-analyses evaluating prophylactic or maintenance oral tocolytics in high-risk pregnancies have not shown any reduction in PTD or PTL (Varma et al. 2006). Nevertheless tocolysis has its value to gain time for eventually necessary lung maturation therapy.
- **Management of PROM** see chapter 18, of intrauterine growth restriction see chapter 10 and of Preeclampsia/eclampsia see chapter 12.

OPERATIVE THERAPEUTIC MEASURES: EARLY TOTAL CERVIX OCCLUSION (ETCO) VERSUS CERCLAGE

CERCLAGE

The risk of PTD is already increased after one previous PTD (see tables 1 and 2) and increases with the number of previous PTD. The **cerclage** (from our point of view an outdated procedure, see next paragraph) is a widespread measure for high-risk pregnancies, particularly after one or more previous premature births or late abortions and also in cases with shortened cervical length. As elective prophylactic measure in cases with anamnestic risk, it has been shown to be effective only in particular high risk groups (e.g. three or more preterm births, see Varma 2006). In contrast, in cases with shortened cervical length and therefore indicated cerclage one meta-analysis showed benefits of cerclage, whereas another meta-analysis didn't.

EARLY TOTAL CERVIX-OCCLUSION (ETCO)

In cases with one or more previous preterm births and/or late abortions, we recommend the Early Total Cervix-Occlusion (ETCO). «Early» means at about 12 gestational weeks and with almost normal anatomical state of the portio. The ETCO has proved to be the best prophylactic countermeasure in cases when an ascending vaginal infection was the cause, or when no other explaining cause was found. (Saling et al. 2005b, 2006b). It has to be emphasized that the ETCO is quite different from a cerclage. The latter only tightens the cervix (and microbes may ascend anyway), whereas the ETCO is a complete occlusion and barrier against the ascension of organisms (see figure 1). In this way, the chance of giving birth to a surviving infant increased to 80% in women who had previously had 2 or more miscarriages and who had only a 17% chance according to our statistics. Whereas after Cerclage there was a survival rate of only 26%. (Saling et al. 2005b, 2006b). The good results of the ETCO have also been proven by a multi-center inquiry in Germany and up to now, the ETCO is performed in over 40 clinical units in Germany, Austria and Switzerland.

In cases with no previous PTD, but shortened cervical length we would also rather recommend a Total Cervix Occlusion (TCO) than a cerclage, although to our knowledge there is

no study yet comparing those measures for this indication, but theoretical thought suggests the TCO, as it both prevents ascending infections and gives some mechanical support. The ETCO/TCO is explained in detail on **www.saling-institut.de** where one can also download a video about the operative technique.

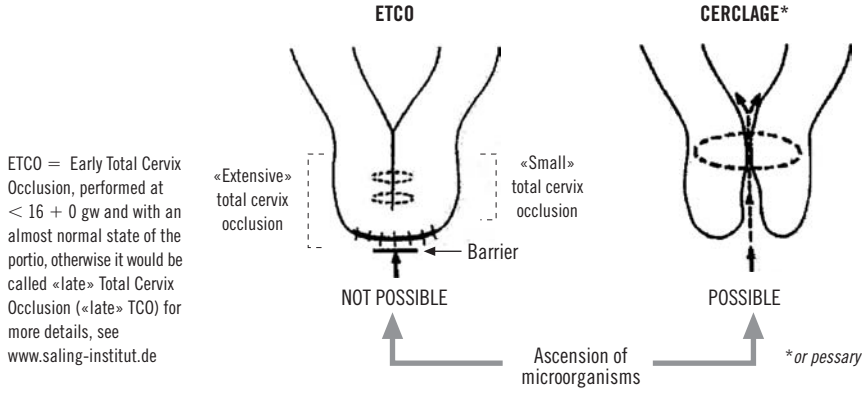

Fig. 1. Comparison between Cervix Occlusion and Cerclage.

Multiple pregnancies (please compare chapter 13) are at particular risk for ending with premature labor or PROM. Schulze (publication in preparation) recommended and performed an ETCO in multiple pregnancies without any other risk factors with excellent results. It is too early to decide, whether in multiple pregnancies the Self-Care-Program (see below) is sufficient, or whether the ETCO gives an additional benefit. But we think in cases with multiple pregnancies with additional risk (e.g. after in-vitro-fertilization) it is worthwhile to consider an ETCO.

PREVENTION BY THE PREGNANT WOMEN THEMSELVES

We recommend that all pregnant patients are informed about risk factors for prematurity and about warning signs (see table 3). If the financial resources allow, they should additionally measure their vaginal pH themselves from the beginning of the pregnancy (Self-Care-Program for pregnant women, for more details see www.saling-institut.de). This can be performed either with the test strip of MERCK (No. 1.09542) or using a CarePlan®VpH-test-glove which we developed in collaboration with a company. We recommend this particular test strip, res. test-glove, as they are easy and reliable to read: The indicator should be compared with a color chart and the pH-value read. If the pH is normal, this means 4.4 or less the indicator turns yellow. If the pH is measured twice a week by the patient herself the intervals between measurements are greatly reduced compared to the usual prenatal care examination.

If any warning signs occur or a pH-value of 4,7 or more is measured, the pregnant patient is advised to consult her doctor as soon as possible to find out the reason, and if necessary start treatment. Other important potential risk factors which can be detected by the patient herself are listed in the information brochure of the test gloves. The most important are listed in table 3:

Table 3. Warning signs of threatened premature birth (as listed in our information brochure for pregnant women).

• Changes in vaginal discharge.	• Vaginal bleeding or spotting.
• Burning and itching in the intimate regions.	• Diarrhea.
• Signs of urinary tract infection.	• Fever.
• Menstruation-like pains in the abdomen.	• Suspicion of leakage of amniotic fluid.

RESULTS

With the Self-Care-Program for pregnant women it is possible to considerably reduce the rate of prematurely born children, particularly of the children at high risk (those born prior to 32 gw, reps. $<$1.500 g). This has been confirmed both in our own studies (Saling et al. 2001, 2005a, 2006a) as well as in two prospective campaigns, one of them in an entire state in Germany, in Thuringia. In the state of Thuringia a significant reduction of early prematurity from 1,58% to 0,99%, and regarding low birthweights a significant reduction of cases in all groups was achieved (Hoyme et al. 2004). Also in pregnancies with multiples the rate of premature births was considerably reduced (Hoyme et al. 2005, Saling 2005a).

CONCLUSION

Prevention of preterm birth is an important issue both in developed and developing countries. As measures applicable on a broad scale, we suggest to have the main emphasis on prevention or detection of infections —while if necessary and possible not neglecting other causes. In this way we have great chances to reduce particularly early prematurity at the presently highest possible extent.

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Fetal demise

CHAPTER 22

Z. Papp

DEFINITION AND EPIDEMIOLOGY

In its narrower sense, intrauterine fetal demise (IUFD) is the death of the fetus in the second or third trimester of pregnancy before the onset of labor. Synonyms include (antepartum/antenatal) intrauterine fetal death and stillbirth. In a broader sense, deaths occurring during labor (intrapartum deaths) are also regarded as intrauterine demise. Not quite correctly, early (first-trimester) miscarriages are sometimes included in this term too. Fetal demise complicates about 1 % of pregnancies. Stillbirths are much less common with increasing gestational age. More than half of the cases occur before 28 weeks and almost 80 percent occur before term. With the advent of obstetric ultrasonography, the rate of stillbirths that are caused by lethal anomalies has dramatically decreased since many of them are now «prevented» by termination of pregnancy.

ETIOLOGY

In the majority of cases, the cause of fetal demise is not known or cannot be determined, although a number of stillbirths previously categorized as unexplained can now be attributed to some specific etiology. An autopsy performed by a pathologist with expertise in fetal and placental disorders, assisted by experts of maternal-fetal medicine, pediatrics, neonatology, and genetics, often identifies the cause of death. However, determining the etiology of fetal demise in preterm infants still presents a challenge.

Causes of fetal death can be categorized as fetal, placental, or maternal, although a sharp distinction between these groups is usually impossible (table 1).

Fetal causes include congenital anomalies, malnutrition, anti-D-isoimmunization, non-immune hydrops, and infections. From the latter, many cases of stillbirth can be attributed to congenital syphilis. Furthermore, parvovirus B19, cytomegalovirus, rubella, varicella, and listeriosis can also cause lethal infections of the fetus.

Table 1. Categories and causes of fetal death[2]

Fetal (25-40 %)	*Placental (25-35 %)*	*Maternal (5-10 %)*	*Unexplained (25-35 %)*
• Chromosomal anomalies. • Nonchromosomal birth defects. • Nonimmune hydrops. • Infections - viruses, bacteria, protozoa.	• Abruption. • Fetal-maternal hemorrhage. • Cord accident. • Placental insufficiency. • Intrapartum asphyxia. • Placenta previa, vasa previa. • Twin-to-twin transfusion. • Chorioamnionitis.	• Antiphospholipid antibodies. • Diabetes. • Hypertensive disorders. • Trauma. • Abnormal labor. • Sepsis. • Acidosis. • Hypoxia. • Uterine rupture. • Postterm pregnancy. • Drugs.	?

Among *placental causes,* placental abruption is the most common single cause of fetal death. Placental infection and chorioamnionitis rarely occur without fetal infection. However, malaria and tuberculosis may affect the placenta without signs of fetal infection. Extensive and centrally located placental infarcts, which are frequently associated with hypertensive disorders, especially preeclampsia, can be fatal by causing placental insufficiency or, if followed by hemorrhage, by leading to placental abruption. Fetal-maternal hemorrhage usually occurs after severe maternal trauma, while twin-to-twin transfusion is a major cause of stillbirth in monochorionic multifetal gestations. Stillbirth in the third trimester is most frequently caused by umbilical cord accidents. Although fetal mortality is increased in the presence of umbilical cord knots, this does not predict fetal death by itself. Decreased amounts of Wharton's jelly, especially at the fetal and placental insertions, can result in occlusion of blood flow if the vessels are twisted sufficiently. Insertion abnormalities such as marginal and velamentous insertion can also lead to stillbirth since these vessels are susceptible to folding, torsion rupture and inflammation, especially if they are located at or near the level of the internal cervical os.

Hypertensive disorders and diabetes are the most common *maternal causes* of fetal death. Maternal obesity is also an important risk factor of fetal demise, partly through the increased rate of hypertension among affected women. Pregnancies of women with lupus anticoagulant and anticardiolipin antibodies may be complicated by decidual vasculopathy, placental infarction, intrauterine growth restriction, recurrent abortion, and stillbirth. Certain types of hereditary thrombophilia (especially factor V Leiden mutation, protein C and S deficiency, prothrombin G20210A mutation, and hyperhomocysteinemia) also increase the risk of fetal death.

As a rule of thumb, we can state that the major causes of pregnancy losses are genetic in the first, infections in the second, and cord accidents in the third trimester.

SIGNS AND SYMPTOMS

Clinically, the first sign of fetal death is usually the absence of fetal movements, which may be preceded by a short period of hyperactive movements of the agonizing fetus. Later on, the patient may complain that her abdomen has become smaller or that her womb has «descended». After 1 or 2 weeks, she may feel some unpleasant metallic taste in her mouth.

In about 80 % of cases, spontaneous labor will start within 2 to 3 weeks of fetal death. In analogy to missed abortion, *missed labor* is defined as the absence of spontaneous labor within this time frame.

DIAGNOSIS

Fetal heart tones cannot be detected using a *Doppler device*. *Ultrasonography* confirms the absence of fetal movements and cardiac activity.

On *amnioscopy,* thick, greenish amniotic fluid can be seen through the fetal membranes. As time passes, its color turns into reddish-brown. In cases of sudden fetal death, however, the amniotic fluid may remain clear.

X-ray examination of the stillborn fetus may reveal overlapping of cranial bones *(Spalding's sign),* extreme bending of the spine *(Kehrer's sign),* bubbles in the heart, aorta and umbilical cord (due to intravasal gas formation) as well as the classical Buddha position and the glory-like rim around the fetal head. These signs can also detected by ultrasound examination, which is the method of choice for confirmation of fetal demise.

POTENTIAL COMPLICATIONS

Fetal death does not generally pose a health risk to the mother within 2 to 3 weeks unless it is caused by placental abruption. Carrying a dead fetus for a longer time, however, increases the risk of coagulation disorders. The condition, known as *dead fetus syndrome,* is a special form of disseminated intravascular coagulation (DIC), which occurs in 10 to 20 % of cases after 4 or more weeks of fetal death. It is probably caused by the release of thrombogenic substances from placental tissue that enter the maternal circulation, leading to severe bleeding disorders during delivery.

MANAGEMENT

Although spontaneous onset of labor occurs within 2 to 3 weeks in about 80 % of cases, *watchful expectancy* is not always an acceptable approach because of the emotional burden of carrying a dead fetus, the possibility of chorioamnionitis and the risk of DIC. *Induction of labor* is therefore advisable if spontaneous contractions do not begin within a few days after intrauterine death. Cervical ripening with the use of prostaglandin E_2 vaginal gel or suppositories, followed by amniotomy and oxytocin infusion is the method of choice. The use of epidural analgesia is preferred for pain relief, which also has a favorable effect on cervical dilatation.

For the prevention of DIC, fibrinogen levels should be monitored closely along with repeated hematocrit and platelet counts as well as measurements of prothrombin and partial thromboplastin times. Mildly decreased fibrinogen levels associated with slightly elevated prothrombin and thromboplastin times in the absence of bleeding do not usually necessitate transfusion therapy. If the coagulation defect is more severe of if bleeding is observed, fresh frozen plasma or specific coagulation components should be given before any obstetrical intervention. Episiotomy is usually avoided during vaginal delivery. Perforation of the fetal head, decapitation, cleidotomy or evisceration of the fetus might be necessary in very rare cases. Internal podalic version followed by breech extraction may be

performed if the fetus is in transverse lie. Cesarean section should be done if maternal indications (e.g., placental abruption, heart disease etc.) are present.

EVALUATION OF THE STILLBORN

In addition to emotional support, determining the cause of fetal death can also help in finding the necessary therapy or intervention to prevent a similar outcome. The fetus, placenta, and membranes should be examined thoroughly at delivery (table 2). Photographs and a full radiograph of the fetus are particularly important if the parents decline a full autopsy.

Table 2. Protocol for examination of stillborn infants[2].

Infant description	• Malformations. • Skin staining.	• Degree of maceration. • Color - pale, plethoric.
Umbilical cord	• Prolapse. • Entanglement - neck, arms, legs. • Hematomas or strictures.	• Number of vessels. • Length. • Wharton's jelly - normal, absent.
Amniotic fluid	• Color - meconium, blood. • Consistency.	• Volume.
Placenta	• Weight. • Staining - meconium. • Adherent clots.	• Structural abnormalities - circumvallate, accessory lobes, velamentous insertion. • Edema - hydropic changes.
Membranes	• Meconium - stained or cloudy.	• Thickening.

If certain types of fetal or placental chromosome disorders are revealed by cytogenetic studies of the stillborn infant, parental karyotyping may also be necessary (table 3). The best tissue for chromosomal analysis is the fascia lata of the fetus. Also, a total of 3 mL of fetal blood should be obtained from the umbilical cord (preferably) or by cardiac puncture. It is of note, however, that it is often impossible to establish a full karyotype in cases with prolonged

Table 3. Procurement of samples for chromosomal and genetic studies[1]

- Obtain consent to take skin, eye, body fluids, and other tissue samples (separate from autopsy consent).
- For cytogenetic and molecular genetic studies, the following samples are acceptable:
  - Umbilical cord blood (3 mL).
  - Skin with attached dermis (1 cm^2).
  - Fascia from thigh, inguinal region, or Achilles tendon (1 cm) especially when maceration of the skin is present.
  - Kidney, skeletal, muscle, liver, lung, and gonads, if indicated.
- Samples should be obtained using sterile techniques as soon as possible.
- Umbilical cord blood should be placed into sterile tube with heparin.
- Tissue samples should be placed in appropriate sterile medium obtained from cytogenetic laboratory or in normal saline if medium is not available. Do not use fixative solutions (e.g., formaldehyde).
- Samples should be kept at room temperature.
- Freeze a 1 cm tissue sample.

intrauterine retention. Fetomaternal hemorrhage can be detected by identifying fetal erythrocytes in maternal blood *(Kleihauer–Betke test)*. This blood sample can be also tested for antiphospholipid antibodies, antibodies against blood group epitopes and lupus anticoagulant as well as for markers of hereditary thrombophilias. Toxoplasma, cytomegalovirus, rubella, and parvovirus studies, and cultures for Listeria may also be indicated.

Compared with all other analyses, a complete autopsy usually yields much more information on the cause of fetal demise, which is why parents should be encouraged to allow full autopsy of the fetus.

PSYCHOLOGICAL ASPECTS

Special attention should be given to women experiencing a stillbirth because of the increased risk for postpartum depression. Emotional support has a very important role in the follow-up of cases with fetal demise. The patient should be isolated from breastfeeding women and ablactation should be started as soon as possible after delivery.

PREVENTION OF RECURRENT STILLBIRTH

Hereditary disorders as well as some maternal conditions, such as diabetes, chronic hypertension, and hereditary thrombophilias increase the risk of repeated stillbirth. In general, earlier losses are associated with a higher risk of recurrence. Knowledge of a hereditary cause may warrant prenatal diagnostic procedures in subsequent pregnancies, such as chorionic villus sampling or amniocentesis. Strict glycemic control starting from the preconceptional period is in order for patients with disorders of carbohydrate metabolism. Prophylactic doses of low-molecular-weight heparin, administered to patients with known thrombophilic conditions throughout their subsequent gestation, can prevent recurrent pregnancy loss. Low-dose aspirin therapy may be effective in preventing severe preeclampsia. As a general rule, antepartum surveillance should begin earlier in women with a history of stillbirth, including regular non-stress tests (NST) and flowmetric studies if indicated by abnormal NST tracings or reduction of fetal movements.

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LABOUR

CHAPTER 23

Management of labour in low-risk pregnancies

J. Alonso | C. Sosa | A. Bianchi

INTRODUCTION

Birth is the most challenging physiological process for the human being. Even in a low risk pregnancy, the chance that complications that may compromise fetal or maternal health and require skilled intervention may appear is around 15 per cent. It is widely accepted that a low risk labour can be defined only retrospectively when the following conditions are met: healthy mother, single fetus, normal unscarred uterus, spontaneous onset between 37 and 42 weeks gestation with intact membranes, vertex presentation, normal duration and evolution of all stages (cervical dilatation, fetal expulsion and delivery of the placenta), unstained amniotic fluid, normal fetal heart rate throughout the process, fetal weight between 2.500 g and 4.000 g, delivery of a vigorous baby without congenital defects and no respiratory distress, expulsion of a complete placenta and membranes, normal maternal blood loss, and no complications for the mother or the newborn in the puerperium.

The fact that even on a low risk labour (at onset) complications may unexpectedly appear has made the World Health Organization and FIGO recommend that every labour should be assisted by qualified health providers and in a setting that allows for immediate medical intervention (availability of drugs, blood for transfusion and equipment for emergency surgery), or timely and appropriate transfer of the laboring mother is granted. Every labour is a risk situation. Nevertheless, in most cases labour is a natural process that may be altered by medical interventions that are not required. This statement applies specifically to low-risk pregnant women in labour and, quoting J. Hofmeyr, «the safest way to help laboring women is to respect nature and not to interfere with spontaneous events unless there is clear evidence that to do so would be beneficial».

This chapter will review the most frequent interventions during the three stages of labour that have been evaluated in order to provide guidelines for the management of labour in low-risk pregnant women. Precautionary mesures have to be taken in order to prepare the appropriate setting and the eventual need for emergency transfer to an adequately equipped hospital facility.

FIRST STAGE OF LABOUR

PUBIC SHAVING AND ENEMAS

Pubic shaving at early stages of labour was formerly believed to decrease the risk of infection. Two controlled trials were unable to detect any beneficial effect of this intervention. In the same way, there is not enough evidence to support the use of enemas after the admission of the pregnant woman in labour. No effects on the duration of labour, neonatal infection or perineal wound infection were found in a systematic review of this standard practice. Therefore, routinely administration of enemas in women in labour confers no benefit and should not be included as part of the obstetrical regular intervention given to pregnant woman in labour.

RESTRICTION OF ORAL INTAKE AND ROUTINE INTRAVENOUS INFUSIONS

Although fasting is commonly used to reduce stomach contents, the restriction of food and drink during labour may result in dehydration and ketosis. There is weak evidence that has shown that withholding food and drink during labour does not ensure an empty stomach. It seems that the use of a low residue, low-fat diet such as tea, fruit juice, cooked fruits and plain biscuits may be a reasonable alternative, and only in the case of a high risk pregnant women fasting should be maintained during labour.

Many randomized controlled trials have evaluated the use of intravenous glucose solutions during labour. The resulting increased blood sugar level in the mother is followed by an increase of insulin in the mother and the fetus, a decrease in umbilical arterial blood sugar and increased levels of blood lactate in the newborn. The use of ringer lactate seems to be a better alternative when allowing women to eat and drink is not possible.

MATERNAL POSITION DURING LABOUR

Observational studies have shown that the supine position during labour may compromise blood flow in the uterus. On the other hand, standing and lying on the side are associated with greater contraction intensity and on average shorter labours than in women that remain on supine position.

Promoting the free choice of women to adopt the position each one of them finds most comfortable, changing position at will, or to walk, sit or lie in bed seems to be the best approach.

EARLY AMNIOTOMY

The use of early amniotomy leads to a reduction of between 60 to 120 minutes in the duration of labour (on average), however, there is evidence that at the same time there is a trend to increase the number of early decelerations of the fetal heart rate. From a recent systematic review, there is no clear evidence (protective or harmful) about the effect of early amniotomy on the condition of the neonate. Therefore, a policy of allowing spontaneous rupture of membranes, and the use of early amniotomy selected in an individual basis seems to be the most adequate approach, until new evidence is available.

CAREGIVER SUPPORT DURING LABOUR

A Cochrane systematic review that includes a total of 14 randomized controlled trials showed that a continuous social support (Doulas) during labour reduced the need of

medication for pain relief, operative deliveries, cesarean sections and depression in the newborn. There was also a reduction in the length of labour and an increased maternal satisfaction. The continuous support involved health care workers, lay people or family members.

FETAL MONITORING

The main objective of fetal monitoring during labour is to identify fetal hypoxia which may cause fetal death or neonatal morbidity and mortality. There are several methods used in clinical practice to evaluate the fetal status. Intermittent direct auscultation of the fetal heart with a Pinard stethoscope or similar, during and after a uterine contraction every 15 minutes during first stage of labour and every 5 minutes during second stage of labour has been used as the main method of fetal evaluation. This method has been replaced by the continuous assessment of the fetal heart rate through electronic monitoring with the use of external devices (Doppler ultrasound) and/or internal devices (electrocardiography). A systematic review compared the efficacy and safety of the use of routine continuous electronic fetal monitoring with the use of intermittent direct auscultation. The published data show a statistically significant decrease of neonatal seizures with continuous electronic fetal monitoring. However, no significant differences were observed in Apgar scores, rate of admission to neonatal intensive care units, perinatal deaths and cerebral palsy. Furthermore, the rate of cesarean delivery and operative delivery were increased in this group. It is important to remark that the population included originally in the different trials involved both high- and low-risk pregnancies, therefore this fact precludes us to extrapolate these results to only low-risk pregnant women (since we should expect fewer adverse outcomes). Thus, a final recommendation for the management of low-risk pregnant women in labour does not require the use of continuous electronic fetal monitoring, since no clear benefits are present. However, direct auscultation as outlined above is mandatory in order to detect fetal heart rate anomalies. This requires at least one qualified health provider to assist every laboring woman.

MONITORING THE PROGRESS OF LABOUR

The purpose of monitoring the progress of labour is to recognize problems in early stages that may be prevented or appropriately managed. The presence of prolonged labour can lead to maternal complications (such as exhaustion) and perinatal complications (e.g. asphyxia). The monitoring of uterine contractions by the trained hand and of cervical dilatation by vaginal examination, together with the evaluation of the descent of the head are the routine maneuvers used for evaluation of the progress of labour. Although abdominal palpation or an external tocodynamometer cannot accurately measure the changes in uterine pressure resulting from the contractions, they provide an indirect measure of the intensity and an accurate record of their frequency. The recommended frequency of vaginal examinations to assess the progress of cervical dilatation varies greatly among the literature. The number and timing should be individualized for each pregnant woman, but at least one assessment at the beginning of labour, one after the rupture of membranes (to exclude cord or arm prolapse) and during the second stage of labour are commonly needed. Normal evolution may be assessed by timing the total duration of each period.

The rate of progress of cervical dilatation may be calculated by comparing 2 successive vaginal examinations. A rate of 1cm/hour during the active phase of labour has been accepted as the cut-off value between normal and abnormal progress of labour. However, many women with slower rates of cervical dilatation proceed to births with normal outcomes. The partogram is a simple tool that has been adopted to record the progress of labour. This graph allows health providers to recognize failure of progress at a glance. Evi-

dence from observational studies, as well as, from a cluster randomized controlled trial conducted by the Word Health Organization, has shown a reduction of the incidence of prolonged labour, the intrapartum stillbirth and the cesarean section rate when an appropriate partogram is used. (http://www.who.int/reproductive-health/impac/Clinical_Principles/Normal_labour_C57_C76.html)

SECOND STAGE OF LABOUR

MATERNAL POSITION

The use of upright positions such as standing or sitting on a specially designed chair is very frequent in different populations. However, in many hospitals women have used supine positions for childbirth. Many randomized controlled trials have shown that the second stage of labour is shorter and severe pain is less frequent when the chosen position was the upright posture. Abnormal fetal heart rate patterns were also decreased in this group. The use of the upright position probably has not been widely accepted based on the fact that it causes some inconveniences to birth attendants. In most cases, the woman's choice regarding position should be supported.

EPISIOTOMY

Episiotomy has been the most accepted routine intervention during the second stage of labour based on the belief that it involved many advantages for the woman and the baby. Currently, there is good evidence that episiotomy should be practiced only when it is necessary, and only three of every ten nulliparas require of this intervention. The so called restrictive use of episiotomy is the standard practice nowadays and should be encouraged. A policy of restrictive episiotomy was associated with a decrease of 12% of posterior perineal trauma complications and 26% of the need of suturing.

THIRD STAGE OF LABOUR

ACTIVE MANAGEMENT OF THIRD STAGE OF LABOUR

Postpartum hemorrhage (PPH) is the leading cause of maternal mortality over the world. The correct management of the third stage of labour and the prevention of PPH during this period are considered a priority in order to decrease this cause of maternal morbidity and mortality. Third stage of labour is defined as the period of time between the delivery of the baby and the delivery of the placenta. The length of this stage and its subsequent complications depend on a combination of the length of time it takes for the placenta to separate from the endometrium and the ability of the uterine muscle to expel it to the vagina. There is strong evidence that the active management of the third stage of labour reduces the risk of postpartum hemorrhage by more than 40%. Currently, the Joint Statement of the International Confederation of Midwifes (ICM) and the International Federation of Gynecology and Obstetrics (FIGO) recommend this practice for all vaginal deliveries as a way to prevent PPH in developed and developing countries. Active management of the third stage of labour involves the administration of an oxytocic agent, early umbilical cord clamping and controlled cord traction for delivery of the placenta. Oxytocin is the current drug of choice for active management of the third stage of labour.

CARE DURING THE IMMEDIATE PUERPERIUM

The mother and the newborn should remain with an adult and capable companion or a qualified caregiver for the following 12 hours after birth.

Specifically, the mother should be observed during the first two hours postpartum because this is the period with the highest likelihood to present a PPH. The most important observations include the measurement of the blood pressure, pulse, temperature, estimation of blood loss and the confirmation of an adequate uterine contraction and involution.

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CHAPTER 24

Intrapartum fetal surveillance and management of fetal distress

LABOUR

H. P. van Geijn

INTRODUCTION

Methods for intrapartum fetal surveillance are:

1. Auscultation of the fetal heart beats with counting the fetal heart frequency.
2. Monitoring of uterine contraction and fetal heart rate patterns, so-called electronic fetal monitoring (EFM) or cardiotocography.
3. Fetal scalp blood sampling (FBS) with assessment of the fetal acid-base balance.
4. Fetal oxygen saturation monitoring (fetal pulse oximetry).
5. Fetal electrocardiography.

Auscultation of the fetal heart rate provides only very limited information and is often inaccurate. Certain fetal heart rate abnormalities as late decelerations, a silent or monotonous pattern may remain unnoticed. Next, in obstetric practice it is very difficult to adhere to the guidelines as recommended by ACOG (American) and RCOG (English) for listening to the fetal heart: i.e. for a minimum of 60 seconds every 15 minutes during the first and every 5 minutes during the second stage of labour. However can be an acceptable method in developing countries.

EFM currently is the standard technique to monitor the fetal condition in the presence of any preconceptional, gestational of intrapartum non-physiologic respectively abnormal condition (e.g. maternal hypertension, fetal growth restriction, twin pregnancy) or any presenting abnormal sign (e.g. blood loss, meconium stained amniotic fluid, sudden absence of fetal movements). The first and most important prerequisite for adequate use of EFM is to obtain good quality recordings of sufficient length.

Fetal scalp blood sampling, pulse oximetry and electrocardiotocography are surveillance methods additional to EFM. The focus in this summary on guidelines for fetal surveillance will be on the techniques applied in EFM, and next how to classify and interpret the maternal uterine contraction curve and the fetal heart rate pattern. Although they go to-

gether and are strongly interrelated, for the sake of clarity, monitoring of the uterine activity and the fetal heart rate will be discussed separately.

UTERINE CONTRACTION MONITORING

TECHNIQUES

Awareness of uterine contractions can result from the patients perception, from manual palpation of the uterus, or from external respectively internal electronic monitoring of uterine activity. Electronic uterine contraction monitoring is an essential part of EFM. Regrettably monitoring of uterine contractions is often omitted, particularly during the second stage of labour, exactly the most critical period for the fetus regarding its condition. Uterine contraction monitoring deserves full attention of the attending midwife, resident or obstetrician responsible for and attending the process of labour and delivery.

External uterine contraction monitoring

Uterine contractions can be recorded externally by a pressure sensitive device on the mothers abdomen. Displacement of the toco-transducer is recorded by a change in the shape of the maternal abdomen as a result from a uterine contraction. Other influences that may cause displacement of the transducer are maternal movements like positional changes, breathing and vomiting, and later on in pregnancy fetal kicking movements, visible as sharp upward deflections on the tracing.

For adequate recording of uterine contractions it is essential to have sufficient tension on the belt keeping the toco-transducer in place and to have the transducer adequately located. Generally the best location is just below or just left/right from the umbilicus. When the transducer is placed next to or at the fundal height the transducer may slide-off during a uterine contraction, which may even result in negative deflections in the tracing during contractions. Awareness of this pitfall is particularly of importance when faced with an imminent early preterm delivery.

External uterine contraction monitoring in comparison with internal monitoring provides only limited information. If used appropriately it informs reliably about the frequency of uterine contractions. One cannot rely on the intensity and duration of contractions, nor the length of the pauses between contractions.

Internal uterine contraction monitoring

Intrauterine pressure can be recorded by application of fluid-filled, tip-sensitive or transducer-tip catheters. Most catheters have a possibility for amnioinfusion.

Intrauterine catheters are blamed to have the associated risk of perforating the uterine wall. It is, though, not the catheter itself but the rigid inserter guiding the catheter that may perforate the uterus. This potential risk definitely can be avoided by taking care that the tip of the inserter at introduction in the cervix always remains below the top of the operators palpating fingers.

Intrauterine pressure monitoring has the advantage that accurate information can be obtained on the frequency, intensity and duration of contractions, on the beginning and end of a contraction, and on the tonus and duration of intervals (pauses) between contractions. Next with currently available centralized systems uterine activity can be quantitated apply-

ing analytic procedures calculating the Montevideo or Alxandria units. In this way trends in uterine activity can be observed objectively and related to the progress of labour.

CLASSIFICATION OF UTERINE CONTRACTION PATTERNS

The classification of uterine contractions is very much dependent on the method applied to monitor uterine activity. The various ways to observe uterine contractions are in order of usefulness: *a)* the patients perception being the least sensitive, *b)* next comes manual palpation, while *c)* internal monitoring is the most sensitive. The results from external monitoring are very variable and are totally dependent on how adequate the technique is being performed.

Uterine contraction curves as they are visible on paper tracings or electronic screens can have various characteristics:

— Normally spaced regular and symmetric contractions at 2-3 minutes intervals (3-4 contractions per 10 minutes).

— Skewed contractions with a delay in relaxation.

— Paired contractions with no pause between two successive contractions.

— Polysystole characterized by no return to the baseline-tonus between two contractions.

— Tachysystole characterized by an increased frequency of contractions (e.g. more than 5-6 per 10 minutes), often occurring in combination with uterine hypertonia.

— Tetanic contractions characterized by a high contraction frequency pattern, a substantially elevated uterine tonus and no relaxation between contractions.

INTERPRETATION OF UTERINE CONTRACTION PATTERNS

Skewed and paired contractions may point to uterine fatigue. Tachysystole, particularly when combined with uterine hypertonia is an indication of excessive uterine activity by example due to uterine overstimulation from too high doses of oxytocin. Sufficient long intervals (pauses) between contractions are essential to avoid deterioration of the fetal condition during the process of labour and delivery. Injudicious use of prostaglandins or oxytocin always should be avoided. The uterus should have sufficient time to relax in between contractions in order to permit opening-up of spiral arteries occluded during the contractions. Likewise the patient should not be stimulated to the extent of overactive pushing during the second stage of labour.

Spontaneously increased uterine activity may result from intrauterine infection, fresh meconium or bleeding. The tetanic contraction pattern may be the first sign of a placental abruption, even prior to manifestation of blood loss or observed changes in the fetal heart rate pattern like decelerations or bradycardia.

FETAL HEART RATE (FHR) MONITORING

TECHNIQUES

Fetal heart rate signals can be obtained externally by placing an ultrasound transducer on the maternal abdomen or an electrode on the fetal scalp.

EXTERNAL FHR MONITORING

The fetal heart rate is recorded by an ultrasound transducer that emits and receives sound waves. Changes in the frequencies of the sound waves (the Doppler-effect) correspond with the frequency of the heart beats. Currently marketed monitors perform autocorrelation to better identify timing of fetal heart beats.

The quality of the recorded tracing depends on correct direction of the sound beam towards the fetal heart. Correct pointing to the fetal heart cannot always easily be reached as in early pregnancy, in case of polyhydramnios or twins, or when the fetus is actively moving. At times repeated adjustment of the ultrasound transducer is necessary, requiring constant attendance of an examiner. Very often externally obtained FHR recordings are of moderate quality and do not fulfill the FIGO-criteria for an adequate tracing.

High frequency filtering of the received sound waves provides information on the movements of the cardiac walls. Any moving object in the sound beam other than the fetal heart may also lead to frequency changes in the sound waves. Pulsations in fetal and also **maternal vessels (aorta)** may then be recorded. Recording of the maternal heart rate may especially occur during the second stage of labour, especially after the birth of the first twin. Frequently the mother then has an elevated 'baseline' heart rate frequency and during pushing efforts heart rate increases mimicking 'accelerations'.

Low frequency filtering of the emitted and received sound waves can provide information on the presence of fetal body movements, which will then be recorded on the cardiotocographic tracing.

INTERNAL FHR MONITORING

A scalp electrode is placed which records the fetal electrocardiogram. Electronic processing of the FECG signal, in particular recognition of the R-peak, forms the basis for recording the fetal heart frequency.

CLASSIFICATION OF FETAL HEART RATE PATTERNS

Many systems have been proposed to classify fetal heart rate patterns. The most widely accepted system has been presented by Rooth and colleagues. Their proposal has been the result of consensus development and is adopted by our international organisation FIGO. These FIGO guidelines for fetal monitoring define fetal heart rate patterns as normal, suspicious or pathological. Simplified characteristics for the intrapartum period are:

NORMAL PATTERN

— Baseline fetal heart rate 110-150 beats/min.

— Amplitude of baseline variability 5-25 beats/min.

— Presence of periodic accelerations.

— Absence of decelerations, or occasional decelerations of very short duration during a contraction and no other FHR abnormalities.

SUSPICIOUS PATTERN

— Baseline heart rate above 150 or between 100-110 beats/min.

— Amplitude of variability 5-10 beats/min for more than 40 minutes.

— Amplitude of variability over 25 beats/min.

— Absence of accelerations for more than 40 minutes.

— Presence of variable decelerations.

PATHOLOGICAL PATTERN

— Baseline heart rate below 100 or above 170 beats/min.

— Persistent heart rate variability less than 5 beats/min for more than 40 minutes.

— Severe variable, prolonged or late decelerations.

— A sinusoidal pattern.

INTERPRETATION OF FHR PATTERNS IN RELATION TO THE UTERINE CONTRACTION CURVE

First of all good quality tracings of sufficient length (at the minimum 30 minutes) are necessary. External recordings often fail to produce good quality tracings, particularly in labours from twin pregnancies.

Next it is of utmost importance to avoid excessive uterine activity. There is a definite association between a decreased fetal umbilical artery pH respectively base excess and uterine overstimulation. Sufficient relaxation time between uterine contractions in case of stimulation or augmentation of uterine contractions prevents avoidable fetal distress and unnecessary obstetric interventions.

Following observation of the uterine contraction curve, assessment of the baseline fetal heart rate is the first —and the crucial— step in the interpretation of a fetal heart rate tracing. The assessment of the baseline is most easy during FHR-pattern A, present during a quiet sleep state of the fetus. Regrettably the pattern A characterized by a stable baseline, normal variability, absence of accelerations and no decelerations often is not easily recognizable, particularly at the advanced stages of labour.

When assessment of the baseline is difficult, one should not strive for it. One should be aware of possible fetal distress since a baseline («the line one thinks there is») may not be present due to recurrent decelerations or a marked increase in variability (the so-called saltatory pattern).

Early decelerations, said to be associated with fetal head compression, should not be confused with variable decelerations occurring simultaneous with contractions. The original definition of an early deceleration includes uniform U-shape occurrence, a begin after the start and finish before the end of a uterine contraction and a lowest heart frequency (the deepest point of the deceleration) not below 100 beats/min. From this description it is clear that in principle early decelerations are not or at most are very rarely present during the process of labour and delivery. Variable decelerations are the predominant type during the first stage of labour and are more frequently present when labour progresses forward to full dilatation. Features of variable decelerations to look for:

— The baseline heart rate between the decelerations.

— Variability in the baseline heart rate.

— Variability during the decelerations.

— Duration of the decelerations.

— Lowest heart rates during the decelerations (the depth).

— Duration and steepness of return to the baseline FHR level

— The lag-time, which is the time-interval between the peak of the contraction and the deepest point of the deceleration, indicating the 'late character' of a deceleration.

— Presence of increases in the heart rate at the beginning and the end of the decelerations («shouldering»).

— A prolonged increase in the FHR following the decelerative phase («overshoot»).

— The time intervals between successive variable decelerations.

Variable decelerations most likely result from (partial, complete) occlusion of the umbilical cord. The fetal heart rate increases at the beginning and end of a variable deceleration can be explained by occlusion of the vein, while the decelerative phase can be explained by occlusion of one or both arteries simultaneous with the vein. Overshoot is an ominous sign, particularly when accompanied in the remaining tracing by low variability and absence of accelerations, and may be the result from cardiac decompensation.

A normal baseline FHR, normal variability and presence of periodic accelerations are the «hallmarks» of fetal well-being. Accelerations with a duration of more than 15 seconds and an amplitude of more than 15 beats simultaneous with fetal body movements indicate a good fetal condition. Accelerations in relation to fetal movements vary in shape, are asymmetric and occur at irregular intervals.

Increases in the FHR simultaneous with uterine contractions lacking these criteria should alert for an endangered fetal condition or may be the result from recording the maternal heart rate. Particularly during the second stage the maternal heart rate will be elevated, often even in a range above 100 beats/min and will further increase during pushing. The so-called **monotonous pattern** characterized by increases in the heart rate at very regular intervals (particularly when in relation to uterine contractions), low variability and a more or less symmetric shape of the heart rate increases may easily be misinterpreted and may lead to false reassurance concerning the fetal condition. The monotonous pattern may be the result of repetitive umbilical vein occlusions, repetitive overshoot or recording the increases in the maternal heart rate during pushing efforts.

ADDITIONAL METHODS

FETAL SCALP BLOOD SAMPLING (FBS)

FBS permits reliable assessment of the fetal blood acid-base status. Capillary blood from the fetal scalp usually correlates well with the arterial values. Regular application of FBS leads to fewer obstetric interventions in particular to fewer cesarean sections. The technique, though, is not very much liked since it is invasive, cumbersome and provides only a spot-check. It is not used in many institutions and may in future be replaced by intrapartum fetal electrocardiography.

FETAL PULSE-OXIMETRY

Monitoring of fetal oxygen saturation is done by applying a reflectance oxygen saturation transducer against the fetal cheek. Particularly fetal movements prevent recruitment of a continuous signal. Although it has been demonstrated that this technique leads to fewer obstetric interventions for fetal distress, it has not lead to a decrease in the overall obstetric intervention rate.

FETAL ELECTROCARDIOGRAPHY

Intrapartum fetal electrocardiography contrary to pulse oximetry has the advantage that it makes use of an already widely instituted technique, namely intrapartum FHR monitoring applying a scalp electrode. Instability in the ST segment of the electrocardiogram and an increase in the T/QRS ratio are signalised using the STAN-method. The overall conclusion from the first large cohort studies point to potential benefits: less obstetric interventions for fetal distress, a decreased incidence of severe asphyxia and a diminished need for scalp blood sampling.

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Induction of labour

CHAPTER 25

LABOUR

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INTRODUCTION

Induction of labour is defined as the initiation of labour by medical or surgical methods before the spontaneous onset of labour leading to birth of the baby. This includes both women with spontaneous rupture of the membranes or intact membranes but who are not in labour.

Induction of labour is indicated when in this way a better perinatal result for both mother and infant should be expected than from a wait-and-see approach. The process of induction of labour should only be considered when vaginal delivery is felt to be the appropriate route of delivery, and thus spare the mother from the trauma of a caesarean section.

INDICATIONS

Induction of labour is indicated when it is felt that the benefits of finishing pregnancy outweigh the potential maternal and fetal risks of continuing with gestation if there are not contraindications for induction and the best conditions for labour and delivery can be provided. These are the most common therapeutic indications:

1. Medical and pregnancy complications.
2. Prelabour rupture of membranes at term.
3. Some maternal diseases (diabetes, hypertension...).
4. Chorioamnionitis.
5. Evidence of fetal compromise.
6. Intrauterus fetal death.
7. Prolonged pregnancy.
8. Logistic factors (e.g. long distance from hospital, history of rapid labour...).

RISKS

Labour induction is an active procedure with potential risks for the mother and foetus. Some of the possible risks are[1, 2, 3]:

1. Increased rate of operative vaginal delivery, caesarean birth.
2. Excessive uterine activity.
3. Abnormal fetal heart rate (FHR) pattern.
4. Uterine rupture.
5. Maternal water intoxication (rare).
6. Delivery of preterm infant due to incorrect estimation of dates.
7. Cord prolapse with artificial rupture of membranes.

CONTRAINDICATIONS

1. Previous classical cesarean section, inverted-T or unknown uterine incision.
2. Previous uterine surgery involving entry of the uterine cavity (except the segmentary caesarean surgery).
3. Previous uterine rupture.
4. Active genital herpes.
5. Presence of placenta previa.
6. Transverse lie or any other labour contraindication.
7. Invasive carcinoma of the cervix.
8. Absence of fetal wellbeing.

INDUCTION PREREQUISITES

1. Each service must use accurate induction protocols and policies.
2. Informed consent should also be obtained from patients. Previously, we must explain to them the risk factors of this procedure (obstetrical risk, advantages and limitations of local maternity care services).
3. Before induction begins, the indication and the method of induction for every patient must be clearly established.
4. Precise gestational age and the Bishop score of the cervix must be established. Different reports about labour induction show that the ripeness of cervix is the most important predictor of success[4]. A Bishop score of ≥ 6 is considered favourable and is likely to result in successful labour induction (table 1).

For induction of labour the following points must be available:

1. A qualified registered nurse familiar with the effects of induction agents must be able to recognize foetal or maternal complications, and initiate and evaluate electronic foetal surveillance.

Table 1. Modified Bishop's score[5].

	Score			
Parameter	*0*	*1*	*2*	*3*
Dilatation	<1	1-2	2-4	>4
Cervical length	>4	2-4	1-2	<1
Station	−3	−2	−1/0	+1/+2
Consistency	Firm	Average	Soft	—
Position	Posterior	Mid/Anterior	—	—

2. Wherever induction of labour happens, facilities should be available for continuous foetal heart rate and uterine monitoring.
3. Foetal wellbeing and uterine monitoring should be established prior to induction of labour. For women who are healthy and have had an uncomplicated pregnancy the evaluation of foetal well-being after the administration of vaginal prostaglandins should include an initial continuous electronic foetal monitoring and once normality is confirmed intermittent monitoring can be used. When oxytocin is being used for induction or augmentation of labour continuous electronic foetal monitoring should be used.

The process of induction of labour should only be considered when vaginal delivery is felt to be the appropriate route of delivery. Nevertheless compared with spontaneous labour, induction is associated with twice the risk of caesarean section. This way, conditions which may affect the safety and efficacy of induction of labour (e.g. previous caesarean section) should also be considered.

For women who are healthy and whose pregnancy was not complicated, induction of labour with vaginal prostaglandin E_2 agents can be done on antenatal wards, prior to the active phase of labour. However, induction of labour of women with recognised risk factors such as previous caesarean section or suspected foetal growth compromise, induction process should not happen on an antenatal ward and the clinical discussion about the method of induction and timing, should take place.

METHODS OF INDUCTION OF LABOUR

There are a variety of methods that can be used to induce labour. You can use one or all of the methods described below according to cervical favourability. There are pharmacologic and non pharmacologic approaches to cervical ripening and labour induction.

NON PHARMACOLOGIC

SEXUAL INTERCOURSE

Sexual relations usually involve stimulation of the breast and nipples, which can promote the release of oxytocin. With penetration, the lower uterine segment is stimulated, that results in a local release of prostaglandin. Female orgasms have been shown to conclude uterine contractions, and human semen contains prostaglandins, which are responsible for cervical ripening (evidence level B)[6].

BREAST STIMULATION

Breast massage and nipple stimulation have been shown to facilitate the release of oxytocin from posterior pituitary gland. The most commonly prescribed technique involves gently massaging the breast or applying warm compresses to the breasts for one hour, three times a day. However, the evidence is lacking to support breast stimulation as a viable method of inducing labour[7].

MECHANICAL MODALITIES

All mechanical modalities share a similar mechanism of action, some form of local pressure that stimulates the release of prostaglandins. The risk associated with these methods includes infection, endometritis and neonatal sepsis. They have been associated with bleeding, membrane rupture and placental disruption.

- **Hygroscopic dilator,** they absorb endocervical and local tissue fluids, causing the device to expand within the endocervix and providing controlled mechanical pressure.
- **Folley** catheter **(26 Fr),** or specifically designed balloon devices can be used.

These methods are effective for cervical ripening in women with an unfavourable cervix (evidence level A).

SURGICAL METHODS

- **Membrane sweeping,** it causes an increase on activity of phospholipasa A_2 and prostaglandin $F_{2\alpha}$ as well as mechanical dilation of the cervix which releases prostaglandins. Membrane sweeping means that the doctor or the midwife insert the finger through the internal cervical ostium and move it in a circular direction to detach the inferior pole of membranes from the lower uterine segment. The technique is not associated with an increase in maternal or neonatal infection, but it is associated with high levels of discomfort during the procedure and bleeding (evidence level C)[8].
- **Amniotomy,** it is hypothesized that amniotomy increases the production of, or cause a release of, prostaglandins locally. Risks associated with this procedure include umbilical cord prolapse or compression, maternal or neonatal infection (vertical transmission of HIV could be increased after the amniotomy), fetal heart rate deceleration, bleeding from low-lying placenta and possible fetal injury. The evidence does not support its use alone for induction of labour (evidence level A)[9].

PHARMACOLOGIC

PROSTAGLANDINS

They should be used in preference to the use of oxytocin when induction of labour is undertaken in unfavourable cervix (Bishop <6). In that case, the use of prostaglandins analogs markedly enhances the success of induction.

Misoprostol

It is a synthetic prostaglandin E_1 (PGE_1) analogue that has been found to be a safe and unexpensive agent for cervical ripening, although it is not labelled in to many countries for that purpose. When given orally, it is rapidly absorbed by gastrointestinal tract. The peak

concentration and half- life of misoprostol acid (the active metabolite) are 12 and 21 minutes, respectively. The total systemic bioavailability of vaginally administered misoprostol is three times grater than that of orally. Misoprostol is associated with significantly lower overall rate of caesarean section, a higher incidence of vaginal delivery with 24 hours of application and reduced need of oxytocin augmentation. But, it also has been associated with an increased induction of tachysystole[10]. Moreover, maternal outcomes, such as a need for caesarean delivery because of FHR abnormalities, the arrest of labour or the need for terbutaline/ritrodine administration, were not significantly different between the misoprostol group and the dinoprostone and oxytocin control group. Although the incidence of meconium staining was found in some studies to be higher with misoprostol, overall neonatal outcomes include the frequency of meconium aspiration syndrome, the incidence of 5 minutes Apgar score below 7 and rate of neonatal resuscitation or admission to a neonatal intensive care unit, showed no significant difference between groups. Other complications resulting for misoprostol use include uterine rupture and foetal device, but not at rates higher than in control subjects. The use of misoprostol in women with prior cesarean birth has been associated with an increase in uterine rupture. Maternal effects like nausea, vomiting or diarrhoea are uncommon (evidence level A).

The primary advantage of misoprostol is the low cost and convenience. The optimal regimen for it is 50 mcg applied in the posterior vaginal fornix every 4 hours, using a maximum of six doses. It is an effective dosage for labour induction and has less adverse effects and complications than 100 mcg vaginally dose. In a closely supervised hospital setting with adequate monitoring, 100 mcg oral misoprostol has the potential to induce labour as safely and effectively as its 50 mcg vaginal analogue. As oral use of the drug is easier for both, the patient and the doctor, oral misoprostol will probably be more preferable than the vaginal route[11]. Continuous fetal monitoring is currently recommended for at least 3 hours after misoprostol application. When oxytocin augmentation is necessary, a minimal interval of three hours is recommended after the last dose.

Dinoprostone (PGE_2)

Administered intravaginally or intracervical it is the pharmacologic agent most widely used for ripening the cervix. Prostaglandins alter the extracellular substance of the cervix, and PGE_2 increase the activity of collagenasa in the cervix. They cause an increase of elastase, glycosaminoglycan, dermatan sulphate and hyaluronic acid levels in the cervix. A relaxation of cervical smooth muscle facilitates dilatation. Finally protaglandins allow for an increase in intracellular calcium levels, causing contraction of myometrial muscle.

Dinoprostone should be administered with the patient in or near labour and delivery suite. The patient should be monitored for a further 30 to 120 minutes. Currently, two PG analog are available for the purpose of cervical ripening, the **gel** containing 0,5 mcg of dinoprostone and its optimal interval of administering another dose is six hours. The manufacturer recommends that no more than three doses be administrated per 24 hours, PGE_2 **vaginal insert** contains 10 mcg of dinoprostone and provides a lower constant release of medication (0,3 mcg per hour) than gel. Its efficacy is similar, and it is inserted and removed more easly if uterine hyperstimulation occurs. The vaginal insert placement seems to be safe for the mother and the newborn.

Extensive use of dinoprostone for cervical ripening has not revealed any serious adverse reactions. Risks associated include uterine hyperstimulation and maternal side effects such as nausea, vomiting, diarrhoea and fever.

End points for ripening include stage uterine contractions, a Bishop score of 8 or higher, or a change in maternal or fetal status.

OXYTOCIN

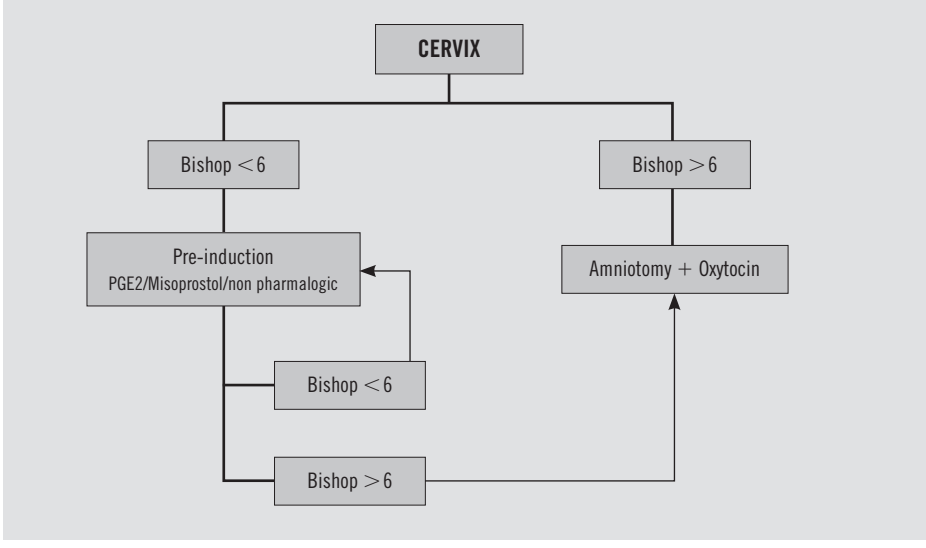
As pregnancy progresses, the number of oxytocin receptors in the uterus increases. Oxytocine activates the phospholipase C-inositol pathway and increases intracellular calcium levels, stimulating contractions in myometrial smooth muscle.

Once the cervix is riped, oxytocin is still the favoured pharmacologic agent for induction of labour. It should not be started from 6 hours after administration of vaginal prostaglandins. In women with intact membranes amniotomy should be performed where never feasible prior to initiate oxytocin induction. When induction of labour is undertaken with it, the recommended regimen is a starting dose of 1-2 milliunits per minute, increased at interval of 30 minutes or more. The minimum dose possible should be used. Adequate contractions may be established at 12 milliunits per minute. The maximum dose is 20 milliunits per minute. To be delivered through a syring drive or via an infusion pump with a non return valve. To reduce error, a standard dilution shoul always be used. Suggested standardised dilutions and dose regimens include 30 UI oxytocin in 500 ml of normal saline, hence 1 ml/h = 1 milliunit oxytocin per minute, however, 10 UI oxytocin in 500 ml of normal saline hence 3 ml/h = 1 milliunit oxytocin per minute.

Oxytocin has many advantages, it is potent and easy to withdraw, it has a short half-life (one to five minutes) and is generally well tolerated. Dose-related adverse effects may occur, however, because oxytocin is close to vasopressin in structure, it has an antidiuretic effect when it is given in high dosages; thus, water intoxication is a possibility in prolonged inductions.

Uterine hyperstimulation and uterus rupture may also occur. It is for these circumstances the importance of continuous FHR monitoring. If a worry FHR occurs during induction, the oxytocin dosage can usually be lowered rather than stopped completely. Induction using oxytocin has side effects, but because the drug does not cross the placental barrier, no direct foetal problems have been observed.

When the labour induction fails or there exists a change in the maternal or foetal status it is necessary to do a caesarean section; it may be the end of this procedure.



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CHAPTER
26

Treatment of premature labour

LABOUR

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INTRODUCTION

In 1972 the World Health Organization (WHO) defined «preterm born» as the outcome of a pregnancy under 37 weeks, considering gestational age from the very last menstruation date to birth. A «low weight born» is a neonate with a weight under 2.500 g, independently of the chronological age.

These terms are usually used with the same meaning but in fact they are different. This is difficult when the last menstruation date is unknown, particularly in developing countries, where ultrasound application is not universal and weight is extensively measured because of its easiness. Both of them are considered as risk factors which increase the possibility of perinatal morbi-mortality.

Giving birth preterm is a major cause of morbidity for pregnant women, and it is the single largest cause of mortality and morbidity for newborns. Severe morbidity, especially respiratory distress syndrome, intraventricular haemorrhage, bronchopulmonary dysplasia and necrotising enterocolitis, are far more common in preterm infants than in term infants. Long-term impairments such as cerebral palsy, visual impairment and hearing loss are also more common in preterm infants.

The scientific community has worked on many treatments to lower the rate of preterm birth; however, its incidence has remained stable around 7% of all pregnancies over the past two decades.

In spite of the long list of risk factors known to be associated to preterm birth, as shown in the previous chapter, only around 25-30% of preterm deliveries have any of them. If we analyze every single factor we reach the conclusion that most of them cannot be avoided or that they are very difficult to eliminate, so primary prevention is unsuccessful. Formal risk scoring for preterm birth (using published scoring systems) offers no advantages over careful clinical assessment, carries several risks of its own, and cannot be recommended.

Clinical parameters such as progressive cervical modifications, uterine activity, vaginal bleeding or changes in the vaginal pH are used to diagnose preterm birth. They are more available than lab markers, especially in developing countries. There are several biochemical markers reflecting the inflammatory condition of choriodecidual and cervical tissue. The first and perhaps the most studied cervical inflammatory mediator is foetal fibronectin. The detection of foetal fibronectin in cervicovaginal secretions has been suggested to be useful in the prediction of preterm labour. However, in view of its poor specificity and a relatively high false positive rate, it is not recommended for routine screening of the general obstetric population[1]. However, recent systematic reviews conclude that, for women with symptoms of preterm labour, cervicovaginal foetal fibronectin is useful in predicting preterm birth.

EARLY MANAGEMENT

Women have been given much advice on how to reduce their risk of preterm birth (eg reduce paid/unpaid work, give up smoking, stop sexual activity, bed rest). While achieving some of these goals may well be beneficial (eg. stopping smoking) such advice is often unrealistic and may itself cause stress or even hardship:

- There is no conclusive evidence that reducing household work, reducing or stopping sexual activity, restricting normal physical activities, or resting in bed at home is effective in preventing preterm birth.
- There is no evidence that paid work increases the incidence of preterm birth, although there is some evidence of a link between very strenuous workloads and preterm birth.
- When pregnant women whose working conditions meet the criteria for occupational fatigue seek a change in work or conditions, practitioners should support this request.
- Women planning to maintain, or begin, regular strenuous exercise in pregnancy should be advised that this may increase the risk of preterm birth and low birth weight.

Current evidence suggests that there is no justification for treatment during pregnancy, in order to reduce the incidence of preterm birth, of carriers of either: *a)* bacterial vaginosis[2], or *b)* group B streptococcus[3].

ADVICE FOR WOMEN

Currently, it would seem wise to advise women, and especially those deemed to be at risk of preterm labour, to seek professional advice promptly, when they experience contractions that have a hallmark of regularity in them. It may be important to emphasise that regularity, is more important than the experience of pain. It is inevitable that in some of these women contractions will have ceased by the time the advice is obtained and that in others contractions will subside spontaneously irrespective of what is done. However, this needs to be offset against the risks of failing to recognise preterm labour before advanced cervical dilatation has occurred.

Equally, one should recommend that women who experience watery discharge that can herald ruptured membranes preterm, especially if it occurs before 35 weeks, should promptly seek assistance at a clinic or labour ward.

ANTENATAL BED REST

Traditionally, bed rest has been thought to provide benefits to both the pregnant woman and her baby. Hypothesised benefits include increasing uterine blood flow, relieving pressure on the cervix, and improving placental transfer of nutrients. Known hazards of bed rest include an increased risk of venous thrombosis, pulmonary embolism, and negative psychosocial effects. Hypothesised hazards include the possibility of increased elective preterm delivery to end a situation that could be becoming intolerable to the woman. Antenatal hospitalisation for bed rest has not been shown to decrease the rate of preterm birth, or to improve perinatal outcome. It may have adverse effects on women, and should be avoided wherever possible.

CERVICAL CERCLAGE

Cervical incompetence, defined as «uterus inability for holding the foetus until viability», is indicative to make a cerclage. This intervention has proved effectiveness in high risk patients, not reducing preterm deliveries rate but improving neonatal survival.

Diagnosis is based on history of one or more second term abortions, with foetal membranes rupture, generally before starting of labour, absence of haemorrhage and minor pain. At clinical exploration we find dilated cervix with membranes showing out of the cervical orifice («sandglass clock») or broken with foetal parts in vagina.

The largest multicentred randomised trial of cervical cerclage suggests that if women have a previous history of three or more early deliveries they are particularly likely to benefit from cervical cerclage. The results from this trial suggest that for women who have a history of second trimester miscarriages or preterm births, cervical cerclage may prevent one preterm delivery for every 25 women who undergo the procedure[4].

Probably, the most efficient measure for preventing ascending genital infections in cases of recurrent late abortions and early prematurity is to establish a total barrier within the cervical canal by «Early Total Cervix Occlusion (ETCO)»[5] (see chapter 21).

TOCOLYSIS

Tertiary prevention involves tocolysis of the patients with preterm birth threat. Due to that most of primary and secondary measures are not efficient enough; prevention is currently based on stopping the uterine contractions once they have appeared.

The main problem is how to know if the preterm birth threat is real or not. That is why so many times, though the diagnosis doubt is reasonable enough, to apply tocolysis is highly advisable. It is thought that up to a 50 % of patients with regular contractions and diagnosis of preterm birth threat would have a term birth without treatment.

Maybe tocolysis does not decrease prematurity rates, but prolongs gestation and improves neonatal survival by the use of corticoids to mature the lungs of the foetus and the possibility to refer the labour to a center with neonatal intensive care unit. There are two circumstances in which a relatively small prolongation of pregnancy is likely to confer measurable benefits in terms of morbidity and mortality:

- When it occurs at a gestational age in which every day or week gained confers a substantial benefit (for instance between 25 and 27 weeks).
- When the time gained is sufficient to institute measures that by themselves can improve infant outcome.

Tocolysis should be considered in all women experiencing very preterm labour with a view to:

- Prolong gestation at gestational ages that offer little hope for intact infant survival.
- Facilitate the use of corticosteroids to enhance pulmonary maturity.
- Transport mother and foetus to a centre with appropriate facilities for care at and after birth.

Tocolysis to inhibit preterm labour should not be undertaken:

- If the mother's condition warrants delivery as soon as possible.
- If the likelihood of intact survival of the infant cannot be altered by prolongation of pregnancy or by any measure that can be taken in the meantime.
- When foetal maturity is considered to be sufficiently guaranteed to forego the effects of corticosteroid administration to the mother.
- In the presence of clinical chorioamnionitis or uterine infection.

BETAMIMETIC DRUGS

Betamimetic agents, or β-agonists, are probably the most widely used tocolytics in preterm labour. All betamimetic agents are chemically and pharmacologically related to the catecholamines, and all act by binding to β-receptors that are present on cell membranes in the uterus and in many organs throughout the body. The occupation of β-receptors activates adenylate cyclase through a guanine nucleotide regulatory protein to convert adenosine 5'-triphosphate to cyclic adenosine 3',5'-monophosphate (cAMP), it then acts as an intracellular messenger. Increases in cAMP relax smooth muscle. Stimulation of β-receptors is responsible for actions such as an increase in heart rate and stroke volume, relaxation of intestinal smooth muscle and lipolysis. Also, β-stimulation mediates glycogenolysis and relaxation of smooth muscle in the arterioles, the bronchi and the uterus.

Ritodrine and terbutaline are the most common drugs used for prevention of preterm delivery. Ritodrine is administrated intravenously or orally. Intravenously, in continuous perfusion, starting with 50 μg/min, and increasing 50 μg/min every 15 minutes until uterine contractions stop. Maximum dose recommended is 360 μg/min or when mother heart rate exceeds 120 bytes per minute. As betamimemetic drugs are powerful agents with adverse effects that are related to the dose administered, this would seem to be undesirable. It has, therefore, been proposed to lower the infusion rate as soon as uterine inhibition is achieved to a level that is sufficient to maintain uterine inhibition. Oral administration (10 mg every 4-6 hours, maximum 120 mg/day) has not proved efficacy in maintenance management and only should be administrated if contractions do not let the mother rest. Terbutaline can be administrated orally (2,5 mg/4-6 h), subcutaneously (0,25 mg/20 min) or intravenously.

It has been known for some time that continuous administration of betamimetic agents results in a loss of efficacy. This is attributed to down-regulation of the β-receptors and desensitisation of the adenylate cyclase activity. It may be possible to overcome this problem by alternative regimens of drug administration, such as intermittent or pulsatile administration but the evidence that this is clinically useful is far from conclusive.

Heart frequency, breath frequency, blood pressure and liquid balance (income and expenditure) must be controlled. If thoracic pain or arrhythmia appears we must do an electro-

cardiogram and stop the perfusion, because a heart attack may happen. Another serious complication is acute lung oedema. In order to prevent it we will reduce sodium chloride intake and liquid volume. It is advisable to measure of serum glucose every 12 hours or every 2 hours if patient is diabetic. Contraindications: *a)* hyperthyroidism, *b)* cardiac disease, and *c)* poorly controlled diabetes mellitus[6].

OXITOCINE ANTAGONIST

Atosiban is a therapeutical agent which competes with oxitocine for miometrial and decidual receptors. This molecule is selective for miometrium, so its side effects are minimal. Start dose is 6,75 mg in bolus intravenously, it is followed by doses of 300 μg/min during 3 hours and finally 100 μg/min during 45 hours. Although its efficacy is waiting to be demonstrated, at the moment it seems similar to ritodrine. The major problem of this drug for developing countries is its high price.

CALCIUM CHANNEL BLOCKERS

They prevent the influx of extracellular calcium ions into the myometrial cell and are nonspecific for uterine as opposed to other smooth muscle cells. Several such agents have become available over the years, but only one, **nifedipine,** has been applied to the treatment of preterm labour. Nifedipine is the calcium channel blocker most used to prevent preterm labour although there is not enough evidence to use it for this indication. Start dose is 30 mg, following 20 mg/4 h during 24 h, and then maintenance with 10 mg/8 h. Main side effect is low blood pressure, detrimental for both, mother and foetus.

PROSTAGLANDINE SYNTHESIS INHIBITORS

There is substantial evidence that an increase in uterostimulating prostaglandins is of critical importance in the onset and maintenance of labour. Suppression of endogenous prostaglandin synthesis is therefore a logical approach to inhibition of preterm labour. There have been numerous inhibitors that have been used to treat preterm labour, but the most widely used has been **Indomethacin.**

Indomethacin action is competitive and reversible**.** It is an effective drug for delaying delivery at least 48 h in pregnant women less than 32 weeks. Starting dose is 100 mg rectal or 50 mg oral, following 25-50 mg/4-6 h orally during maximum 48 h. It can't be used in gastrointestinal ulcer, coagulation diseases, asthma and allergy to aspirin. It cannot be used in pregnancies over 32 weeks, and during not more than 48-72 h, because the risk to cause oligohydramnios (which is reversible stopping the administration) and foetal ductus arteriosus closure. The occurrence of ductal constriction has been related to gestational age (the younger the foetus the lower the risk), so that this effect is less marked at the gestational ages in which the infant is more likely to benefit from prolongation of pregnancy.

MAGNESIUM SULPHATE

Magnesium competes with calcium, so a decrease of intracellular calcium reduces uterine contractility. However, there is actually little solid information on the mechanism by which magnesium sulphate administration may affect uterine contraction in preterm labour. This drug has several serious side effects, as cardiac arrest. In addition, its efficacy hasn't been demonstrated yet. Given the level of evidence on its effects, as well as the availability of alternatives treatments, this cannot be recommended as a first line drug for the inhibition of preterm labour.

GLYCERYL TRINITRATE

It was recently reported to have some effects in the inhibition of uterine contractions in preterm labour. It acts as a nitric oxide donor. Nitric oxide released by endothelial cells acts as a natural vasodilator and there is evidence that it inhibits contractility in smooth muscle. Whether it actually relaxes the pregnant uterus has not been clearly demonstrated, however.

PRENATAL ADMINISTRATION OF PROGESTERONE FOR PREVENTING PRETERM BIRTH

Progesterone is a hormone that inhibits the uterus from contracting and is involved in maintaining pregnancy. The review of trials found that where progesterone was given (by injection into the muscle in some studies and as a pessary into the vagina in another study), there were beneficial effects, including prolonging the pregnancy, but there is insufficient information about potential harms[7].

There are some treatments for the preterm labour that are not considered to be true tocolytic agents, but they have been reported to delay delivery or to improve the outcome of the foetus. They are the antibiotics and the corticosteroids.

ANTIBIOTICS

In recent years a great deal of attention has been devoted to the possible infective origin of preterm labour and to the potential of antimicrobial agents to either prevent preterm labour or drastically alter its outcome. That attention has been spurred by evidence for a microbial stimulation of intrauterine synthesis of uterotonic prostaglandins and for the decline in intrauterine catabolism of prostaglandins in the presence of inflammation as well as by the discovery of a whole range of inflammatory mediators known to trigger biochemical mechanisms that enhance uterine contractility.

However, antibiotics should not be routinely prescribed for women in spontaneous preterm labour without evidence of clinical infection. There is currently no evidence that any antibiotic regimen used as an adjunct to tocolytic treatment in preterm labour with intact membranes provides substantial benefit, either in a worthwhile prolongation of pregnancy or improved infant outcome[8].

CORTICOSTEROIDS

Hormonal changes in the foetus before parturition are thought to prepare the various organ systems for postnatal function. When birth occurs preterm, mortality is increased and morbidity from a number of disorders is common due to dysfunction of a variety of organ systems. Of particular importance is the development of the lungs that must take over respiratory functions from the placenta following birth. Immaturity leads to the development of **respiratory distress syndrome** (RDS), a major cause of mortality and morbidity.

Benefits from corticosteroids are observed at all gestations below 34 weeks, independent of foetal sex. Maximum respiratory benefit occurs when treatment is started more than 24 hours and less than 7 days before birth. The cerebral protective effect occurs even if treatment is given for less than 24 hours before birth. At gestational ages beyond 33 weeks, the incidence of RDS as well as the associated mortality and morbidity, is low and corticosteroids would have to be given to a large number of women to obtain significant

benefits. The majority of obstetricians recommend its use at a later gestational time only if there is suspected lung immaturity.

Two intramuscular doses of **betametasone** (12 mg/24 h) or 4 doses of **dexametasone** (6 mg/12 h) are indicated in all pregnant women with preterm labour threat between 24 and 34 complete weeks. Beneficial effects start 24 hours after administration of the first doses. Corticoids decrease neonatal respiratory distress syndrome, ventricular haemorrhage and neonatal mortality[9].

It is common practice to administer repeat courses of corticosteroids if the pregnancy continues for more than one week after the previous course. There are no data to support this practice and it seems difficult to justify if there is no immediate threat of birth.

Maternal corticosteroid treatment should be considered in order to improve neonatal outcome before all births at less than 34 weeks of gestation; for all causes of spontaneous and elective preterm birth, including preterm prelabour rupture of the membranes and hypertensive disorders of pregnancy.

Treatment should be commencing as soon as there is an indication that birth is imminent (within a week) even when there is no plan to delay birth since the cerebral protective effects occur even if birth is within 24 hours.

There are no absolute contraindications to the initiation of treatment, although further delay of birth may be contraindicated in the presence of chorioamnionitis, foetal distress or maternal bleeding and the management of diabetes may be more difficult.

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Chorioamnionitis

CHAPTER 27

LABOUR

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INTRODUCTION

The chorioamnionitis (CA) is the inflammation of chorioamniotic membranes normally caused by infection. Some authors reserve this name to the histological changes of CA, and the name of Intraamniotic Infection (IAI) for the clinical picture[1, 2]. This is characterized by fever (usually ≥38 °C), maternal tachycardia (>100 bpm), and signs of intrauterine localization of infection as uterine tenderness, uterine irritability, vaginal secretion with aspect of «pus» malodorous or not, fetal tachycardia (>160 bpm), loss of fetal reactivity in the NST and a low Fetal Biophysical Profile. In the blood analysis there is a maternal leukocytosis >15.000/mm^3, accompanied by a % of non segmented leukocytes (band) >5%, and a high C reactive protein level (CRP) (>20 mg/L). As could be an IAI without the clinical described signs, we will use in this chapter the name of Clinical Chorioamnionitis (CCA) to describe the typical clinical picture.

Their importance is that Intraamniotic Infection (IAI) that is the main cause of CCA, and after Romero's meta-analysis and other studies[3, 4] is accepted that has an important role in Pre Term Premature Rupture of Membranes (PROM) and in Pre Term Labor (PTL) (near 30% of positive cultures in AF obtained by amniocentesis at admission in PROM without signs of CCA, and near 10% of PTL).

Their frequency is quoted in a wide range 0,5-11%. In our Hospital in the last three years from 11.498 deliveries 145 cases of CCA were detected (1,27%), although this % is changing for different groups of pregnancies: Preterm or Term, and with or without PROM (table 1).

CONSEQUENCES

CCA and IAI are that is the main causes of puerperal fever and exceptionally of the puerperal septic shock in the mother, but also of other maternal pathology as postpartum hemorrhage produced by uterine atony, transfusion, DIC, pelvic abscess or wall abscess in

Table 1. Frequency of CCA by groups of weeks of gestation, without or PROM.

Groups of gestacional age	*No PROM*		*PROM*	
	No CA	*CA*	*No CA*	*CA*
< 28	63 (79,7 %)	15 (19,0 %)	8 (36,4 %)	14 (63,6 %)
28,0-< 32	111 (87,4 %)	16 (12,6 %)	42 (66,7 %)	21 (33,3 %)
32,0-< 34	123 (96,85 %)	4 (3,15 %)	47 (79,7 %)	12 (20,3 %)
34,0-37	589 (99,33 %)	6 (0,67 %)	186 (94,6 %)	7 (3,6 %)
≥ 37	9.390 (99,5 %)	40 (0,47 %)	781 (98,7 %)	10 (1,2 %)
Total	**10.276 (99,1 %)**	**81 (0,9 %)**	**1.064 (94,2 %)**	**64 (5,7 %)**

case of cesarean section, and trombophlebitis. For the fetus and the newborn (NB) is important because is linked to an important neonatal morbidity as NN sepsis, but also through the Fetal Inflammatory Response Syndrome (FIRS)[5] may increase rates of intraventricular hemorrhage, periventricular leukomalacia, broncopulmonary dysplasia, patent ductus arteriosus, and necrotizing enterocolitis, and all these pathologies increase the possibilities of handicaps in these babies[6, 7].

ETHIOLOGY

The first cause of clinical CCA is a ascendant infection with germs from lower genital tract after PROM, although following Romero[3], Asrat[4] and other studies, nowadays is admitted that an important part of the Preterm PROM are caused by previous and sub clinical IAI (table 2).

Table 2. % of cases with positive cultures in amniotic fluid obtined by amniocentesis at admission[4].

Autor	*Year*	*Number de cases*
Garite	1982	20/86
Broelzmizen	1985	15/83
Vinzileos	1986	12/54
Romero	1988	65/221[a]
Dudley	1991	29/79
Gauthier	1992	56/117
Romero	1993	42/110
Ayerbuch	1995	32/90
Carroll	1996	30/82
Total		**301/811 (37,41 %)**

But after PROM, CCA is more frequent (10-60 %) depending of the weeks of gestation, the latency time and the management applied. Cases of CCA without PROM can be possible by trans placental pass of germs (Lysteriosis) although the colonization through unruptured membranes can't be excluded.

From studies of Gibbs and Blanco[8] it is known that the IAI can be produced by more than one germ may occur simultaneously by aerobe and anaerobe microorganisms and by germs with high and low virulence? These last although don't cause severe maternal or fetal infections, and they do not concern as others more aggressive bacteria, it doesn't mine that they are not capable to produce an inflammatory response and perhaps PROM, Preterm labor or FIRS.

In our Hospital between 2002 and 2004, in 11.498 deliveries of a unique fetus, we had 145 (1,27 %) cases of CCA, with 42 cases of amniotic positive cultures of known pathogen. Of them 40 (76,9 %) were monomicrobial and 12 (23,0 %) polimicrobial. 41,8 % of microorganisms were aerobic Gram (+), and 38,8 % aerobic Gram (−), as well as 16,4 % of anaerobes and 3 % of yeasts (table 3). We compare in this table two periods before and after the systematic screening for *Streptococcus agalactiae*.

The responsible of neonatal sepsis and deaths (table 4) are the usually considered more transcendent microorganisms: *Escherichia coli* and *Proteus mirabilis*, and this is specially true since the instauration of systematic screening of *S. agalactiae* as we are performing the systematic treatment from admission in all cases of PROM or chorioamnionitis in women known as carriers, or in all women not known if are or not carriers of *S. agalactiae*.

This may be the reason of the low rate of neonatal sepsis and death by this microorganism in the second period of this table.

Table 3. Microorganisms identified in cultures of AF, maternal blood or placenta, in cases de Chorioamnionitis in two periods 1986-1991 y 2002-2004 with similar number of deliveries.

Years	*1986-2001*	*2002-2004*
N	**47**	**52**
Monomicrobial	31 (65,9 %)	40 (76,9 %)
Polimicrobial	16 (34,1 %)	12 (23,1 %)
Aerobic bacteria	**57**	**54**
Gram (+)	38 (60,3 %)	28 (41,8 %)
Streptococcus agalactiae	17	4
Streptococcus viridans	7	7
Enterococcus	5	6
Gardnerella vaginalis	4	5
Stafylococcus aureus	3	1
Streptococcus bovis	1	0
Lysteria monocytogenes	1	3
Streptococcus pneumoniae	0	1
Stafylococcus hemolyticus	0	1
Gram (−)	19 (30,2 %)	26 (38,8 %)
Escherichia coli	12	19
Proteus mirabilis	2	4
Morganella morgani	2	0
Haemophilus influenzae	2	0
Klebsiella pneumoniae	0	1
Citrobacter freundii	1	0
Enterobacter cloacae	1	0
Pseudomonas aeruginosa	1	0
Anaerobic bacteria	**6 (9,5 %)**	**11 (16,4 %)**
Peptoestreptococos sp	4	1
Clostridium perfingens	1	0
Bacteroides sp	1	3
Bacteroides fragilis	0	5
Fusobacterium sp	0	2
Yeasts	0 (0 %)	2 (3 %)
Candida albicans	0	3

AF: Amniotic Fluid.

Table 4. Clinical chorioamnionitis: bacteria isolated in NNS by groups of weeks.

Groups of weeks	*< 28*	*28,0-< 32*	*32,0-< 34*	*34,0-< 37*	*≥ 37*	***Total***
Chorio Amn. (%)	14 (63,6)	21 (33,3)	12 (20,3)	7 (7,6)	10 (1,26)	64 (5,7)
NNSepsis (%)	6 (27,2)	7 (33,3)	3 (25)	—	2 (20,0)*	18 (28,1)
Death of Infect. (%)	2 (33,3)	2 (28,5)	—	—	—	4/18 (22,2)
Escherichia coli	1/3	2/4	—	—	—	3/7 (42 %)
Klebsiella sp.	—	—	0/1	—	—	0/1
Proteus mirabilis	1/1	0/1	—	—	—	1/2 (50 %)
Enterococcus sp	0/1	—	—	—	—	0/1
S. agalactiae	0/1	0/1	—	—	—	0/2
S. pneumoniae	—	0/1	—	—	—	0/1
Lysteria monoc.	—	0/1	—	—	0/2	0/3
Candida albicans	0/1	0/1	—	—	—	0/2

NNS: Neonatal Sepsis.

DIAGNOSIS

The clinical Chorioamnionitis is diagnosed by maternal fever ≥38 °C, plus two of the following signs, without other known reason of fever:

- White Blood Cells (WBC) >15.000/mm^3.
- Maternal tachycardia >100 beats/m.
- Fetal tachycardia >160/bpm.
- Tender uterus.
- Foul-smelling discharge.

In other less clear cases is possible to suspect that IAI is starting when appear uterine contractions, temperature between 37 and 37,5 °C, NST previously reactive that becomes non reactive, decrease of FBP, and especially if in blood analysis there is an increase in white cell count over 15.000/mm^3, or the % of bands >5, or CRP value increasing over the previous values.

In all cases is very important to perform an early, quick but also sure diagnose, as it means usually to take the decision of finishing the pregnancy, and this has important consequences before 32 weeks. In these cases we try to get more information through an US guided amniocentesis that, even in cases with PROM usually with few AF, is possible in more of 90 % of cases. We take AF for culture, but are necessary a quick diagnose of levels of AF glucose, presence of microorganisms in a Gram stained extension, and the number of leokocytes/mm^3. If glucose values are <14 mg/dL, germs are present, or leukocytes are >50/mm^3 the suspicious is clear and especially if gestational age is >32 weeks, is better to finish the gestation. Before this gestational age we recommend to have not only laboratory but also clinical signs of CCA, or at least all laboratory data coincident. Some recent

data suggest that having values of Interleukin-6, metalloprotease-8 or a proteomic study of AF, will give more predictive results, but they are expensive and usually not available through 24 hours, that limit their advantage.

TREATMENT

The CCA treatment is based *in a sure but early diagnose*. *Antibiotic treatment* should be start after AF cultures, or at least cultures from endocervical discharge, and *finishing the gestation*. This should be performed not on emergency bases but after short time-few hours-of the diagnosis. If it is not possible a cesarean section has to be considered, although for the mother is better a vaginal delivery, and for both the mother and the baby is very important to start with antibiotic treatment as soon as possible. This treatment need to cover at least *S. agalactiae, E. coli,* other enteric Gram negative, and *Enterococcus sp*. The more usual combination is *ampicillin* and *gentamycin*[9], and if a cesarean section is performed clindamycin is added to decrease maternal wall or peritoneal abscess. All these antibiotics are inexpensive and available everywhere in the world. If the combination ampicillin and gentamycin has been used in the last three weeks then is recommended to change gentamycin by *cefoxitin,* trying to decrease the resistance to this antibiotic.

We can see in the table 3 and 4 that aerobic Gram positive microorganisms were the leading cause (17/57) of CCA and NN sepsis in the 1986-1991 period before starting the systematic screening of *S.agalactiae.* In the 2002-2004 period the *E. coli* become the predominant germ in CCA and NN sepsis (19/54), with also an increase of anaerobic germs, and the appearance of some yeast.

Finally if we look to a the combination of antibiotics more effective we can see in the table 5, that ampicillin plus gentamycin is still a very good choice with low frequency of resistances[10]. Amoxicillin-clavulanic acid is by the moment not recommended, at least before

Table 5. Susceptibility to combination of antibiotics used in IAI or NNS.

Antibiotics	*All strains %*	*Only aerobic strains %*
Ampicillin	59,6	64,7
Ampicillin + Gentamycin	79,0	88,2
Ampicillin + Gentamycin + Clindamycin	83,9	88,2
Ampicillin + Gentamycin + Metronidazol	90,3	88,2
Clindamycin+ Gentamycin	71,0	72,5
Erythromycin	33,8	35,2
Erythromycin + Gentamycin	64,5	72,5
Ampicillin + Cefoxitin	90,3	92,2
Ampicillin + Cefotaxime	85,5	96,1
Amoxicillin/clavulanate*	82,2	86,3
Imipenen	96,8	98,0

* This combination is currently not recommended by the risk of Necrotizing Enterocolitis after ORACLE Study.

term, because can increase the risk of necrotizing Enterocolitis, after ORACLE STUDY. After this study many units have changed to erythromycin or a combination erythromycin plus gentamycin, but in our opinion and according to our data this combination has an efficacy of 64,5% over the most frequent germs in front of 79,0% of the combination amoxicillin plus gentamycin. This is the reason why in our center and in consensus to the neonatologists and microbiologists we have returned to the classic combination amoxicillin plus gentamycin.

CONCLUSION

The CCA is a possibly severe infection for the mother and the fetus and the newborn. It needs to be identified as early as possible, even using an invasive procedures and treated, in case of being confirmed, with an effective antibiotic combination and ending the gestation in a short period of hours.

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Prolonged labour

CHAPTER 28

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INTRODUCTION

Prolonged labour is a leading cause of death among mothers and newborns in the developing world. It is most likely to occur if a woman's pelvis is not large enough for her baby's head to pass through or if a woman's uterus does not contract sufficiently. If her labour does not progress normally, the woman may experience serious complications such as obstructed labour, dehydration, exhaustion, or rupture of the uterus. Prolonged labour may also contribute to maternal infection or haemorrhage and to neonatal infection.

Skilled management of labour using a partograph, a simple chart for recording information about the progress of labour and the condition of a woman and her baby during labour, is key to the appropriate prevention and treatment of prolonged labour and its complications. Following the recommendation of the World Health Organization (WHO), the Maternal and Neonatal Health (MNH) Program promotes the use of the partograph to improve the management of labour and to support decision-making regarding interventions. When used appropriately, the partograph helps providers identify prolonged labour and know when to take appropriate actions.

The partograph is a vital tool for providers who need to be able to identify complications in childbirth in a timely manner and refer women to an appropriate facility for treatment.

APPROPRIATE USE OF THE PARTOGRAPH

HOW THE PARTOGRAPH WORKS

The partograph is a printed graph representing the stages of labour (pag. 275). Once a woman is in active labour, the skilled provider regularly plots the descent of the baby as

well as the dilation of the woman's cervix to help keep track of whether the woman's labour is progressing normally and identify when intervention may be needed. In addition, the provider records details about the condition of both mother and fetus, including the fetal heart rate, the colour of the amniotic fluid, the presence of molding, the contraction pattern, and the medications that have been given to the woman.

Already plotted on each printed partograph are an alert line and an action line. The alert line is plotted to correspond with the onset of the active phase of labour (dilation of the cervix to 4 centimeters). When the woman's cervix reaches 4 centimeters, the provider should expect dilation to continue at about the rate of 1 centimeter per hour. The action line is plotted 4 hours after the alert line. If the woman's labour is not following the expected course after 4 hours, the plot of her labour will begin to approach the action line, signaling the need to take action. Interventions that may be appropriate when the action line is crossed include the use of oxytocin to augment labour, vacuum-assisted birth (if the cervix is fully dilated), or cesarean section.

AN AID IN CLINICAL DECISION-MAKING

Having a visual representation of the conditions of both mother and fetus helps providers determine whether and when to intervene if labour is not progressing normally. Every time data is plotted on the graph, the provider should be thinking, «Is this what should be happening at this point?» If the answer is yes, the provider should think ahead to what to expect in the next 2 to 4 hours. If the answer is no, the provider must consider what to do to address the woman's condition. In this way, use of the partograph helps providers ensure that women are being carefully monitored during labour, avoid unnecessary interventions, and recognize and respond to complications in a timely manner.

IMPORTANCE OF PROTOCOLS

The partograph gives providers objective data on which to base their clinical decisions and enhances communication among members of the team of providers who are caring for the mother, so that decisions can be made in a timely manner. The partograph is of little use, however, without management protocols that give clear directives about what actions should be taken at what point.

Each hospital and healthcare setting needs a set of rules to guide decision-making in that setting, so that providers know what actions to take when the partograph shows that a woman needs additional care. Providers in peripheral settings, for example, may need to refer a woman to a centre capable of performing oxytocin augmentation and caesarean section. Protocols should address issues such as when and what action should be taken, when referrals should be made, and the procedure for referrals.

CAUSES OF PROLONGED LABOUR: IMPORTANT POINTS

- A careful and thorough physical examination must be performed. The examination must include a complete abdominal examination with Leopold manoeuvres in order to ascertain the presentation of the fetus and to estimate the fetal weight. Clinical estimation of the fetal weight may not be accurate, especially at higher ranges of birth weight. This is also the case with ultrasound estimation of fetal weight. Note that the margin

of error increases with gestational age and weight, especially for fetuses heavier than 4-4,5 kg.

- The focus of the pelvic examination is broader than just determining the degree of cervical dilatation, effacement, and station. Pelvic examination provides an excellent opportunity to assess the patient's pelvis and to perform clinical pelvimetry. Finally, fetal presentation and position must be assessed. Evaluating the position once cervical dilatation is advanced or completed appears to be a common practice, but knowing the fetal position as early as possible is beneficial because fetal position can be a major contributor to dystocia.

- The examiner, preferably the same person each time, should perform a careful cervical examination every 2 hours once the patient is in active labour (certain clinical situations may require modification of this time interval). All of the above named factors (ie, cervical dilatation, effacement, station, position, presentation) should be reevaluated during each examination. A diagnosis of dystocia should be made in a prompt manner so that an attempt to correct the dysfunction can be made without jeopardizing the mother or fetus.

- Normal labour is a coordinated interplay between maternal expulsive forces (power), fetal position (passenger), and maternal pelvic shape and structure (passage); therefore, before making a diagnosis of dystocia, evaluating each of these 3 parameters (Ps) is important. One or more of these factors can contribute to dystocia.

- **Abnormalities of maternal expulsive forces** (power)

  — The first criterion for diagnosis of an abnormality of the expulsive forces is that the patient must be in the active phase of labour, which is defined as a phase of maximal cervical dilatation. With adequate contractions in the active phase, a cervical dilatation rate of at least 1,2 cm/h in nulliparous women and 1,5 cm/h in parous women can be expected. For most women in spontaneous labour, these rates of cervical dilatation are achieved with at least 3-5 contractions in a 10-minute period. If the rate of dilatation is less than expected, the diagnosis is a protraction disorder. If the evaluation has demonstrated no cervical dilatation in a 2-hour period, the diagnosis is arrest of dilatation.

  — Before determining a diagnosis of arrest of dilatation, the adequacy of contractions must be evaluated. The rate of uterine contractions should be at least 3 every 10 minutes to be considered minimally effective. The intensity of contractions should also be at least 25 mm Hg above the baseline. The health care provider attending the labour can perform the assessment of these characteristics of uterine activity. An intrauterine pressure catheter can be used to measure the adequacy of the uterine contractions. Intensity is measured in Montevideo units, which are calculated as the intensity of contractions in millimeters of mercury multiplied by the frequency for a 10-minute period. An adequate contraction pattern exceeds 200 Montevideo units in a 10-minute period. If this pattern is present for 2 hours without cervical change, the diagnosis of arrest of dilatation can safely be made.

  — The effect of anesthesia on the pattern of labour has been extensively reviewed. Recent studies indicate that epidural anesthesia prolongs the active phase and the second stage of labour. Despite these findings, studies have noted neither an increase in nor correlation of epidural anesthesia and the rate of caesarean delivery. However, a few studies suggest an increased prevalence of malpresentation and operative vaginal deliveries.

- **Abnormalities of fetal presentation, position, and development** (passenger)

  — Any presentation other than occiput increases the probability of dystocia. In face or brow presentations, dystocia can develop with mentum posterior face presentations. With these presentations, flexion of the head is impeded by compression of the fetal brow under the symphysis pubis.

  — As labour progresses, the examiner should ascertain if asynclitism (the relationship between the anterior and posterior parietal bones and the sagittal suture with the maternal pelvis) is present. If one of the parietal bones precedes the sagittal suture, the head is considered asynclitic. When asynclitism is persistent in either the occiput anterior or the posterior position, forceps-assisted vaginal delivery can be helpful for correcting the problem. Kielland forceps is the most commonly used type of forceps for this purpose. The sliding lock of the instrument allows accurate cephalic application followed by correction of the asynclitism; however, other types of obstetrical forceps can also be used. Persistent occiput posterior position, leading to a prolonged second stage, can also be corrected by performing a forceps-assisted vaginal delivery.

  — Forceps delivery is discussed in more detail in Surgical Care. The number of practitioners who remain comfortable using these types of forceps maneuvers has gradually diminished.

  — Another fetal factor that can contribute to dystocia is macrosomia, which is defined as a fetal weight of 4.500 g or more. Estimated fetal weight should be assessed by Leopold manoeuvres in all patients upon presentation to labor and delivery. Obtaining an estimated fetal weight using ultrasound may be considered in the presence of diabetes mellitus or if maternal obesity makes the estimation of fetal weight difficult. Overall, ultrasound predictions of fetal weight fall within 20% of actual fetal weight in the third trimester. Some clinicians opt to proceed with caesarean delivery without a trial of labour in primigravid patients with a fetus believed to be macrosomic. Elective caesarean delivery in this situation is not supported by sound clinical evidence.

  — Fetuses with anomalies such as hydrocephaly, enlarged abdomens, or neck masses can also present with dysfunctional labours. Risk factors for shoulder dystocia cannot be identified prior to labour. Macrosomia and maternal diabetes are the 2 most frequently cited risk factors. Prolonged second stage of labour and the use of midpelvic instrumental delivery has been shown to be associated with shoulder dystocia. Again, it is extremely important to understand that shoulder dystocia is unpredictable.

- **Abnormalities of the maternal bony pelvis or birth canal** (passage)

  — The female pelvis can be classified into 4 types based on the shape of the pelvic inlet. Boundaries of the pelvic inlet are (anteriorly) the posterior border of the symphysis pubis, (posteriorly) the sacral promontory, and (laterally) the linea terminalis. The 4 basic types are gynecoid, anthropoid, android, and platypelloid. The gynecoid and anthropoid types have a good prognosis for vaginal delivery, while android and platypelloid types have a poor prognosis for vaginal delivery.

  — Clinical pelvimetry is used to obtain an indirect measurement of the obstetrical conjugate, ie, a measurement of the anteroposterior diameter of the pelvic inlet. The average obstetrical conjugate is 11-12 cm. An estimate of the obstetrical conjugate is obtained by subtracting 1,5-2 cm from the diagonal conjugate, ie, the distance from the inferior border of the symphysis pubis to the sacral promontory. Another mea-

surement of clinical pelvimetry is the bi-ischial diameter, which is the distance between the ischial tuberosities. This distance is obtained with the patient in the lithotomy position, with a measurement of 8 cm or greater considered adequate.

MANAGEMENT OF DISTOCIA: PRACTICAL POINTS

Management of dystocia depends on the underlying factors. When dystocia is the result of inadequate uterine contractions, oxytocin is used (see Medication). Dystocia resulting from abnormal fetal position can be corrected and managed by forceps or acesarean delivery.

UNSATISFACTORY PROGRESS OF LABOUR

PROBLEMS

- The latent phase is longer than 8 hours.
- Cervical dilatation is to the right of the alert line on the partograph.
- The woman has been experiencing labour pains for 12 hours or more without delivery (prolonged labour).

GENERAL MANAGEMENT

- Make a rapid evaluation of the condition of the woman and fetus and provide supportive care.
- Test urine for ketones and treat with IV fluids if ketotic.
- Review partograph.

DIAGNOSIS

Diagnosis of unsatisfactory progress of labour

Findings	*Diagnosis*
Cervix not dilated. No palpable contractions/infrequent contractions.	False labour.
Cervix not dilated beyond 4 cm after 8 hours of regular contractions.	Prolonged latent phase.
Cervical dilatation to the right of the alert line on the partograph • Secondary arrest of cervical dilatation and descent of presenting part in presence of good contractions. • Secondary arrest of cervical dilatation and descent of presenting part with large caput, third degree moulding, cervix poorly applied to presenting part, oedematous cervix, ballooning of lower uterine segment, formation of retraction band, maternal and fetal distress. • Less than three contractions in 10 minutes, each lasting less than 40 seconds. • Presentation other than vertex with occiput anterior.	Prolonged active phase. • Cephalopelvic disproportion. • Obstruction. • Inadequate uterine activity. • Malpresentation or malposition.
Cervix fully dilated and woman has urge to push, but there is no descent.	Prolonged expulsive phase.

MANAGEMENT

False labour

Examine for urinary tract or other infection or ruptured membranes and treat accordingly. If none of these are present, discharge the woman and encourage her to return if signs of labour recur.

Prolonged latent phase

The diagnosis of prolonged latent phase is made retrospectively. When contractions cease, the woman is said to have had false labour. When contractions become regular and dilatation progresses beyond 4 cm, the woman is said to have been in the latent phase.

> Misdiagnosing false labour or prolonged latent phase leads to unnecessary induction or augmentation, which may fail. This may lead to unnecessary caesarean section and amnionitis.

If a **woman has been in the latent phase for more than 8 hours** and there is little sign of progress, reassess the situation by assessing the cervix:

- If there has been **no change in cervical effacement or dilatation** and there is no fetal distress, review the diagnosis. The woman may not be in labour.
- If there has been a **change in cervical effacement or dilatation,** rupture the membranes with an amniotic hook or a Kocher clamp and induce labour using oxytocin or prostaglandins:
  - Reassess every 4 hours.
  - If the **woman has not entered the active phase after 8 hours of oxytocin** infusion, deliver by caesarean section.
- If there are **signs of infection** (fever, foul-smelling vaginal discharge):
  - Augment labour immediately with oxytocin.
  - Give a combination of antibiotics until delivery:
    - Ampicillin 2 g IV every 6 hours.
    - PLUS gentamicin 5 mg/kg body weight IV every 24 hours.
  - If the **woman delivers vaginally,** discontinue antibiotics postpartum.
  - If the **woman has a caesarean section,** continue antibiotics PLUS give metronidazole 500 mg IV every 8 hours until the woman is fever-free for 48 hours.

Prolonged active phase

- If there are no signs of cephalopelvic disproportion or obstruction and the membranes are intact, rupture the membranes with an amniotic hook or a Kocher clamp.
- Assess uterine contractions:
  - If **contractions are inefficient** (less than three contractions in 10 minutes, each lasting less than 40 seconds), suspect inadequate uterine activity (page S-66).
  - If **contractions are efficient** (three contractions in 10 minutes, each lasting more than 40 seconds) suspect cephalopelvic disproportion, obstruction, malposition or malpresentation (see below).
- General methods of labour support may improve contractions and accelerate progress.

Cephalopelvic disproportion

Cephalopelvic disproportion occurs because the fetus is too large or the maternal pelvis is too small. If **labour persists with cephalopelvic disproportion,** it may become arrested or obstructed. The best test to determine if a pelvis is adequate is a trial of labour. Clinical pelvimetry is of limited value.

- If **cephalopelvic disproportion is confirmed** (Table S-10), deliver by caesarean section.
- If the **fetus is dead:**
  - — Deliver by craniotomy.
  - — If the **operator is not proficient in craniotomy,** deliver by caesarean section.

Obstruction

Note: Rupture of an unscarred uterus is usually caused by obstructed labour.

- If the **fetus is alive, the cervix is fully dilated** and the **head is at 0 station or below,** deliver by vacuum extraction.
- If there is an **indication for vacuum extraction and symphysiotomy** for relative obstruction and the fetal head is at −2 station:
  - — Deliver by vacuum extraction and symphysiotomy.
  - — If the **operator is not proficient in symphysiotomy,** deliver by caesarean section.
- If the **fetus is alive but the cervix is not fully dilated** or if the **fetal head is too high for vacuum extraction**, deliver by caesarean section.
- If the **fetus is dead:**
  - — Deliver by craniotomy.
  - — If the **operator is not proficient in craniotomy,** deliver by caesarean section.

Inadequate uterine activity

If **contractions are inefficient** and **cephalopelvic disproportion and obstruction have been excluded,** the most probable cause of prolonged labour is inadequate uterine activity.

> Inefficient contractions are less common in a multigravida than in a primigravida. Hence, every effort should be made to rule out disproportion in a multigravida before augmenting with oxytocin.

- Rupture the membranes with an amniotic hook or a Kocher clamp and augment labour using oxytocin.
- Reassess progress by vaginal examination 2 hours after a good contraction pattern with strong contractions has been established:
  - — If there is **no progress** between examinations, deliver by caesarean section.
  - — If **progress continues,** continue oxytocin infusion and re-examine after 2 hours. Continue to follow progress carefully.

Prolonged expulsive phase

Maternal expulsive efforts increase fetal risk by reducing the delivery of oxygen to the placenta. Allow spontaneous maternal «pushing», but do not encourage prolonged effort and holding the breath.

- If **malpresentation and obvious obstruction have been excluded,** augment labour with oxytocin.
- If there is **no descent after augmentation**:
  - — If the **head is not more than 1/5 above** the symphysis pubis or the leading bony edge of the fetal **head is at 0 station,** deliver by vacuum extraction or forceps;
  - — If the **head is between 1/5 and 3/5 above** the symphysis pubis or the leading bony edge of the fetal **head is between 0 station and −2 station:**
    - ○ Deliver by vacuum extraction and symphysiotomy.
    - ○ If the **operator is not proficient in symphysiotomy,** deliver by caesarean section.
    - ○ If the **head is more than 3/5 above** the symphysis pubis or the leading bony edge of the fetal **head is above −2 station,** deliver by caesarean section.

CHAPTER 29

Abnormal fetal presentations

LABOUR

P. Barri

INTRODUCTION

The presence of an abnormal presentation (detected in the early third trimester) worries pregnant women and their attendants. Abnormal presentations carry a 22,2 % chance of persisting at term. Continuance of abnormal presentation at each subsequent week of the third trimester increases the risk of a breech delivery at term. Conversely, in very few cases, a cephalic presentation at 28-30 weeks converts to a breech or other presentation during the third trimester (0,75 %) (see pag. 277).

OCCIPUT POSTERIOR

It is defined by an abnormal fetal position with occiput at maternal sacrum. The fetal face looks towards maternal pubic symphisis. It represents a 10 % of all fetal positions.

The fetus presents a less favorable head diameter for delivery, due to the deflexion of the fetal head and the posterior presentation. Fortunately, in 90 % of cases it usually rotates to occiput anterior.

The main symptom is a prolonged second stage of labour, that is more than two hours in a nulliparous woman and more than one hour in multiparous. The main signs at digital exam are an asymmetric cervical dilation (persistence of anterior cervical lip) and a characteristic palpation of fetal head (fetal anterior fontanel is easily palpable, and following the sagital suture in posterior direction the lambdoid fontanel will be found).

The most frequent complications are a failure to progress and an extended episiotomy or perineal laceration.

There are several options to manage the situation. In 45 % of cases the delivery will be spontaneous. Maternal position changes might help, but its efficacy is unclear. A manual rotation may be performed during vaginal exam. The first step consists on flexing the fetal head by placing the operator's hand in posterior pelvis behind occiput and wedging the

head into flexion. The second step is the head rotation. It has to be performed during contraction while the mother is pushing.

Direct Occiput posterior: examiner pronates dominant hand.

Right occiput posterior: examiner pronates left hand clockwise.

Left occiput posterior: examiner pronates right hand counter-clockwise.

The vacuum delivery is also feasible. The vacuum cup should be placed as posterior as possible in order to favor flexion of the fetal head. However, using the vacuum for head rotation should be avoided due to its high risk of scalp laceration.

Finally, the forceps delivery should be reserved to skilled birth attendants; specially the forceps rotations (Kjelland or Scanzoni maneuvers). If all these options fail to succeed or are found to be contraindicated, a caesarean section should be performed.

FACE PRESENTATION

Face presentation (0,1 % of singleton deliveries) is an extended fetal attitude. The fetus presents its largest head diameter (occipitomental), which is increased 3 cm over flexed head (24 %). This presentation may often result in a failure to progress.

In this cases the head is hyperextended, with the face as presenting part. The main causes are grand multiparous, large fetus and contracted pelvis, neck swelling (cystic hygroma or thyroid goiter) and anencephaly.

At the digital exam, facial features are palpable (mouth, nose). A differential diagnosis should be made with the breech presentation, much more common than the face.

In the management of this situation, one should never attempt to convert face presentation to vertex. Never apply vacuum extractor to face presentation. Avoid oxitocin in most cases. Consider large episiotomy if fetus delivers vaginally.

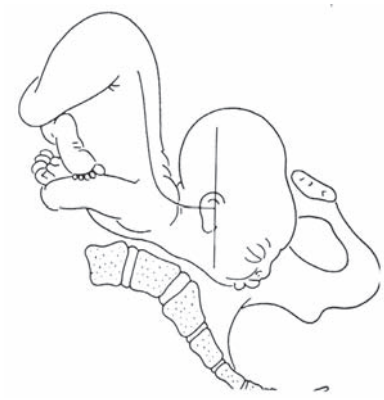

Figure 1. Face presentation, mentum anterior: vaginal delivery is possible.

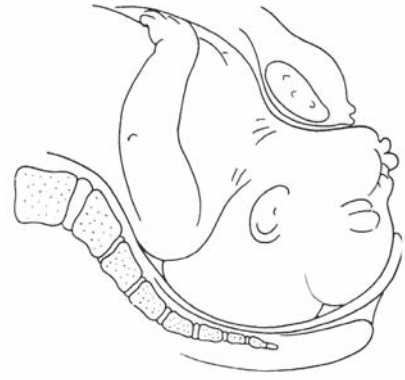

Figure 2. Face presentation, mentum posterior: indication for cesarean delivery.

Different varieties of face presentation are described. In general, vaginal delivery is possible in mentum anterior (face anterior) and brow (0,02 %) not converted to face or occiput (figure 1). However, mentum posterior or face posterior are an indication for caesarean section (figure 2).

COMPOUND PRESENTATION

It is defined by the prolapse of the hand alongside the fetal head. The incidence is low (0,1 to 0,04 %) and it is more common in preterm deliveries. At the vaginal digital exploration, the hand is easily palpated beside the fetal head. A differential diagnosis should be made with the fetal foot.

The management of this presentation requires expectancy. In most cases, spontaneous vaginal delivery occurs. One can consider repositioning if the descent is arrested. The examiner may elevate the fetal hand or bring the head downward.

TRANSVERSE PRESENTATION

Transverse lie is perpendicular to mother's long axis (figure 3). When the fetus is transverse with the back down, the shoulder sits over the pelvic inlet (shoulder presentation). Its incidence is low (0,3 %).

The most frequent causes are prematurity, placenta previa, abnormal uterus, contracted pelvis or relaxed abdominal wall, and the presence of polyhidramnios,

The diagnosis may easily be made by Leopold's maneuvers. At the digital cervical exam there is no presenting part.

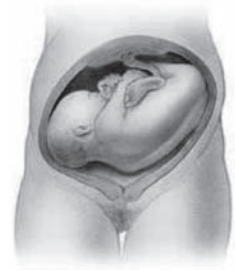

Figure 3. Transverse lie. Shoulder presentation.

Caesarean section is indicated in most cases. An external cephalic version may be attempted, as long as the membranes are intact and there is no labour.

BREECH PRESENTATION

The incidence of breech presentation at term is around 3-6 %. There are different types of breech presentation.

a) Frank breech (45-50 %): hips flexed over anterior body. Knees extended (figure 4a).

b) Complete breech or full breech (10-15 %): Hips flexed, knees flexed (figure 4b).

c) Footling breech or incomplete breech (35-45 %): one or both hips and knees extended. One or both feet presenting (figure 4c).

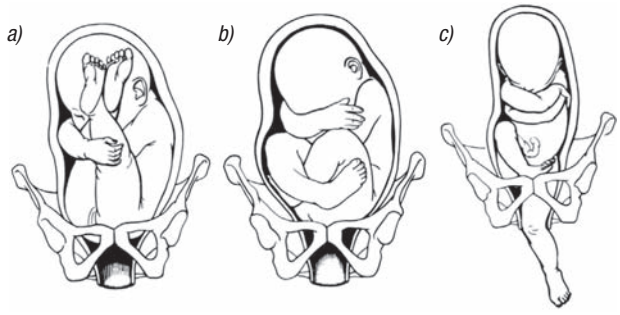

Figure 4. Breech presentations. *a)* Frank, *b)* Complete or full and *c)* Incomplete (single footing).

The risk factors for breech presentation are: prematurity, multiple prior pregnancies, polyhydramnios or olygohydramnios, uterine abnormalities, fetal abnormalities (Down syndrome, hydrocephallus), macrosomia, twin gestation, breech presentation in prior pregnancy and absolute cephalopelvic disproportion.

The signs of breech presentation are:

a) Leopolds' maneuvers: longitudinal fetal lie, being the head palpated in the uterine fundus, although it may be obscured by maternal ribs.

b) Fetal heart tone auscultation. Breech fetal heart is best heard above the umbilicus.

c) Vaginal examination. No hard head palpated in the pelvis. Fontanels and sutures are not palpable. Soft buttocks palpated with hard irregular sacrum. The skin of the buttocks is smooth. Feet may be presenting part in the pelvis.

Before labour, there is a higher risk of premature rupture of membranes and cord prolapse.

The management of the breech presentation requires an evaluation for the possible causes of the situation. In frank or complete breech, an external version may be attempted. In case of failure, according to the operator's experience, a vaginal delivery or a caesarean section should be performed. In footling or incomplete breech, a caesarean section should be indicated the indications for caesarean section should be liberal (table 1).

Table 1. Breech presentation: indications for cesarean section.

The indications for cesarean section should be liberal:

- Pelvis contraction or nongynecoid pelvis.
- Previous cesarean section.
- Bad obstetric history.
- Maternal stature less than 150 cm.
- Elderly primigravida.
- Excessive maternal obesity.
- Hypertension/Preclampsia.
- Diabetes.
- Dysfunctional labor.
- Uterine myomata.
- Prolonged rupture of membranes.
- Premature rupture of membranes.
- Bicornuate uterus.
- Placenta previa.
- Abruptio placenta.
- Oligohydramnios.
- Cord prolapse.
- Large fetus (more than 4.000 g).
- Footling brech.
- Hyperextension on the fetal head.
- Prematurity.
- Fetal distress or suspected fetal compromise.
- Hemolysis disease.
- IUGR.
- Fetal hydrocephalia
- Uncooperative patient.

EXTERNAL CEPHALIC VERSION

The main indication is the breech presentation at 34-36 weeks of gestation. It may also be performed in transverse or oblique presentations.

The contraindications are: pregnancy induced hypertension, prior uterine surgery (e.g. caesarean section), multiple gestation with first twin breech (might be attempted if first vertex and second breech), non-reassuring fetal heart tracing, utero-placental insufficiency and placenta previa.

A preparation is required. Two attendants must be present. One examiner performs manual version and the other monitors the fetus. An immediate caesarean section must be available if needed. Ritodrine 15 min before should be considered. Administer RhoGAM if

the patient is negative. The patient needs to have an empty bladder and an intravenous access.

The technique needs a thorough fetal assessment. Before starting, a non-stress test or a biophysical profile should be made. During the procedure, ultrasonographic assessment of the fetus is recommended. The position of the mother is supine, Trendellenburg and with the knees slightly bent; in order to help breech fetus to rise above the pelvic brim.

The first examiner elevates the breech by pushing the buttock up suprapubically. The second examiner flexes the head and rotates the fetus into oblique lie. 2/3 of the pressure is applied to the breech and 1/3 to the head. A massaging motion should be used to rotate the baby, without an excessive force. Once the fetus has rotated past the transverse lie, the examiners hands push the fetus into vertex position.

Under these conditions, the success rate of the version is around 60 %.

The procedure should be stopped if the mother feels sharp pain, there is no success after 20 minutes or a fetal bradicardia appears. If such bradicardia persists, one should return the fetus to its original breech position. If it still persists, a caesarean section should be pursued.

The most frequent reasons for failed procedure are fetal macrosomia, olygoamnios, fully extended position of the fetus, fetal malformations, short umbilical cord, anterior placenta, nulliparity, obesity, or gestational age of 37 weeks or more.

The most common complication is the fetal bradicardia or fetal heart rate decelerations. They spontaneously resolve in 40 % of the cases. Some rare, serious complications are partial placental abruption, uterine rupture, umbilical cord accident, or amniotic fluid embolism.

BREECH DELIVERY

The indications of a planned vaginal breech delivery are a complete or full breech presentation, an estimated fetal weight of 2 to 4 kg and the presence of an expert birth attendant.

The contraindications are unfavorable pelvis (e.g. android or platypelloyd, small), fetal macrosomia, utero-placental insufficiency, intrauterine growth restriction, footling breech, fetal hydrocephalia, inexperienced attendant, hyperextension of the fetal head,(assessed by ultrasound) and severe prematurity.

The breech delivery requires experience and patience. In most cases, nothing should be done until the inferior angle of the scapulas appear. The complete spontaneous delivery is uncommon in nulliparous women and might take too long, jeopardizing the fetus wellbeing. Therefore, **some active maneuvers should be performed.**

A large episiotomy is desirable.

BRACHT. Delivery of a fetus in breech position by extending the legs and trunk of the fetus over the pubic symphysis and abdomen of the mother, which leads to the spontaneous delivery of the fetal head (figure 5 and 6).

DEVENTER-MÜLLER. If the shoulders cannot be exteriorized, the Deventer-Müller maneuver should be performed. The fetus needs to be rotated until its biacromial plane is parallel to the mother's sagital plane. Then it is stretched downwards until the anterior shoulder appears and the arm is exteriorized. The posterior shoulder is then converted to anterior and the second arm is liberated (figure 6).

MAURICEAU-VEIT-SMELLIE. A method of delivering the head in an assisted breech delivery in which the infant's body is supported by the right forearm while traction is made upon the shoulders by the left hand. The operator's index is introduced in the fetus' mouth to ensure the maximum flexion of the head (figure 7).

Use of the **FORCEPS** for the extraction of the head, once all the maneuvers result unsuccessful (figure 8).

The most frequent **maternal complications** are placental abruption and fourth degree tear. The described **fetal complications** are intracranial hemorrhage (ruptured tentorium cerebelli, ruptured falx cerebri), neck trauma due to traction (dislocation of the neck, Erb-

Fig. 5. Bracht (*a* and *b*).

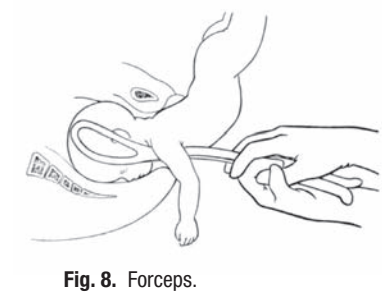

Fig. 8. Forceps.

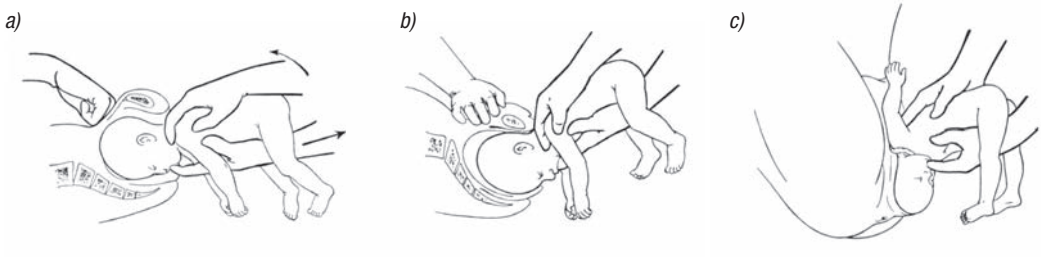

Fig. 6. Deventer-Müller (*a, b* and *c*).

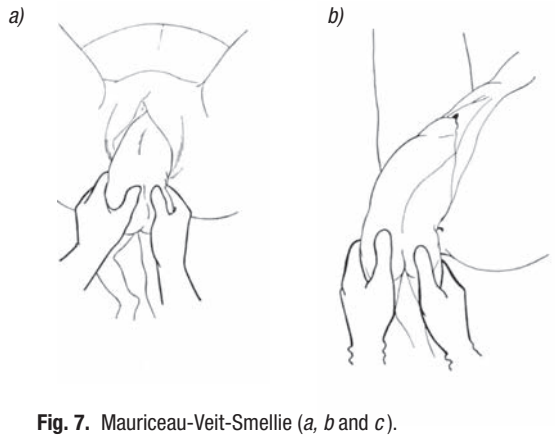

Fig. 7. Mauriceau-Veit-Smellie (*a, b* and *c*).

Duchenne paralysis, torticollis from sternocleidomastoid muscle trauma), ruptured viscera secondary to abdominal grasp (kidney or liver), genital edema due to caput formation, shoulder and arm trauma on delivery of the arms (shoulder dislocation, humerus or clavicle fracture), cord prolapse (more common in footling breech), hip and leg trauma from traction (hip dislocation, femur fracture, knee joint dislocation).

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CHAPTER 30

Macrosomia and shoulder dystocia

G. P. Mandruzzato

INTRODUCTION

The prevalence of dystocia and neonatal and maternal trauma is proportional to the neonatal weight.

The most important complication of the delivery is the shoulder dystocia. A common neonatal consequence of this complication is represented by the Obstetrical Palsy (Erb's or Klumpke's according to the level of brachial plexus injury).

As 10% of newborns present a birthweight (BW) superior to 4.000 grams and 1,5% are surpassing 4.500 grams the dimension of the clinical problem is relevant.

The aim of this chapter is to discuss definition,etiology,diagnosis, complications, prevention and management of macrosomia.

DEFINITION

A newborn presenting a BW of 4.500 grams or more is defined as macrosomic according to the ACOG[1] and the International Classification of Diseases (ICD 9:766.0).

As far as the fetus is concerned macrosomia can only be «suspected» on the basis of clinical examination,fundal height (FH) measurement or ultrasonic fetal biometry. Therefore macrosomia is defined on absolute gravimetric values (objective post-natal) or estimated (pre-natal). The observation of a weight superior to the 90th percentile cannot be considered as synonymous of macrosomia. In fact it is unlikely that a fetus or a newborn presenting a weight over the 90th percentile at 30 weeks will reach 4.500 grams. Unfortunately in many articles dealing with macrosomia the cases that are presented have a BW between 4.000 and 4.500 grams. The threshold of 4.500 grams better reflects the risk of complications.

ETIOLOGY

Many factors are regulating the normal fetal growth and not all are precisely known. Schematically they can be divided into:

1. Genetic.
2. Fetal hormones (Insulin, Insulin-like Growth factors, Leptin).
3. Utero-Placental (nutrients availability, placental function).
4. Maternal (obesity, height, weight gain, parity).

The insulin can be considered the true fetal growth hormone.

Factors inducing excessive fetal growth can be primary or secondary.

Primary factors are some fetal syndromes or tumors. The most important secondary factor is the maternal diabetes mellitus.

DIAGNOSIS

As already said an exact diagnosis of macrosomia can be only performed after birth. Of course this postnatal recognition is of no utility for guiding the obstetrical management. Before birth the fetal weight can only be estimated in order to make a prevision of the macrosomia. Different methods have been proposed.

1. LEOPOLD'S MANEUVERS

Studies comparing the efficacy of Leopold's Maneuvers and obstetric ultrasound in identifying macrosomic fetuses have shown that they are comparable but both are lacking of sufficient precision.

2. FH MEASUREMENT

This method is poorly predictive of macrosomia.

3. ULTRASONIC FETAL BIOMETRY

Many formulas have been proposed for fetal weight estimation. The most commonly used are that of Shepard[2] and Hadlock[3]. In the majority of the modern equipments a software for the automatic calculation of the weight is available. Unfortunately all the formulas have a systematic error of 7-10% in excess or in defect as compared to the actual weight. The Hadlock formula has a mean absolute error of 13% when the fetal weight is superior to 4.500 grams. In conclusion the utility of ultrasound biometry is very limited for the exact recognition of macrosomia.

COMPLICATIONS

According to the severity the complications can be indicated:

1. Cephalo-pelvic disproportion.
2. Shoulder dystocia.
3. Brachial plexus injury.
4. Hypoxic-ischaemic encephalopathy.

CEPHALO-PELVIC DISPROPORTION

The most common complication in case of macrosomia is represented by labor anomalies. First and second stage can be prolonged and arrest of progression can occur.

Prolongation is defined when a dilatation inferior to 1,2 cm is observed in nulliparas and inferior to 1,5 cm per hour in multiparas is observed and a progression of the head inferior to 1 cm(nulliparas) and 2 cm per hour(multiparas).

Arrest of the dilatation is defined when there is no cervical modification for 2 hours.

Arrest of the progression is the absence of descent of the head for 1 hour.

The possibility of prevision of cephalo-pelvic disproportion is poor. In fact it depends not only on the fetal size but also on the characteristics of the maternal pelvis.

In case of labor arrest for cephalo-pelvic disproportion the only management is represented by caesarean delivery. In some circumstances tocolysis can be performed in order to avoid fetal hypoxaemia while waiting for the operative delivery.

SHOULDER DYSTOCIA (SD)

This condition is characterized by the impact of the anterior shoulder on the pubis or of the posterior on the sacrum. It has been defined as «an unfrequent, unexpected, unpredictable nightmare for the obstetrician[4]. SD is the major complication of labor in case of macrosomia but it can be observed also when the BW is lower than 4.000 grams. The reported frequency is between 0,6 and 1,4 %. This difference is mainly due to lack of uniformity in definitions.

The so called «turtle sign» is characteristic. At any contraction the fetal head pushes against the perineum and than goes back.

In this situation it is necessary to extract the fetus as quickly as possible in order to avoid the catastrophic hypoxic-ischaemic encephalopathy.

RISK FACTORS AND PREVISION

Risk factors for shoulder dystocia, also in absence of macrosomia, can be divided in antepartal and intrapartal.

Antepartal	*Intrapartal*
Diabetes	Labor induction
Obesity	Epidural analgesia
Multiparity	Operative vaginal delivery
Prolonged pregnancy	
Previous macrosomic	
Previous shoulder dystocia	

Unfortunately their predictive value is insufficient for a clinical use.

MANAGEMENT

Many maneuvers have been proposed for treating the shoulder dystocia.

1. **Mc Roberts.** The maternal thighs must be flexed (45 degrees) against the abdomen and abducted. In this way pelvic diameters can be modified and the shoulders can be engaged and enter into the pelvis.

2. **Gaskin or four points maneuver.** The mother should lie on hands and knees.
3. **Rubin.** Pression should be applied posterior to the anterior fetal shoulder in order to facilitate rotation and reduction of bisacromial diameter.
4. **Woods.** Internal maneuver. A pression is applied on the anterior surface of the posterior shoulder.
5. **Joaquemier.** Internal maneuver for extracting the posterior arm.
6. **Zavanelli.** Replacement in utero of the head and caesarean delivery.
7. **Suprapubic sympfisiotomy.**

In case of internal maneuvers epysiotomy is required.

It must be stressed that for any maneuver neonatal trauma are observed in about 20% of the cases.

BRACHIAL PLEXUS INJURY

The most relevant neonatal complication after shoulder dystocia (but not only) is the brachial plexus injury. According to the level of the lesion it is possible to distinguish between the **Erb's Palsy** when it is at C5-C6 or **Klumpke's Palsy** when at C7-T1. It must be stressed that it is true that the prevalence of this complication is proportional to the BW and therefore more frequent in case of vaginal delivery of macrosomic fetuses but it can be present also for BW inferior to 4.000 grams and also in case of CS[5, 6].

Clavicola or humeral fractures usually do not have functional consequences.

Clavicola fractures have a frequency of 1,65 to 2,03%. In the 50% of the cases they occur in absence of risk factors like macrosomia or operative vaginal delivery.

HYPOXIC-ISCHAMIC ENCEPHALOPATHY

In case of shoulder dystocia the fetal extraction should be performed as quickly as possible (six to ten minutes). Acute fetal hypoxaemia can occur leading to permanent damage of the CNS or death.

MATERNAL COMPLICATIONS

The frequency of maternal complications is proportional to the BW particularly if it exceeds 4.500 grams. These complications are mainly represented by:

1. Risk of CS.
2. Postpartum hemorrhage.
3. Uterine rupture.
4. Infections.
5. III and IV degree perineal lesions and pelvic floor disfunction.

RISK OF CS

In case of macrosomia there is a 2 to 3 forld increased risk of CS. The risk is even greater for BW exceeding 5.000 grams.

POSTPARTUM HEMORRHAGE

The risk of postpartum hemorrhage is doubled in case of macrosomia without regard to the modality of the delivery.

UTERINE RUPTURE

The relationship between macrosomia and uterine rupture is controversial also in case of previous CS.

INFECTIONS

The rate of infections(chorioamninitis and endometritis)is significally increased in case of CS after trial of labor as compared to vaginal delivery or elective CS[7].

PERINEAL LESIONS

It has been observed that when the BW is between 4.500 and 4.999 grams there is a 4 fold increase in the risk of IV degree lacerations and 7 fold for BW exceeding 5.000 grams.

PREVENTION OF COMPLICATIONS

In case of macrosomia fetal/neonatal lesions are mainly observed after vaginal delivery.

The maternal are only observable after vaginal delivery.

The possible strategies for their prevention are:

1. Induction of labor in case of suspected macrosomia.
2. Elective CS for suspected macrosomia.

ELECTIVE INDUCTION

From the analysis of the available studies it is possible to conclude that a policy of elective induction for suspected macrosomia does not improve the clinical outcome but increases the caesarean section rates[8].

ELECTIVE CESAREAN SECTION

The target of a policy of elective CS in case of suspected macrosomia is the prevention of shoulder dystocia and brachial plexus injury. All the considered studies conclude that the number of CS necessary to avoid one single case of shoulder dystocia or brachial plexus injury is so large that a trial of labor is suggested also for estimated weight between 4.500 and 5.000 grams in absence of maternal diabetes[9].

The ACOG suggests elective CS for estimated weight superior to 5.000 grams.

PREVIOUS CS

Macrosomia per se is not a contraindication for a trial of labor in case of previous CS.It is recommended that in this case emergency CS facilities must be available.

DIABETES

The characteristics of the somatic fetal growth in case of maternal diabetes increases the risk of shoulder dystocia. In this condition a threshold of 4.500 estimated fetal weight can be considered as an indication for elective CS.

CONCLUSIVE REMARKS

The frequency of labor complications and trauma,neonatal and maternal,is proportional to the BW.

In case of macrosomia (BW more than 4.500 grams) the vaginal delivery carries an increased risk. As far as the neonate is concerned the most important complication is represented by brachial plexus injury,often consequence of shoulder dystocia. All the proposed maneuvers for the management of this complication are frequently followed by neonatal traumatic lesions. The possible prevention by elective CS in case of suspected macrosomia cannot be recommended for the following reasons:

1. The estimation by ultrasound biometry has a systematic error(in defect and in excess as well) up to the 13% in case of large fetuses.
2. The majority of newborns weighing more than 4.000 and also 4.500 grams are delivered vaginally without complications.
3. It has been estimated that the number of CS necessary to avoid one single case of permanent brachial plexus injury is excessively high with consequent increase of maternal morbidity.

RECOMMENDATIONS

1. The ultrasound estimation of fetal weight is not superior to the clinical evaluation. Both do not have sufficient accuracy in predicting macrosomia.
2. The Xray pelvimetry, the feto-pelvic index and the Friedmann partogram have limited value in predicting feto-pelvic disproportion.
3. Induction of delivery for estimated weight superior to 4.000 grams is not recommended.
4. Elective caesarean for suspected fetal macrosomia in a general population is not recommended.
5. Elective CS can be advisable for diabetic pregnancies with estimated weight superior to 4.250 grams.
6. Trial of labor should be offered for estimated weight between 4.000 and 4.500 grams in absence of maternal diabetes.
7. Previous CS does not represent a contraindication to trial of labor in case of suspected fetal macrosomia. Facilities for performing emergency CS must be available.
8. As shoulder dystocia is unpredictable it is advisable that in any delivery room a written protocol of the possible maneuvers exists. The McRobertst maneuver is the first one to be performed.
9. When macrosomia is suspected a complete counselling with the family must be carried out.

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Vaginal operative obstetrics*

CHAPTER 31

LABOUR

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INTRODUCTION

Assisted operative vaginal delivery is an integral part of wise obstetric world-care; it refers to any operative procedure designed to effect vaginal delivery.

The first time men began to think of an instrument to aid difficult delivery through vagina was in the Roman era after Christ; the first modern forceps was invented by the Chamberlen brothers in England in the late sixteenth century, while the first vacuum extractor was described as «cupping-glass fixt to the scalp with an air-pump» by James Yonge in 1706[1].

The goal of operative vaginal delivery, that has an incidence stable between 10% and 15%, is to mimic spontaneous vaginal birth, thereby expediting delivery with a minimum of maternal or neonatal morbidity. The complexity, independent of the type of instrument used, demands a high level of clinical and technical skill[2].

Vaginal operative delivery includes:

1. Forceps delivery, in which the instrument cradles the parietal and malar bones of the fetal head, and applies traction to these areas.
2. Vacuum extraction, in which the system applies suction and traction to an area of the scalp.

Operative vaginal delivery has been clearly identified as a major risk factor for fetal morbidity and mortality as well as early and late maternal morbidity[2].

CONDITIONS AND INDICATIONS

To identify the conditions in which to effect an operative delivery, we can consider the following **indications** for the procedure[2, 3]:

1. Fetal: non-reassuring conditions.

2. Maternal: medical indications to avoid Valsalva manoeuvre (e.g., cardiac disease Class III or IV, hypertensive crises, uncorrected cerebral vascular malformations, myasthenia gravis, spinal cord injury).

3. Inadequate progress of the presenting part:
   - **Nulliparous women:** lack of continuing progress of the presenting part for 3 hours (total of active and passive second stage labor) with regional anesthesia, or 2 hours without regional anesthesia.
   - **Multiparous women:** lack of continuing progress of the presenting part for 2 hours (total of active and passive second stage labor) with regional anesthesia, or 1 hours without regional anesthesia.
   - **Maternal fatigue/exhaustion.** No indication is absolute and each case should be considered individually.

There are several and essential **prerequisites** for safe operative vaginal delivery[2, 3]:

CLINICAL SITUATION OBTAINED THROUGH ABDOMINAL AND VAGINAL EXAMINATION

a) Head is ≤1/5 palpable per abdomen.

b) Vertex presentation.

c) Cervix is fully dilated and the membranes ruptured.

d) Exact position of the head can be determined; so proper placement of the instrument can be achieved.

e) Bishop score is pre-labour scoring system used to determine how successful an induction of labour may be. The total score is achieved by five components on vaginal examination: cervical dilatation, cervical effacement, cervical consistency, cervical position and fetal station. Each component has a score of 0-2 or 0-3 and the highest possible score is 13. A score of 9 is ideal.

f) Pelvis is deemed adequate.

MOTHER

a) Informed consent must be obtained and clear explanation given.

b) Appropriate anesthesia is in place, for mid-cavity rotational deliveries. It will usually be a regional block, i.e., epidural, caudal or saddle block anesthesia.

c) A pudendal block may be appropriate, particularly in the context of urgent delivery. This is easy to perform because the pudendal nerve passes below the ischiatic spine which can be promptly located by vaginal examination.

d) Maternal bladder has been emptied recently.

e) Indwelling catheter should be removed or balloon deflated.

f) Aseptic techniques.

STAFF

a) The obstetrician must have the knowledge, experience and skill necessary to properly use the instruments.

b) Adequate facilities and back-up personnel must be available.

c) Back-up plan must be in place in case of failure to deliver the fetus.

d) Anticipation of complications that may arise (e.g. shoulder dystocia, postpartum hemorrhage).

e) Personnel trained in neonatal resuscitation must be present.

Operative vaginal births have a **higher rate of failure** if associated with[2]:

- Maternal body mass index >30.
- Estimated fetal weight >4.000 g or clinically a big baby.
- Occipito-posterior position.
- Mid-cavity delivery or when 1/5 head is palpable over the abdomen.

Operative vaginal delivery should be abandoned when there is no evidence of progressive descent with each pull with forceps or vacuum or when delivery is not imminent following three pulls of a correctly applied instrument by an experienced operator. Persisting with the attempt of operative delivery can lead to fetal *cephalohematomas, subgaleal or subaponeurotic hemorrhage.*

Thus, operative deliveries anticipated to have a higher rate of failure should be conducted in a place where an immediate caesarean section can be performed; cord prolapse, abruptio placentae, fetal asphyxia or persistent bradycardia at a high station, even at full dilation with an engaged head, are best managed by C.S.

The use of outlet forceps following failed vacuum extraction may be judicious in avoiding a potentially complex, in the second stage of labor, C.S., associated with an increased risk of major obstetric hemorrhage, prolonged hospital stay and admission of the baby to intensive care unit (I.C.U.)[2].

The **Classification for Operative Procedures According to Fetal Station and Cranial Position** allows to distinguish[2-4]:

— ***Outlet***

- Fetal scalp visible without separating the labia.
- Fetal skull has reached the pelvic floor.
- Sagittal suture is in the antero-posterior diameter or right or left occiput anterior or posterior position (rotation does not exceed 45 degrees).
- Fetal head is at or on the perineum.

— ***Low***

- Leading point of the skull (not caput) is at station plus 2 cm or more and not on the pelvic floor.

Two subdivisions:

a) Rotation of 45 degrees or less.

b) Rotation of more than 45 degrees.

— ***Mid***

- Fetal head is 1/5 palpable per abdomen.
- Leading point of the skull is above station plus 2 cm but not above the ischial spines.

Two subdivisions:

a) Rotation of 45 degrees or less.

b) Rotation of more than 45 degrees.

COMPLICATIONS

Vacuum and forceps delivery can be associated with significant complications[2, 3]:

MATERNAL COMPLICATIONS

Early complications: lacerations to the cervix, vagina, perineum, or bladder, extension of episiotomies, increase in blood loss, hematomas, and intrapartum rupture of the unscarred uterus.

The incidence of severe *perineal lacerations* (i.e., third- and fourth-degree lacerations) ranges from 5-30%. Women who sustain vaginal lacerations in a previous delivery are at a significantly greater risk for a repeat laceration in subsequent deliveries. Women at greatest risk are those who experienced a laceration in the first delivery followed by another delivery combining both an instrumental delivery and an episiotomy.

Late complications (mainly related to the injury of the pelvic support tissues and organs): urinary stress incontinence, fecal incontinence, anal sphincter injuries and pelvic organ prolapse.

- *Urinary incontinence*: all women undergoing an operative vaginal delivery should have continuous monitoring, e.g., fluid balance, for at least 24 hours, to detect postpartum urinary retention. A post-void residual should be measured if retention is suspected. It must be noted that urine retention with bladder overdistension is a frequent complication of spinal or epidural blocks.
- *Anal incontinence: o*perative vaginal delivery involves sometimes a reversible and/or permanent injuries to connective tissues of the maternal pelvis, damaging these support structures.

FETAL COMPLICATIONS

Early complications: transient facial forceps marks, scalp lacerations, cephalohematomas; facial nerve injuries; skull fractures, intracranial or subaponeurotic hemorrhages. The use of protective covers over forceps has been found to decrease superficial skin lacerations[3].

- *Caput succedaneum* is normally a benign complication not necessarily due to forceps/vacuum delivery, which appears and disappears within few hours after birth; it surpasses the bone cranial sutures unlike the cephalohematoma.
- *Cephalohematoma* is an external blood collection between the bone and the periostium without surpassing the cranial sutures, which appears in the parieto-occipital region during the second-third day after delivery and normally is reabsorbed within a couple of weeks to three months. As red blood cells are broken down, causing anemia, increased production of bilirubin occurs, which increases the risk of jaundice. Sometimes it is bilateral.
- *Subgaleal or subaponeurotic hemorrhage* is a rare but a much more dangerous condition whereby a large volume of blood from damaged blood vessels collects between the periostium and the epicranial aponeurosis of the scalp, surpassing the cranial sutures. The volume of blood may reach 260 ml, i.e., equivalent to neonatal volemia. The collection of blood may reach the orbital, neck's and temporal fascia region. Fetal mortality is 25%[5]. It may not be clinically apparent until some hours postpartum or few days of life. If not detected within few days, anemia, metabolic acidosis, renal insufficiency, DIC, and respiratory distress develop causing death. It should be noted that both cephalohematoma and subgaleal hemorrhage may complicate a small percent of normal vaginal delivery (6-8) and that no risk and benefit difference was found between vacuum extraction and low forceps delivery[9]. However, the risk of retinal hemorrhage and paralysis of lateral rectum is higher with vacuum (3,2%) than for forceps (2,4%) delivery[9].
- *Ecchymoses* and, uncommonly, *scalp lacerations* can follow vacuum extraction.
- *Brachial plexus injury*, the nerve is damaged particularly during forceps delivery causing paralysis of the arm, hand or fingers.

Late complications: cerebral palsy, mental retardation, and behavioral problems may be more related to the hypoxic episodes that required emergent delivery.

Reports exist of an increased incidence of shoulder dystocia in patients delivered with forceps (although this has not been confirmed in other studies).

FORCEPS DELIVERY

Obstetric forceps are hand-held instrument designed to guide the fetus out of the birth canal during delivery by applying traction to the fetal head.

Many different types of forceps have been described and developed throughout time; the instruments have two blades, sequentially inserted into the vagina, and are constituted of 4 parts[10]:

- **Blades:** the blades grasp the fetus; they have a cephalic curvature to fit around the fetal head, and a pelvic curve.
- **Shanks:** the shanks connect the blades to the handles and determine the length of the instrument.
- **Lock:** articulation between the shanks.
- **Handles:** where the operator holds the device and applies traction to the fetal head.

INDICATIONS FOR FORCEPS DELIVERY

An undiagnosed breech presentation at full cervical dilation or for delivery of the second twin; assisted vaginal delivery of a fetus with a face presentation, in which vacuum extraction is contraindicated; delivery of premature fetuses because vacuum extraction has a highest risk of cephalohaematoma and intracranial haemorrhage. However, in most centers delivery of preterm fetuses is rightly performed by C.S. Additionally, there are medical conditions (cardiac, respiratory, and neurological) that preclude maternal efforts, required for successful vacuum extraction, in the second stage of labor. Forceps may also be chosen when maternal effort is minimal, e.g., secondary to epidural analgesia as a consequence of the lack of rotation of fetal head due to the paralysis of elevator ani muscle (table. 1)[11].

Table 1. Indications for forceps delivery[11].

Specific indications *(forceps delivery is usually superior to vacuum extraction)*	Delivery of the head at assisted breech delivery (singleton or twin). Assisted delivery of preterm infant (< 34 weeks' gestation). Controlled delivery of head at cesarean section. Assisted delivery with a face presentation. Assisted delivery with suspected coagulopathy or thrombocytopenia in the fetus. Instrumental delivery for maternal medical conditions that preclude pushing. Cord prolapse in the second stage of labor. Instrumental delivery under general anesthesia.
Relative indications *(vacuum extraction may be an alternative option)*	Delay or maternal exhaustion in the second stage of labor. Epidural block with diminished urge to push. Rotational instrumental delivery for malpositioned fetus. Suspected fetal distress.

APPLICATION TECHNIQUE

The cervix must be fully dilated and the bladder emptied, with the use of a catheter. Since mid and high application of the forceps are rarely performed, the station of the head must be at least +2. The woman is placed in the lithotomy position and a mild anesthetic is administered unless an epidural anesthesia has been performed. It is very important that adequate pain control is achieved. After ascertaining the precise position of the fetal head (by accurately feeling the posterior fontanelle), an episiotomy is performed and the two sections of the forceps are individually inserted and then locked into position around the baby's head. The fetal head is then rotated to occiput anterior position if it is not already in this position. Then the traction is applied and the baby is delivered[10]. The traction force must not overcome 0,6 kg (440 mmHg)/cm^2. A traction of 0,8 kg (588 mmHg)/cm^2 increases the risk to fetal scalp trauma[12].

CONTRAINDICATIONS

- Any contraindication to vaginal delivery.
- Refusal of the patient to consent to the procedure.
- Cervix not fully dilated or retracted.
- Unfeasibility to determine the presentation and fetal head position.
- Feto-pelvic disproportion.
- Absence of adequate anesthesia.
- Inadequate facilities and support staff.

VACUUM EXTRACTION

A **vacuum extractor** is a system of traction that, inserted into the vagina, through the suction adheres to the fetus's head to facilitate the delivery. Vacuum extraction devices consist of:

- A **cup** made of soft or rigid material which can be attached to the fetal scalp.
- A **vacuum pump** that provides suction for the cup's attachment.
- A **traction system** that allows the operator to assist the mother.

Good results with the vacuum extractor depend mainly from correct applications of the cup on the fetal scalp and from the ability of the operator. When the fetal head is malpositioned, particularly when deflexion and asynclitism are present, the design of many of the cups currently in use makes it difficult and sometimes impossible to achieve a correct cup application. Over the years, various cup designs have been used to perform vacuum extraction. The metal cups most widely used are the Bird modification ones (Bird 1969), composed of a central traction chain and a separate vacuum pipe. More recently a number of soft cups, e.g., silicone rubber cup, have been developed. The soft cups deform following the contour of the baby's head during application[13]. The Kiwi OmniCup Vacuum Delivery System (Clinical Innovations, Inc., Murray, Utah) is a new vacuum extraction device featuring a number of innovations that include an integral vacuum PalmPump™ for single-person use and the incorporation of Bird's «posterior cup» concept that makes the OmniCup suitable for use in occiput posterior and transverse positions of the head as well as in occiput anterior positions[14].

Indications for vacuum extraction are the same of forceps delivery.

APPLICATION TECHNIQUE:

The technique is vitally important to the safety and success of vacuum extraction (VE) operation. The VE delivery includes various and fundamental steps[10]:

1. The accuracy of cup application: the cup must be perfectly sticked to the fetal head, considering some fundamental parameters like:
   - The cup design.
   - The fetal cranial position and fetal station at the time of application.
   - The feto-pelvic relationship.

   Once an appropriate cup application is established, a sufficient vacuum to fix the cup to the fetal head is applied. The following step is a check of cup placement using the anterior fontanelle as the principal reference point for checking the instrument application. If a correct application has been executed the edge of a standard 60-mm cup lies approximately 3 cm or 2 fingerbreadths behind the center of the anterior fontanelle in the midline over the sagittal suture.
2. The traction technique is defined by:
   - Degree of effort used.
   - Vector of traction.
   - Method of applied force.

   After an appropriate placement of the cup, the obstetrician performs the vacuum until about 550 mmHg and than follows the traction. The traction efforts are timed to coincide with uterine contractions and the axis of traction follows the pelvic curve.

   The safe parameters for maximum number of pulls and the maximum time of use are not well defined. Most deliveries are effected within four contractions. If delivery has not occurred after 3-4 contractions or when there is some evidence of fetal scalp trauma, the intended method of delivery should be gived up[3, 12]. As each contraction wanes, the tension on the extractor handle is relaxed.

CONTRAINDICATIONS

Are the same of the forceps delivery with the exeption of specific contraindications, i.e., malpositioning (breech, face, brow) and prematurity (fetuses $<$ 36 wk gestation)[2, 3].

FORCEPS VS. VACUUM

Both forceps and vacuum extractors are acceptable and safe instruments for operative vaginal delivery. Operator's experience must determine which instrument should be used in a particular situation[4], although in most countries forceps delivery is almost abandoned in favour of vacuum extraction and C.S.

With the exception of those cases in which the indication to the use of the forceps is specific, the vacuum extractor should be used as an instrument of first choice because it decreases significantly the maternal pelvic floor injuries while there are no significant differences relative to serious neonatal morbidity. The use of the vacuum extractor has another important advantage over forceps: it is associated with a lower use of regional or general anesthesia and therefore with less pain in delivery and in the first 24 hours. On the other hand, the

vacuum extractor is more likely to fail at achieving vaginal delivery than the forceps. This may be due to the fact that it is not possible to pull hardly with this instrument, but also to the errors in the technique, i.e., incorrect cup application or pulling in the wrong direction. Moreover, all types of disposable vacuum extractors, including the new Kiwi OmniCup, present a higher incidence of cephalohematoma and retinal hemorrhage, causing a major maternal worry for the baby, even if the highest incidence of other facial/cranial injuries, i.e., corneal abrasions and external ocular trauma, is referred to the use of the forceps.

No differences have been noticed between the two methods with regard to: 1) number of newborns requiring phototherapy; 2) Apgar scores at 1 minute; 3) long-term outcome for both mother and child[2-4, 15].

EPISIOTOMY

An episiotomy is an incision performed between the vagina and the anus (excluding the rectum and its muscles) when the baby's head is exposed to a diameter of 3 to 4 centimeters to increase the opening of the vagina to assist in delivery of a baby.

According to the direction of the cut there are two different types of episiotomy[10]:

- Mediolateral, angled down away from the vagina and into the muscle.
- Midline, straight down between the vagina and anus.

The aim of this procedure is:

1. To shorten the pushing phase, thereby reducing the chance the baby will suffer from oxygen deprivation, so that it protects the fetal skull and the brain from damages.
2. To prevent ragged perineal tears and permanent relaxation of the pelvic floor with its possible sequelae of cystocele, rectocele, and uterine prolapse.

An eventual complication of the episiotomy could be represented by the extensions or tears into the muscle of the rectum or even the rectum itself. Other complications include local pain, bleeding, infection, swelling and incontinence.

The typical healing time for an episiotomy is about 4-6 weeks, depending on the size of the incision and the type of suture material used to close the episiotomy. Normal activities can be resumed shortly after birth. The stitches are absorbed by the body and do not need to be removed.

About the routine episiotomy into operative vaginal delivery, there is not agreement in literature. According to some data the use of episiotomy does not influence the risk of significant perineal trauma for forceps delivery but it is associated with an increased risk of significant perineal trauma when vacuum delivery is performed[2]. A subsequent study has underlined that executing the episiotomy in forceps delivery, especially the medio-lateral one, the incidence and severity of maternal perineal and vaginal trauma are reduced[16].

CONCLUSION

Assisted operative vaginal delivery remains one of the milestones in obstetrics and perinatology, although the incidence has dropped in favour of C.S. The serious maternal and fetal complications of forceps delivery up to about 20 years ago have significantly decreases

with the use of low forceps delivery and the introduction of vacuum extraction. The techniques, however, must be used by properly trained physicians and be tailored to each patient considering the obstetric situation.

Both of them must be stopped if there is no progress of the presenting part in due time and replaced by C.S. delivery. Although no significant difference in the incidence of intracranial hemorrhage between these 3 methods of delivery has been found[6], the indications for one of the 3 methods should strictly adhered to. Episiotomy remains an undiscussed method to favour the delivery of the presenting part and thus speed the second stage of labour.

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CHAPTER 32

LABOUR

Caesarean section

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INTRODUCTION

Conscious that in the developing countries the practice of the Caesarean Section (CS) is carried out in hospitable centers provided with a minimum of infrastructure and in order to favours the obstetric practice in the countries economically most depressed and therefore least endowed with sanitary resources, the authors of the present chapter have chosen to develop a protocol of the practice of the Caesarean specially directed to the professionals that are employed in these countries.

DEFINITION

Caeserean section is defined as the birth of a foetus through incision in the abdominal wall (laparotomy) and the uterine wall (hysterotomy). We must do only the *strongly* indicated caesareans, because the morbi-mortality is 3-10 higher than the normal delivery due to infections, haemorrhages…

The main aim of the above mentioned intervention is to diminish the mother mortality and/or to save to a foetus in serious suffering when we are sure that we have the possibility to for do CPR (cardiopulmonary resuscitation).

CLASSIFICATION

1. *Indication's Type*
   - — Elective: Indicated before starting delivery.
   - — Intrapartum: Indicated during labour or delivery.

2. *Urgency's Type*
   - — Urgent: Need to act very quickly (with increased mortality and risk for the child and the mother, for example in some haemorrhage ante partum, abruption placenta).
   - — Semi urgent: For example dystocia during the delivery.
3. *In function of uterine incision*
   - — Low transverse segment: Transverse incision in the uterus segment. It's the most frequently used, because less risk of bleeding and uterine ruptures.
   - — Corporal: Incision inside the uterus body. It would be longitudinal (classical) or transverse.

INDICATIONS: BE PRECISE, BE SPECIFIC

We summarize the more frequent indications, divided in to those indicated before the delivery and the ones decided during the course of delivery.

ANTEPARTUM

In the Prenatal Consultation we can identify some potential/risk situations it show us the contraindication to have a home delivery or in health centres, and it advise us, to carry out the delivery in a Hospital because the increased risk in the maternal and foetal morbimortality.

a) **High risk delivery.** Several illnesses that do not make possible a delivery: as pelvic malformation which causes contracted pelvis, etc. or genital maternal infection as herpes genital active, very extensive condilomatose.

b) **Uterine scars.** For previous CS it is the most principal indication.

A new CS must be done when two previous CS had been performed. If it is a corporal caesarean, normally few frequent, we must do a CS before the labour of delivery. In reference to other uterine scars not obstetrical, as a myomectomy, we can try the vaginal trial, with much caution and close monitoring.

c) **Malpresentations.** Definition: all presentations, which are not cephalic presentations.

- Refer to the hospital from antenatal care (ANC) in case of breech presentation.
- Transverse or oblique lie.
- Twin pregnancies.

About twin pregnancies, they depend on the parity and the good recommendation of the person who decides if the place of delivery foreseen or desired by the mother is adapted to the need. Let us not forget the twin's pregnancies of primipara; especially if the foetuses presents a breech (non vertex) 1st twin, possibly not vertex for 2nd twin.

Table 1 indicates the more frequent reasons of caesareans, the principal risk factors and potential complications.

These are the most frequent and we must do a diagnosis during the antenatal care, so to prescribe the best delivery place and capable to do a CS (Referral).

Table 1. Risk factors.

RisK factors to notice →	*Maternal and Neonatal Risks*
Age Primipare less than **16 years.**	Dystocic delivery.
Grand **multipara** (more than 6 deliveries).	Haemorrhage post-partum/Abnormal Presentation.
Age woman older than **35 years.**	Frequently big multipare.
Previous C-Section.	Uterus rupture.
Several Anaemia/Maternal Haemorrhage.	Foetal distress/Still-Birth/Maternal Death.
Large Fundal Height (more than 35 cm) (Possible polyhydramnios/big fœtus or multiple).	Premature Rupture Membranes/Cord Prolapsed/Uterus Rupture.
Abnormal Presentation.	Cord Prolaps/prolonged labour/Uterus Rupture/Obstructed labour.
Completely Breech Presentation or complicated.	Fœtal Distress/Head Retention still-birth.
Contracted pelvis or limited.	Not engaged in pelvis.
Rupture Membranes more than 48 hours.	Ammionitis/ Neonatal Sepsis/Endometritis.
High blood pressure (Pre-eclampsia).	Retro placental Haematoma/Foetal death/Foetal Distress/Cerebral Vascular Accident (the mother).
Multiple pregnancy.	Foetal growth Restriction/Pre-eclampsy/Dystocia 2^{e} foetus.
HIV serologist positive (mother).	Transmission HIV mother-child.

INTRAPARTUM

EMERGENCY

Caesarean section to be avoided at all times unless no other possible alternative.

- Ruptured uterus.
- Placental abruption when not in labour.
- Failed internal rotation. Transverse presentation.
- Failed vacuum and forceps.
- Obstructed labour when all other options have failed.
- Retained second twin when all other options failed.
- Massive obstetric haemorrhage for previous placenta.
- Severe preclampsia/eclampsia only when all medications and treatment have been done.
- Foetal Distress (example: cord prolaps when se we were sure a little earlier that the foetal heart was OK).

SEMIEMERGENCY

LABOUR DYSTOCIA

Definition: Dilatation period or expulsion much prolonged. It could be a Cephalo-pelvic disproportion (dystocia) or not enough contractions (dyscinesie) as failure to progress.

In order to prevent mistakes in the dystocia diagnosis, it is recommended to use all over the world (home delivery, health centres and hospital) the WHO parthograph, as for example (figure 1).

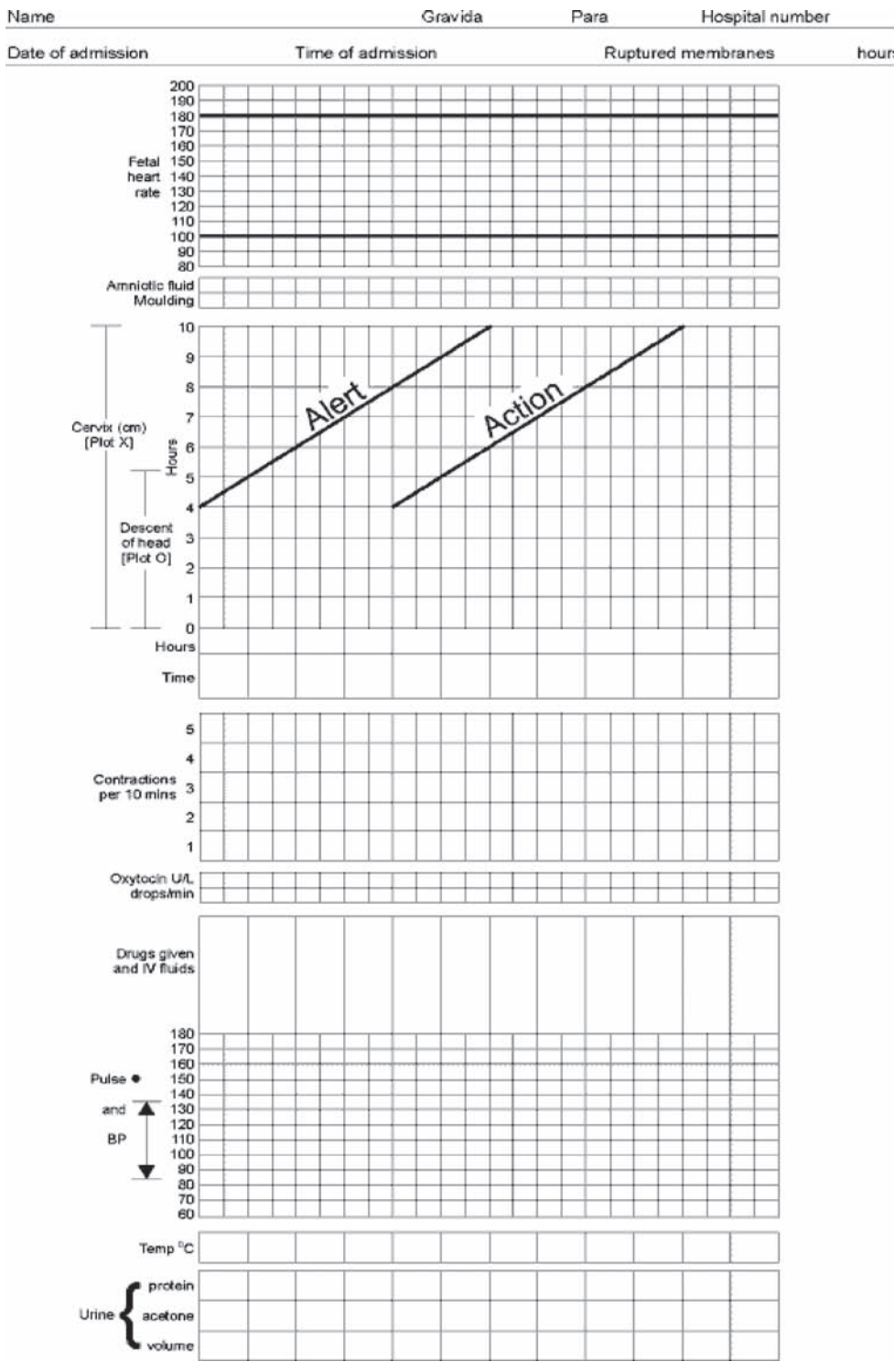


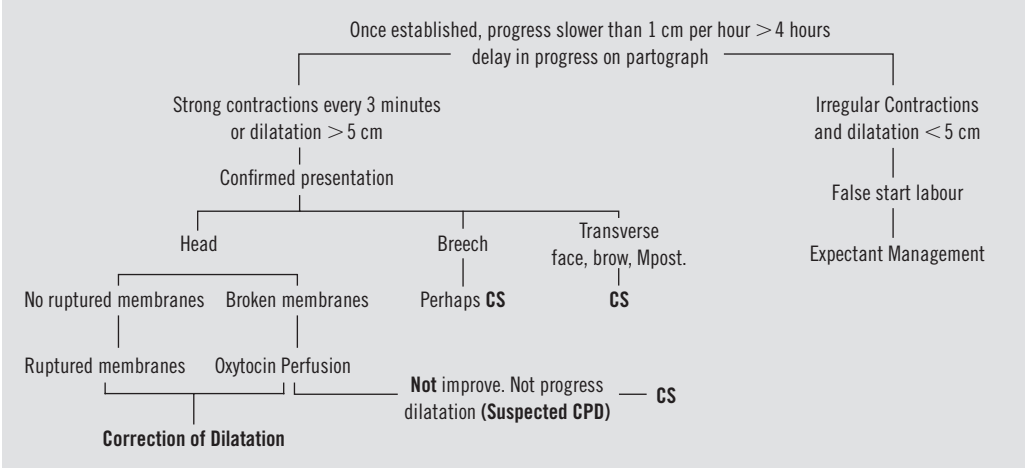
Figure 2. WHO partograph.

DIAGNOSIS

1. **Time limits of work for dilating the cervix 2-3 cm; dilatation** of 1 cm per hour with good contractions.
2. **Theoretical limits for expulsion time:** 1 hour from start correct push and childbirth delivery for multiparas and 2 hours for primigravidas.

Figure 2 shows one possible work algorithm for the handling of dynamic dystocias in the hospital control.

Figure 2. Labour dystocia.



HOW TO RECOGNIZE CPD

Clinical signs of Cephalo-pelvic Disproportion Failure of Delivery	• No descent of presenting part. • No cervical dilation/progress. • Internal Rotation.	• Formation of caput. • Succedaneum. • Excessive moulding.

How to effectively monitor for CPD and prevent maternal and neonatal morbidity

1. Recognise high risk cases.
2. Use the partograph CORRECTLY.
3. Recognise indicators of CPD... no progress, slow progress, no descent of presenting part, large caput, thick fresh meconium.
4. ***Take action*** when slow or no progress is noticed.

MALPRESENTATIONS OR DEFLECTED PRESENTATIONS

There are presentations of face, brow and bregma.

FACE. When we practise the vaginal exploration, the nose is in the centre of the presentation, the mouth; the chin (mentum) in one side and in the other side the occiput is in contact with the foetal back.

Management: We have good progression of labour if the chin is in menton anterior **try vaginal delivery.**

If limited pelvis, stationary dilatation or posterior chin considerer eventual CS.

BROW. We note in vaginal exploration the front at centre of presentation, the big fontanel in one side and the nose in the other side. We don't feel the mouth not the chin.

Management: Systematically CS, **no possibility to deliver!** (see chapter 29).

BREGMA. It's the presentation of the big fontanel that who does the vaginal exploration feels in the centre of the presentation.

Management: Vaginal delivery possible if we have good pelvis or premature, so far expulsion with vacuum extractor often needed.

BREECH. A completely independent topic.

OTHERS PRESENTATIONS. The oblique presentations or 1st shoulder are always indications to referral for C-section, vaginal delivery not possible.

Table 2 shows the «guides points» and possible findings in a vaginal examination and also its possible repercussion in the progression of delivery.

Table 2. Malpresentations.

Presentation	*Vaginal exploration*	*Progression labour*
Face	• No suture or fontanelle. • Prominence delimitate one triangle with the mouth. • Easy palpation eyes and nose. • Possible palpation ears.	• All depends on the position the mentun; mentum posterior: cesarean. • Mentum anterior: possible vaginal delivery with episiotomy.
Brown	• Palpation nose, orbits, sometimes the eyes. • No touch of chin or posterior fontanelle.	• **Cesarean** except if it is very small foetus.
Deflexed (bregma)	• Bregma or big fontanel in the center of pelvis. • Not fontanelle posterior (occipitum) nor nose.	• To perform one episiotomy if head descends normaly . • If head can't engage: **cesarean.**
Breech	• Soft mass separated in two. • One or two legs felt in case of complete breech. • More down mass in the pelvis with incomplet breech.	• Incomplet breech: normal delivery possible. • Complet breach: **cesarean** except for the very small foetus.
Shoulder	• Feel back if broken membranes. • Sometimes hand or arm fall in to vagina.	• Impossible vaginal delivery. • **Cesarean.**

FOETAL DISTRESS

It may originate during pregnancy (chronic pathology of more or less prolonged duration that origins FGR). The prolonged pregnancy is not an indication before for CS.

The authors considered indicated for this chapter, to only summarized about the acute foetal distress

Foetal Distress during labour

During the labour there are some situations that can cause foetal distress: Cord prolaps, abruption placenta or total occlusive placenta previa.

The indications for foetal Distress that mandate a CS are: **Cord Prolaps not for a long time, abruption placenta that compromises life of mother, and total occlusive placenta before and/or during labour.**

Also eclampsia or grave preeclampsia can cause foetal distress. **Do a CS on after 1 hour with convulsing patients and no observation of good progress of delivery labour.**

Problems

— Abnormal Foetal Heard Rhythm (less than 100 beats/min.) or more than 180 beats/min.

— Presence of thick meconium in the amniotic fluid.

General management

— Place the patient in left side (to correct a possible maternal hypotension and with it improve the uterus-placental perfusion).

— If treatment with oxytocine started, stop it.

— Place glucose for the mother: Helps to restablish the foetal depot, prevent the ketoses and improve glycaemia.

— Uterus inhibitors: Salbutamol IV improves the maternal and foetal heart rhythm. Indicated in foetal distress due to too many contractions, or during the time lag between indication of CS and realization, to prevent uterine contractions and improve the foetal status.

Abnormal Foetal heart rythm

- Sometimes the normal foetal heart rhythm is less during one contraction but after it normal when the uterus is relaxed.
- When the FHR is too **slow (bradycardia)** without contractions or if it is too slow when the contraction has finished, it is a sign for foetal distress.
- The rapid foetal heard **(tachycardia) can be caused by maternal fever**, or drugs which produce acceleration in the maternal heart rhythm (for example the tocolytics —Salbutamol), Maternal Hypertension or Amniotitis. If the maternal heart rhythm is not quick, we must consider this abnormal foetal heart rhythm as a sign of foetal sufferance.

1. If we are sure that the foetal distress originates from the mother (for example, maternal fever or absorption of drugs), start a good treatment.
2. If the foetal distress is not of maternal origin and the foetal heart rhythm is abnormal during three contractions, do a vaginal exam and found the signs that could explain this foetal distress:
   — If there is a haemorrhage with intermittent or permanents pain in abdomen, consider retroplacental haematoma.
   — If the patient has some signs of infection (fever, bad smell discharges) administer antibiotics to treat amniotitis.
   — If the umbilical cord is presenting or if it is outside the vagina, treat as indicated for a cord prolaps.

3. If the abnormalities in the foetal heart rythme continue or if it has another distress signs (thick meconium fluid) plan the delivery:

   — If the cervix is well dilated, and the foetal head palpable below the pubis symphyse, proceed to extraction with obstetrical ventouse, or in its absence with a episiotomy and controlled fundal pressure (Kristeller manoever).

Presence of meconium in the amniotic fluid

— It is normal to observe meconium coloration in the amniotic fluid when the foetus is at term and it isn't an indication of Foetal distress. Meconium coloration without abnormalities in the Foetal cardiac rhythm is an indication for VIGILANCE.

— The presence of thick meconium indicates that we need to accelerate the delivery and suction the respiratory tract of the newborn in order to prevent meconium aspiration.

— In the breech presentation, the expulsion of meconium during the work of delivery is not a distress sign except when started at first of the delivery.

TECHNIQUE

Nowadays, the most recommended technique is to act through the low segment of the uterus. The access is transperitoneal and the abdominal incision may be a medium infraumbilical laparotomy or transverse suprapubic (Phannenstiel incision).

The second one has some advantages: less postoperative pain and best aesthetical results. However the Phannestiel incision needs more time to enter into the uterus, so it needs more ability from the surgeon.

The high incision is indicated when:

— An inaccessible lower segment due to dense adhesions from previous caesarean sections.

— Transverse lie (with baby's back down) for which a lower uterine segment incision cannot be safely performed.

— Foetal malformations (e.g. conjoined twins).

— Large fibroids over the lower segment.

— A highly vascular lower segment due to placenta previa.

— Carcinoma of the cervix.

— Emergency caesarean.

Follow the pre/intra and postoperative cares described for all kinds of surgery.

Empty the bladder of the patient, trough an urine catheter before, doing the operation.

In all cases and especially in isolates places, and when we don't know with certaint which are the aseptical conditions:

Administer intravenous antibiotic before opening the cavity (example with: Ampicilline 2 gr or Cefazolin 1 gr) and continuous 24-48h i.v. then change to oral until to complete 5-7 days treatment (table 3).

Table 3. Intra/postsurgery protocol.

Antibiotics	*Urine catheter*
All women undergoing CS get a prophylactic dose of antibiotics in the operating theatre. Next women should receive antibiotics after CS following: • Prolonged labour >24 hours. • Attempted home delivery. • Ruptured membranes for more than 12 hours. • Fever during labour. • Fever during more than 24 hours Post-operative (if Para check negative).	Early catheter removal educes the risk of infection and encourages the woman to walk. Wait 48 hours after surgery before removing the catheter if there was: • Uterine rupture. • Severe obstructed labour. • Massive perineal or vulvar oedema. • Puerperal sepsis with pelvic peritonitis. Leave the catheter in place for 7 days or more if the bladder was injured.
Ambulation	*Analgesia*
Ambulation enhances circulation and deep breathing and stimulates return of normal gastro-intestinal function. Encourage foot and leg exercises and mobilize as soon as possible, usually within 24 hours.	Adequate postoperative pain control is important. A woman who is in severe pain does not recover well.

DAY	
0 Day of surgery: if surgery happens after 4 P.M., consider next day as day of surgery, day 0.	– Diet: NPO. – Fluids: 1500 ml dextrose 5% + Ringer lactate 1.000 ml. – **Ampicilin 2 gr i.v. intraoperative or Cefazolin 1 gr.** – **Ampicilin 1 gr i.v. tid** (intraoperative dose counts as 1st dose). – **Paracetamol 1 gr i.v. bid.** – **Tramadol 50 mg i.v. prn** (slow i.v.: 3 min).
1	– Diet: liquid, soft. – Remove i.v. line and Foley. Ambulate patient. – **Amoxyciline 500 mg p.o. tid.** – **Paracetamol 1.000 mg p.o. tid.**
2	– Diet: normal. – Ambulate patient.
3 or **4** (discharge)	– Check wound. Remove suture in 4 days. – Send to family planning in 6 weeks . – **Amoxyciline 500 mg p.o. tid (4 days).** – **Paracetamol 500 mg p.o. tid (4 days).** – **Ferrous 200 mg p.o. bid (15 days).**

After the asepsis for abdomen, perineum and vagina with iodine povidone and to put sterilised surgical lines, we continue like this:

1. Skin incision and underlying tissues.
2. Incision and detach the vesicouterine peritoneum at the level of inferior segment and descend downwards (figure 3).
3. Segmentary Hysterotomie (small transverse incision continues with stretching with the fingers) (figure 4).
4. Broken Membranes.
5. Foetal Extraction as quick as possible (figure 5).

Figure 3.

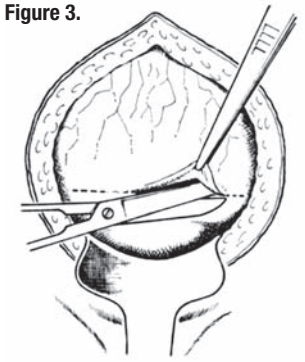


Figure 4.

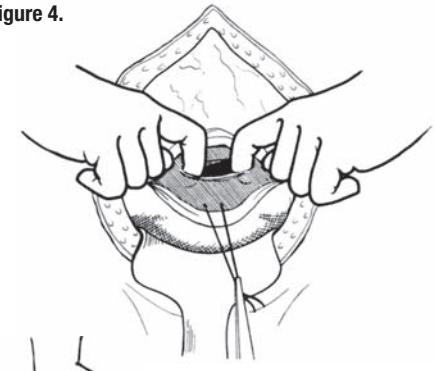
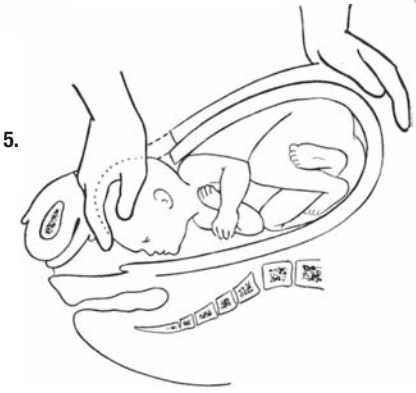


Figure 5.



6. Wash (stimulation) and aspiration of foetal respiratory tract.
7. Cut umbilical cord and give the newborn to the person who looks after the cares and the reanimation (paediatrician or midwife).
8. Artificial Extraction of placenta (check if it is complete and do if it is necessary a review of the cavity).
9. Administration of 10 UI of Oxytocine I.V.
10. Take the edge of the uterine incision with the Duval clothes.
11. Hysterorrafie: Suture (separate or cross) of the uterus in 1/2 plane with reabsorbable yam 1/0.
12. Clothe the visceral peritoneum with reabsorbable suture 2/0.
13. Clothe the planes of abdominal wall in separates planes.
14. Apply a sterile bandage.
15. Do a vaginal washing to take out the sewage coagulum.

Some big problems with the surgery:

- Primary Hemorrhagie with uterus atonie and possible hypovolemic shock.
- Septicaemia with postoperative peritonitis.
- Secondary Hemorraghie.
- Formation of Retrovesical Haematoma.
- Pulmonary Embolism.
- Wound infection.
- Thrombophlebitis.
- Vesico-vaginal Fistulae.

CONCLUSIONS

The present chapter is only a small theoretical - practical guide to help to consolidate some clear indications.

It is not necessary to forget that the Caesarean involves a high morbi-mortality in all countries, but specially in the third world due to the lack of resources. So, it is necessary to be very strict when deciding the indications and, if we do not believe that we have the necessary resources to realize it adequately, it is preferable to derive the patient to avoid major complications. We must not forget that in the foreground, in agreement with the aims of the millennium, the foremost objective is to manage to reduce maternal mortality.

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CHAPTER 33

Labour after genital mutilation

M. Tajada Duaso | L. Ornat Clemente | B. Carazo Hernández | E. Fabre

The objective of this chapter is to present the main characteristics of the female genital mutilation and a number of recommendations for health professionals who have to deal with the labour of a woman with a history of any kind of genital mutilation.

DEFINITION AND TERMINOLOGY

The World Health Organization defines Female Genital Mutilation (FGM) as «all procedures involving partial or total removal of the female external genitalia or other injury to the female genital organs whether for cultural or other non-therapeutic reasons».

This is a term used to emphasise the mutilating nature of the practice, as part of a worldwide campaign to eliminate the procedure. The United Nations identifies FGM as a form of human rights abuse on the female child and supports the eradication of this practice in countries where it is prevalent.

However, the word mutilation may cause offence to some who practice or have experienced the procedure. Most women from affected communities would understand that the intent of their mothers and female relatives would have not been to mutilate, but to enhance their daughter's opportunities for marriage and economic security, and success in the world. Its use in consultation may have the potential to be counterproductive to forming an effective professional relationship with the patient and hence detrimental to the provision of her ongoing care for what is a sensitive issue.

There are other accepted forms of description for FMG such as traditional female surgery or cutting or female circumcision. Terms that women may use include circumcision, cutting, traditional female cutting or surgery, or sunna.

CLASSIFICATION

There are various classifications for the different types of female genital mutilation but the procedures most frequently performed are removal of the prepuce, excision of the clitoris, excision of the clitoris and labia minora, and occasionally excision of much of labia majora with suturing of the two sides together to occlude the vagina. This latter procedure is known as infibulation and is sometimes referred to as pharaonic circumcision.

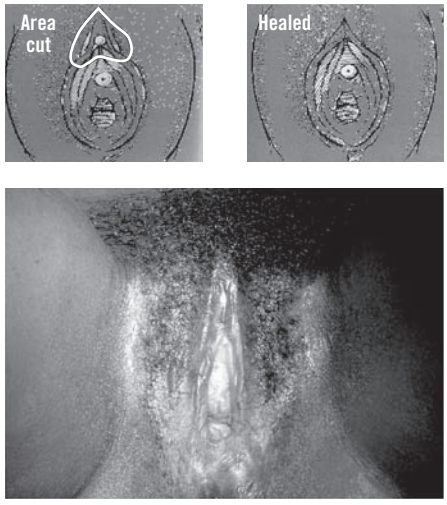


Figure 1. *FGM type I.* 24 years old woman from Gambia (Sarahole) FGM performed at the first weeks of her life. Labour assisted at Hospital Clínico Universitario Lozano Blesa of Zaragoza, Spain.

The World Health Organization (WHO) classifies the different types of FGM by the extent of the surgery:

- **Type I.** Excision of the prepuce, with or without excision of part or the entire clitoris (figure 1).
- **Type II.** Excision of the clitoris with part or total excision of the labia minora (figure 2).
- **Type III.** Excision of part or all of the external genitalia and stitching/narrowing of the vaginal opening (infundibulation) (figure 3).
- **Type IV.** Unclassified, but includes: pricking, piercing or incising the clitoris and/or labia, stretching of the clitoris and/or labia, cauterization by burning of

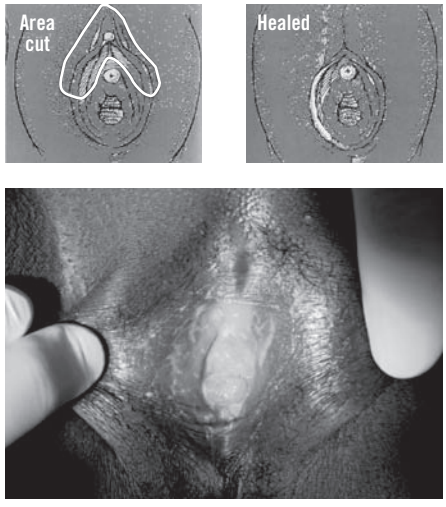


Figure 2. *FGM type II.* 21 years old woman from Senegal (Oulof) FGM performed at 3 years of life. Labour assisted at Hospital Clínico Universitario Lozano Blesa of Zaragoza, Spain.

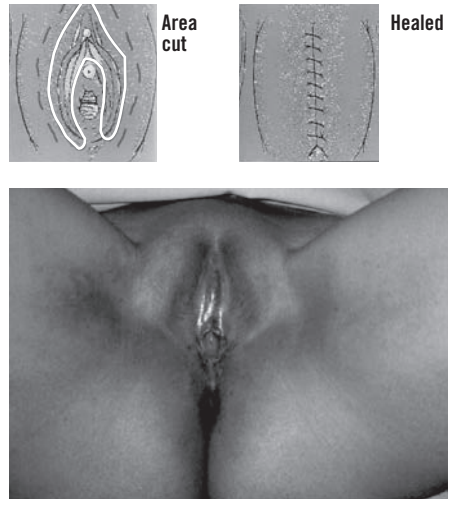


Figure 3. *FGM type III.* 26 years old woman from Sudan FGM made at 10 years of life. Labour and intrapartum defibulation performed at Hospital Clínico Universitario Lozano Bles of Zaragoza, Spain.

the clitoris and surrounding tissue, scraping of the tissue surrounding the vaginal orifice or cutting of the vagina, the introduction of corrosive substances or herbs into the vagina to initiate tightening, bleeding or narrowing of the vagina, as well as any other procedure which falls under the WHO definition of FGM.

PREVALENCE OF PRACTICE

The WHO estimates that as many as 100 to 140 million women and girls were affected world wide in the year 2000. This extrapolates to approximately 2 million girls per year at risk of being circumcised.

It is practiced mainly in 28 African countries, where prevalence rates range from 5% to 98% (figure 4). In Senegal and Gambia, for example, the majority of the women of some ethnic groups have suffered some kind of female genital mutilation (mostly types I and II). Despite global and local attempts to end FGM, the practice persists in these countries and has spread to non-traditional regions through immigration.

REASONS FOR THE PRACTICE

FGM origins are traditional and cultural rather than religious. Reasons for its practice are complex, arising from a belief system based on cultural and social tradition and it is also suggested that FGM was associated with patriarchal societies in which men needed assurance of family blood lines.

The act of FGM is thought to have arisen out of ancient Egypt. It predates both Christianity and Islam and does not pertain to any specific religion. While some people believe FGM is confined to Muslims, this is in fact not the case.

Figure 4. Source: Toubia N. Caring for women with circumcision. A Technical Manual for Health Care Providers. Women Ink. New York, 1999.

Figure courtesy of Rainbo Publications.

HEALTH CONSEQUENCES OF FGM

Many health problems may be associated with FGM but not every author accepts all of them. The most frequents cited in literacy are the following:

SHORT TERM HEALTH CONSEQUENCES

- Severe pain during and after the procedure.
- Local infection.
- Damage to adjacent tissues.
- Urinary retention.
- Haemorrhage, shock and, some times, death of the girl.

LONG TERM HEALTH CONSEQUENCES

- Recurrent urinary tract infections.
- Dysuria, dysmenorrhoea.
- Perineal lesions: Implantation cysts, neuromas, keloidal scars…
- Vaginal infections and sexual transmission diseases that may lead to pelvic inflammation disease and infertility.
- Higher prevalence of bacterial vaginosis and herpes simplex virus 2[1]. It suggests that cut women may be at increased risk of HIV infection.
- Sexual problems: dyspareunia, frigidity, necessity of surgical reversal of scar tissue in order to achieve intercourse.
- Psychological problems: Anxiety, humiliation, terror nightmares…

REPRODUCTIVE CONSEQUENCES

- Higher perinatal morbidity because labour complications.

There is controversy about this last point. Some authors suggest that adverse obstetric and perinatal outcomes must be added to the known harmful immediate and long-term effects of FGM since they estimate that FGM can cause one to two extra perinatal deaths per 100 deliveries to African women who have had FGM.

The mechanism by which FGM might cause adverse obstetric outcomes is unclear. Although practices vary from country to country, FGM is generally done in girls younger than 10 years and leads to varying amounts of scar formation. The presence of this scar tissue, which is less elastic than the perineal and vaginal tissue would normally be, might cause differing degrees of obstruction and tears or episiotomy. A long second stage of labour, along with direct effects on the perineum, could underlie the findings of an increased risk of perineal injury, postpartum haemorrhage, resuscitation of the infant, and fresh stillbirth associated with FGM[2].

In the opposite, Abdulrahim[3] work shows that, with proper management, there is no statistically significant difference in outcome of labour between women who deliver vaginally, with and without defibulation. This is consistent with other published reports[4]. They

observe that commonly cited negative consequences of FGC such as damage to the perineum or anus, vulval tumours, painful sex, infertility, prolapse and other reproductive tract infections are not significantly more common in cut women.

However, a recent collaborative prospective study in six African countries about female genital mutilation and obstetric outcome promoted by the World Health Organization[5] showed that deliveries to women who have undergone FGM are significantly more likely to be complicated by caesarean section, postpartum haemorrhage, episiotomy, extended maternal hospital stay, resuscitation of the infant, and in-patient perinatal death than deliveries of women who have not had FGM. They show no significant association between FGM and the risk of having a low birth weight infant.

In conclusion, I think that the relationship between FGC and long-term reproductive morbidity still remains unclear, especially in settings where type I and II cutting predominates and that a good management of labour with a woman with FGM type III may reduce or minimize her complications.

CARE OF FGM DURING LABOUR

If the woman presents a FGM type I or II with a well healed scar and no complications, no special measures or treatment is necessary during the labour. It is sufficient to reassure the patient that she and her baby are under no special risk.

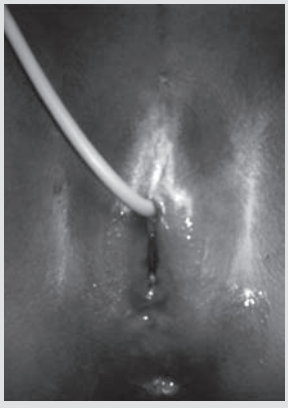
If FGM is type III (infibulation), defibulation is needed to remove the obstruction in front of the vaginal opening. Under no circumstance should a woman be subjected to caesarean section solely to avoid defibulation, regardless of whether she requests it or the provider suggests it[6].

Protocols for the timing of defibulation vary among practitioners. For some authors the optimum time for a defibulation is the second trimester under local or spinal anaesthesia. This is thought to prevent acute problems at the time of delivery related to the risk of unfamiliarity of the staff on duty with defibulation. Other professionals and a number of women prefer de-infibulation during labour as part of the birth process as they then only have to experience a painful procedure once.

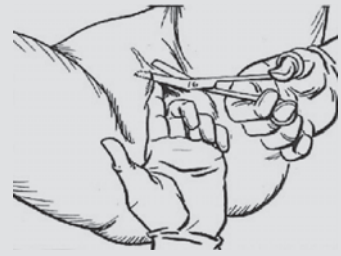
TECHNIQUE OF INTRAPARTUM DEFIBULATION

- Before the procedure, the woman is placed in the lithotomy position.
- The vulva and perineum are cleaned with chlorhexidine and the bladder is emptied using a catheter.
- The defibulation involves infiltrating the anterior scar tissue with 1 % or 2 % lidocaine solution and inserting the index and middle fingers of the left hand between the crowning head and the scar tissue, and then cutting the scar in the middle between the two fingers during uterine contractions. Care must be taken not to injure intact parts of the clitoris that may be buried under the anterior part of the hood.
- Midline or mediolateral episiotomy may or may not be necessary.
- After delivery, sutures are inserted for haemostasis if required. The edges of the skin are stitched apart with a running absorbable, non reactive suture. Any extension of the anterior incision above the urethra may be repaired at this time. A routine repair of the episiotomy or perineal tear is also frequently required post labour.

Index finger of the left hand between the crowning head and the scar tissue prior to injection of the anaesthesia.

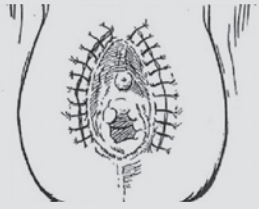


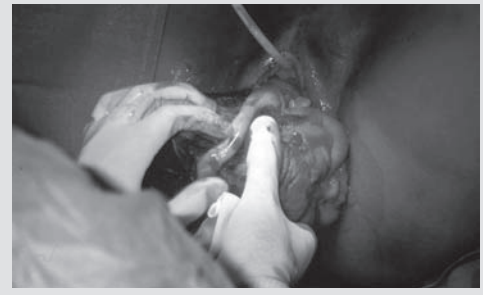
Foley catheter to identify the urethra.

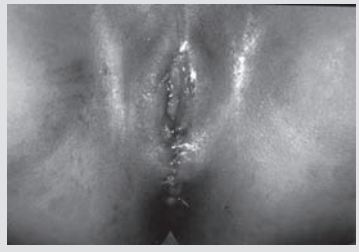


Careful cut of the scar between two fingers to avoid injuring urethra or intact parts of the clitoris.

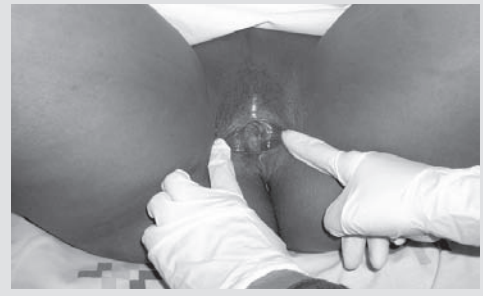
Delivery of the baby, suture edges of the skin above the urethra and reparation of the episiotomy.







Final result 3 months after the labour.



Pictures from a procedure performed at Hospital Clinico Universitario Lozano Blesa Zaragoza, Spain, to a 26 year old Sudanese woman with FGM type III. Draws courtesy of Rainbo.

Figure 5. Intrapartum defibulation.

- Foley catheter may be kept in situ for 24 hours and local care for the vulval area may be necessary for two-four weeks. Sexual intercourse abstinence is also advisable for six weeks (figure 5).

Although defibulation has been shown to be safe and effective, health care professionals cannot fail to be concerned about the overall problems associated with female genital mutilation. There is a continuing need for health education which stresses the risks and complications of female genital mutilation, while explaining that the origin is more of tradition than of religion. However in the Muslim world, such a change of attitude towards the procedure has to come from within and cannot be successfully imposed from outside.

In conclusion, although the surgical technique of intrapartum defibulation is simple and safe, this should not undermine the continuing efforts towards abandoning female genital mutilation altogether[7]. Doctors and every health professional have a role in eliminating FGM by educating patients and communities.

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CHAPTER 34

Obstetric anaesthesia and analgesia

LABOUR

J. C. Melchor Marcos | M. Miño Mora | J. Cordón Scharfhausen

INTRODUCTION

One of the greatest fears of pregnant women is labour pain, than is described as very intense by more than half of them. This pain becomes more intense during the second phase of labour.

Pain has no advantages and besides the negative psychological impact on the mother, it can produce low placental perfusion by different ways that at the end can cause fetal hypoxia.

Nowadays, women demand pain release, and some of them even consider this fact as a right. With all the respect to women who desire a «natural labour», just the desire of a woman to have pain release in absence of contraindications should be enough to guarantee obstetric analgesia.

By anaesthesia we assume the lack of sensations, mainly painful ones, associated to lack of conscience, and this can be achieved with general anaesthetics drugs. Analgesia is the lack of pain sensation, and this has no effect on conscientious; this is what is desirable in obstetrics and what is achieved with loco-regional analgesia.

MECHANISMS OF PAIN RELEASE DURING LABOUR

1. Non farmacological.
   - 1.1. Proven efficacy.
     - — Labor support.
     - — Sterile water blocks.
     - — Immersion in water
   - 1.2. Low evidence efficacy.
     - — Psychoprophylaxis.
     - — Hypnosis.
     - — Acupuncture.

1.3. Proven inefficacy.

— Transcutaneous electrical nerve stimulation (TENS).

2. Farmacological.

2.1. Inhalatory analgesia.

2.2. Parenteral analgesia (im o iv).

2.3. Paracervical block.

2.4. Pudendal block.

2.5. Local analgesia.

2.6. Spinal analgesia.

2.7. General anaesthesia.

NON PHARMACOLOGICAL METHODS OF PROVEN EFFICACY

LABOR SUPPORT

The conclusion of Cochrane review is that labour support must be considered effective in labour pain relief, (evidence level Ia, recommendation grade A)[1]. Fifteen trials involving 12,791 women met inclusion criteria and provided usable outcome data. Women who had continuous intrapartum support were more likely to have a spontaneous vaginal birth [14 studies, n = 12,757, relative risk (RR) = 1,08, 95% confidence interval (CI): 1,04-1,13], and less likely to have intrapartum analgesia (11 studies, n = 11.051, RR = 0.87, 95% IC: 0,79-0,96) or to report dissatisfaction with their childbirth experiences (6 studies, n = 9.824, RR = 0,73, 95% CI: 0,65-0,83).

STERILE WATER BLOCKS

Intradermally injection of 0,05-0,1 ml of sterile water in 4 sites over the sacrum (2-3 cm below and 1-2 cm medial to the posterior superior iliac spine, after 30 seconds with itching and/or local pain, induces low back pain relief that lasts 60-90 min. This can be applied by a doctor or a nurse and can be repeated in an hour.

A systematic review of four randomized control trials (RCT) published in 2002[2] with a total of 254 women in study group, are coincident with respect to it efficacy; so this method of low back pain relief can be recommend (evidence level Ia, recommendation grade A). Moreover it is easy to apply, cheap, without known risks besides the transient local pain. Its main indication is the relief of low back pain in early labour, women with no desire of epidural analgesia o contraindication for it.

IMMERSION IN WATER

Cochrane systematic review (8 studies, 2.939 women)[3] refers that women who used water immersion during the first stage of labour reported statistically significantly less pain than those not labouring in water (40/59 versus 55/61) [odds ratio (OR) = 0,23, CI: 0,08-0,63, one trial]. There was a statistically significant reduction in the use of other type of analgesia amongst women allocated to water immersion during the first stage of labour compared to those not allocated to water immersion (OR = 0,84, 95% CI: 0,71-0,99, four trials). The effects of immersion in water during pregnancy or in the third stage are unclear.

It is recommended the immersion in 37 ºC water and only to the level of superior abdomen, once cervical dilatation is more than 4-5 cm, and for a maximum of 1-2 hours[2].

NON PHARMACOLOGICAL METHODS OF LOW EVIDENCE EFFICACY

PSYCHOPROPHILAXIS

Classes for women labour pretend a good psychological preparation and generally teach breathing and relaxing techniques, designated to diminish pain. Though in medical literature there is little evidence about its efficacy.

HYPNOSIS

Women taught self-hypnosis had decreased requirements for pharmacological analgesia (RR = 0,53, 95 % CI: 0,36-0,79, five trials 749 women) including epidural analgesia (RR = = 0,30, 95 % CI: 0,22-0,40) and were more satisfied with their pain management in labour compared with controls (RR = 2,33, 95 % CI: 1,15-4,71, one trial)[4].

The effectiveness of this method is limited in a small group of patients, and it should only be used in previously selected women as it can produce severe psychiatric alterations.

ACUPUNCTURE

Although some studies have appointed the benefit of acupuncture on pain relief, and some have quoted an efficacy about 60 % or a reduction in the need of analgesia up to 94 %, published data reflects low evidence of its efficacy, because series are of small number and the study design is often doubtful[5].

NON PHARMACOLOGICAL METHODS OF PROVEN INEFFICACY

TRANSCUTANEOUS ELECTRICAL NERVE STIMULATION (TENS)

Analgesic efficacy of electrical nerve stimulation though skin of cranial, dorsal or suprapubic nerve has been reviewed systematically including 10 RCT with 877 patients[6]. It has been proved that it produces no pain relief, no difference with the use of other types of analgesia and it should be formally dissuaded (evidence level Ia, recommendation grade A).

FARMACOLOGICAL METHODS OF PAIN RELEASE DURING LABOUR

INHALATORY ANALGESIA: NITROUS OXIDE

Although it is not known in many countries, it is widely used in others. A systematic review of 11 RCT concludes that although nitrous oxide relieves pain of many labouring woman and it is secure for both mother and foetus, there is no clear, objective, and measurable evidence to support any analgesic effect during labour[7].

PARENTERAL ANALGESIA (INTRAMUSCULAR OR INTRAVENOUS): OPIOIDS

Actually the most used drug for parenteral analgesia are opioids, and they are also the most secure. Systematic opioids have proven that women under their effect seem more

satisfied (1 RCT: 83 vs 71%, p = 0.05), even though the pain relief is inferior to that achieved with epidural analgesia (systematic review of 5 RCT, evidence level Ia)[8].

The most popular opioid in obstetric is *meperidine,* that has a quick action and is very cheap. The secondary effect include sedation, respiratory depression, nausea and vomit in the mother; for this reason it is usually used in combination with drugs, like fenotiacide or metoclopramide, that have the opposite effect. Moreover, because it can cross the placental barrier, it can produce a reduction in fetal heart rate variability and sedation in the newborn that can be easily reverted with naloxone. All this effect it has questioned the use of meperidine for labour pain relief.

There are other opioids, like *fentanyl,* which produces less newborn sedation, but there is no evidence that they are a better choice for pain relief during labour.

PARACERVICAL BLOCK

Local anaesthetic punction in cervical perimeter is useful for pain relief during the first phase of labour, although its efficacy is reduced in the second one.

This efficacy is supported by 4 RCT systematically reviewed (level of efficacy Ia)[9], but nowadays it is poorly recommended as its use has been associated with fetal bradicardia, it has a short duration in time and it fail in10-30% of women.

PUDENDAL BLOCK

Blockade of internal pudendal nerves with their three branches reduces pain over the second phase of labour, in which pain is generated by pelvic distension. To reach these nerves we can use a perineal or transvaginal approach, been the latest easier and, quicker, and so we need to puncture less tissue and use less anesthetic.

If we position women as for normal vaginal labour, we can introduce the needle, guided by the second and third finger of our hand in the vagina, with a lateral and slight medial direction with respect to the sciatic spine, over the supraspinous ligament. To avoid tissue lesion a long needle (12-15 cm) is usually used with a covering and an outcoming point of 15 mm. Before injection it is advised to aspirate to avoid pudendal vase lesion[10].

This high efficacy technique for second phase of labour has the advantage of easiness, has no need of vigilance and decreases the rate of vaginal tear.

LOCAL ANALGESIA

To repair tears and episiotomy several mucous or cutaneous analgesics can be used over the vagina or perineum. The best are those with quick action, like lidocaine, that has action over 20-40 min. To ensure no vascular injection, a soft aspiration is advised, and this way most severe complications are avoided[11].

SPINAL ANALGESIA: EPIDURAL AND SUBARACHNOID

Spinal analgesia is the suppression of pain and other sensations in a part of the body by injection of a analgesic drug or local anaesthetic into the space around the spinal cord. Two forms are commonly employed: epidural and subarachnoid routes. There is some confusion in the terminology - spinal analgesia is commonly taken to mean the subarachnoid route, and extradural is another term for epidural.

EFFICACY

Spinal analgesia provides pain relief for the three phases of labour superior to that of any other method and it is of greatest security. For this reason, this is the method of election and should be available for all women in labour (evidence level Ia, recommendation grade A)[11].

INDICATIONS

Simply, the request of a labouring woman (in absence of contraindications) should be enough to guarantee the most secure and efficient analgesia, the spinal one. In addition, in some circumstances it provides benefits not contributed by other analgesic methods, and so it is medically indicated. These are[10]:

a) Obstetrical indications:

1. Dynamic dystocia.
2. Preterm labour.
3. Instrumental vaginal delivery.
4. Multiple gestations.
5. Previous caesarean section.

b) Medical indications:

1. Preeclampsia.
2. Heart disease.
3. Severe respiratory disease.
4. Cronical neural diseases.
5. Epilepsy.
6. Contraindication for maternal effort: detachment of the retina, cerebral vascular pathology.
7. Contraindication of general anaesthesia.

CONTRAINDICATIONS[10, 11]

a) **Absolute:**

1. Severe hypotension resistant to treatment, severe bleeding, shock.
2. Intracranial hypertension due to a lesion. Eclampsia.
3. Local (on punction site) or general infection.
4. Coagulopathy: although reassuring, it is not considered necessary a platelet recount in a previous sane women (evidence grade C), and women with platelets between 50.000 and 100.000/μL are candidates after an individual evaluation (evidence grade B)[11].
5. Anticoagulant: women with therapeutical doses of heparin are candidates if they have a normal partial time of activated tromboplastine (TTPa), and those with prophylactic doses of heparin or with low dose aspirin present no contraindication. Low weight heparins has longer mean life, and its anticoagulant effect does not affect the TTPa. Moreover, regional analgesia in women under this anticoagulant has been associated with spinal or epidural haematoma. So a woman with a single dose of low weight heparin can only receive regional analgesia after 12 hour from last dose, and she is not to receive any other until 12 hours after catheter with drawal. There are not enough studies about women with two doses of low weight heparin a day. For women under the effect of any anticoagulant therapy, intradural analgesia is preferred.

b) **Relative:**

1. Woman refusal, not understanding or acceptance of the method, no signature of written consent.
2. Lack of professional staff, or material to initiate, continue or treat the complications derived from the technique.

3. Opioids or local anestesic allergy.
4. Severe cardiopathy (New York Heart Association classe III-IV).
5. Spine deformity.
6. Benign endocraneal hipertensión.
7. Not reassuring fetal cardiotogrogram.
8. Tattoo in puncture site.

REQUIREMENTS

1. Indication, rule out contraindications.
2. Adequate information, before labour as preferred.
3. Technique comprehension and acceptance. Obtain informed consent.
4. Qualified anaesthesiologist. Suitable material.
5. Anamnesis and occasionally physical exam and/or blood analysis.
6. Previous fetal cardiotocography.
7. Maternal blood pressure and temperature.

TYPES / TECHNIQUE

Spinal analgesia can be epidural, intradural (subarachnoid) or combined. Epidural analgesia can be administered by intermittent bolus, by continuous infusion technique or by woman self-controlled. The most effective is continuous perfusion[11].

Epidural analgesia allows leaving a catheter though which continuous infusion can be administered. Intradural analgesia does not allow the insertion of a catheter so the analgesic effect derived from a single bolus.

From a Cochrane systematic review (fourteen trials involving 2047 women) combined analgesia (epidural-intradural or walking epidural) shows a reduced time from first injection to effective maternal analgesia −5,50 minutes (95% CI-6,47 to −4,52; four trials), an increased incidence of maternal satisfaction (OR = 4,69, 95% CI 1,27-17,29; three trials). No difference was found between combines spinal-epidural and epidural techniques with regards to maternal morbility, rescue analgesia requirements, the incidence of post dural puncture headache or blood patch, hypotension, urinary retention, mode of delivery, or admission of the baby to the neonatal unit[12].

CONSEQUENCES OF EPIDURAL ANALGESIA

Up to now there are five systematic reviews published about collateral effects of epidural analgesia. As a summary, we have the following conclusions[13]:

1. Studies are all very heterogeneous regarding technique and drugs.
2. They all conclude that there is not enough evidence to support that epidural analgesia increases caesarean rate.
3. There are not enough data to analyze neonatal effects.
4. Epidural analgesia is associated, not always as a cause, with:
   — Longer second phase of labour (14 minutes approximately).
   — More alterations with fetal rotation during second phase of labour.
   — More operatory vaginal deliveries (15% with epidural vs 9% with parenteral opioids; number needed to treat: 15).

— More need of oxitocine administration (45 % with epidural vs 32 % with parenteral opioids, number needed to treat: 7,9).

— More maternal fever (23 % with epidural vs 5 % with parenteral opioids, number needed to treat: 5,6). The mechanism is unknown, but it does not seem to be infectious.

It is necessary to accept these effects because there are mechanisms to diminish its consequences.

COMPLICATIONS OF EPIDURAL ANALGESIA[13]

Complications are many, but more frequent are:

1. Maternal hypotension. Blood presure descends 20-30 % with respect to basal and affects close to 10 % of women.
2. Headache after dural puncture: accidental dural punction affect 3 % of women and after severe headache develops in 70 % of them.
3. Itching: beside hypotension it is the most frequent complication and it is related to opioids administration.
4. Fetal cardiotocographic alterations: epidural analgesia increases cardiac fetal decelerations (RR = 3,7; CI 95 %: 2,2-6,2).
5. Failed technique: 10 % women.

SURVEILLANCE/CONTROL DURING EPIDURAL ANALGESIA[13]

1. Maternal blood pressure control.
2. Maternal temperature.
3. Fetal cardiac and uterine activity continuous surveillance.
4. Bladder emptying.

GOOD-QUALITY EPIDURAL ANALGESIA

1. **Early onset.** Although some observational studies show higher rates of caesarean section when epidural is started early in labour, the four RCT designed for this purpose have failed to shown this event. With actual information there is no justification to delay epidural instauration[13].
2. **Walking epidural.** There are new techniques that avoid motor block, which was related to fetal malposition, pushing sensation and operatory delivery. COMET study was designed for this purpose and it shows that low dose analgesia can reduce operatory deliveries 25 % when compared to conventional epidural analgesia, women having a similar satisfaction about pain relief[14].
3. **Maintain analgesia until delivery.** In an attempt to diminishing the frequency of foetal malpositions and operative deliveries, it has been tested to diminish the intensity of the analgesia during second phase of labour. A Cochrane review demonstrates insufficient evidence this performance be effective; besides it produces an evident increase of the pain during this phase[15].
4. **Delay maternal pushing.** The RCT PEOPLE (pushing early or pushing late with epidural)[16], compares the beginning of pushing as soon as complete cervical dilatation is achieved with the beginning of pushing two hours later, and it demonstrates a decrease in operative deliveries with late pushing (RR = 0,79, CI95 %: 0,66-0,95) with a similar index of neonatal morbidity. Approximately 22 women must delay pushing to avoid an operatory delivery (number needed to treat: 22), and this number diminishes to 8 in

women whose foetus is in posterior or transverse position at the beginning of the second phase of labour.

GENERAL ANALGESIA

The mother mortality related to the obstetric anaesthesia is of 1.7 for every million newborn children. When a caesarean section is performed under general anaesthesia the mortality is close to 32 per million, whereas if spinal anaesthesia is used it is of 1.9 for million. The identification of this risk has meant a change in the anaesthetic practice towards the utilization of regional analgesia during the caesarean. This change is associated with a decrease of almost 50 % in the obstetric mortality associated with the anaesthesia[13].

Nowadays, for caesarean section it is recommended the spinal analgesia (evidence grade C)[11]. Only it has to be realized under general anaesthesia when the mother specificaly demands it or if a contraindication exists for the spinal blockade[10].

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PUERPERAL PERIOD

Postpartum care

CHAPTER 35

PUERPERAL PERIOD

N. Y. Aguilar-Jaimes | O. E. Ordoñez-Mosquera

INTRODUCTION

The postpartum care are activities in health promotion and prevention, diagnosis and treatment planned with the purpose of achieving an appropriate return of the pregnant woman to her previous state and an appropriate development of the nursing. The postpartum period or puerperium has different stages, each one with specific activities, which are:

— Immediate puerperium: from childbirth to the first 24 hours.

— Mediate puerperium: from the firts 24 hours to the 7th day.

— Late puerperium: from the 8th to the 42th day.

OBJECTIVES OF POSTPARTUM CARE

1. Facilitate the maternal adaptation to postpartum state.
2. Prevent complications during the puerperium.
3. Early detection of any complication.
4. Begin the appropriate treatment of possible complications in the puerperium.
5. Develop an appropriate maternal nursing.
6. Begin the contraception to achieve adequated intergenesic period.

IMMEDIATE PUERPERIUM

THE FIRST HOUR

1. *Clinical surveillance:*
   — Transfer to postpartum service with permanent surveillance and trained personnel.
   — Control vital signs every 15 minutes (arterial pressure, heart and breathing frequency).

- Control the uterine involution: The uterine size should be below the navel, and the uterus must be with hard consistency.
- Control of the vaginal bleeding.

2. *Postpartum hemorrhage prevention:*
   - Uterine massage.
   - Uterotonic drugs administration. Anyone of the following options can be used:
     a) Oxitocin: 10 units in 500 ml of saline solution to infuse intravenous in 20 min.
     b) Metilergometrin: 0,2 mgs intramuscular.
     c) Misoprostol: 400-600 mcgs rectal.
   - Intravenous solutions: it must be a permeable vein road to infuse liquids in case of hemorrhage persisting.

3. *Begin the nursing:* after childbirth the mother should spend time with her newborn and begin their contact skin to skin, the appropriate technique for the breastfeeding should be given, except if the mothers or newborn's clinical condition does not allow for it.

THE FIRST 24 HOURS

1. *Clinical surveillance:*
   - The mother should stay in a postpartum service with trained personnel and adequate surveillance.
   - Control of vital signs every 4-6 hours, including the temperature.
   - Control of skin and mucous coloration for anaemia detection.
   - Control of diuresis: there should be an urine production of 0,5-1 ml/kg/hour; during the first days this may increase because of the redistribution and elimination of the corporal liquids that are increased during pregnancy.
   - Control of the uterine involution: a bladder globe can increase the perception of the uterus size, reason why it is necessary to observe the uterus after miction.
   - Control of vaginal bleeding: the quantity and aspect of the lochia should be observed, which is hematic during the first three days.
   - Control of milk production and the breast state, stimulating the production and the drainage.

2. *Perineal care:* in case of episiotomy or perineal lacerations the mother should do adequated hygiene every 12 hours. In case of edema and inflammation apply local ice.
3. *Early walking:* it should begin when the patient's clinical condition allows for it, ideally between the first 2 and 4 hours; this helps to prevent thrombotics phenomenons, urinary retention and constipation.
4. *Diet:* the patient can receive a free diet, at her tolerance, with a high income of oral liquids.
5. *Analgesics:* they can be administered if need, but without influencing in the clinical monitorization, for example opiates non narcotics.
6. *Stimulation of the nursing:* insist in exclusive nursing and by demand of the newborn,

avoiding the use of baby bottles. In case of delayed nursing feed the newborn with spoon or syringe.

IN CAESAREAN SECTION BIRTH

In general care is the same as vaginal birth, but there are special considerations and delayed ones:

1. *Diet:* it can begin with clear liquids at 6-8 hours, and according to tolerance give soft and normal diet after the 24 hours.
2. *Endovenous liquids:* as the blood lost is higher and the diet is restricted, the infusion of 2.000-2.500 ml should be ordered for 24 hours, until the patient has an appropriate oral income.
3. *Diuresis:* the bladder catheter should be maintained during the first 6-8 hours to watch over the urine volume; in case of normal being and tolerance to the oral income, it could help to improve early walking.
4. *Surgical wound care:* the wound should remain covered during the first 24 hours unless there is evidenced of active bleeding.
5. *Walking:* it should start early, but the difficulty that implies the surgical procedure makes it to be delayed for 6-8 hours depending on the tolerante walking.
6. *Nursing:* in this case the immediate beginning is not possible for the maternal impossibility of attention the newborn, but as soon as the maternal condition allows for the process of the maternal nursing should be stimulated.

MEDIATE PUERPERIUM

The clinical surveillance should persist for the early detection of complications, to emphasize tolerance of oral income and walking, and also for the newborn care.

1. *Control of vaginal bleeding:* the lochia's aspect change during the mediate puerperium, it is hematic during the first 72 hours, serohematic until the 5-7th day, and serous until disappearing around the 15th day.
2. *Control of uterine involution:* the uterine size decreases 2 cm per day, found it throught abdominal wall until the 10th day.
3. *Milk production:* during the first 3 days the calostro appears and has a yellowish aspect and contains more minerals and proteins (especially globulins), but less sugars and fat than the mature milk. This last level is reached from the 4-5 day arriving at its maximum maturity level at 4 weeks.
4. *Prevention and treatment of postpartum anemia:* the pregnancy demands the increase of the iron requirements for the fetal growth with decrease of the reserve, the childbirth produces blood loss, and the nursing demands iron for milk production. Iron suplementation is recommended with 30-60 mgs of elementary iron and 400 mcgs of folic acid, during the first two months of puerperium.
5. *Education:* during the first and second days postpartum the patient should receive information about the changes in puerperium, newborn care, maternal nursing, early detection of complications, sexual activity and contraception.

HOSPITALARY DISCHARGE

During the last years the discharge time has been varied in a considerable way due to external influences of the puerperium process. In the developed countries the influence is due to health insuranse companies and their cost studies. In developing countries it is the shortage of appropriate obstetric services with trained personnel for the attention of childbirth and puerperium; in this guide we propose an early but safe discharge.

The discharge time depends of the type of patient, includes tolerance to walking and oral income, appropriate maternal nursing, education in normal evolution of puerperium, puericulture, and contraception. The minimum time of hospitalary stay for each particular patient depends on the childbirth type and the presence of risks.

1. *Low risk vaginal birth:*
   - — Normal clinical surveillance during the first 24 hours postpartum.
2. *High risk vaginal birth:* includes patients with prolonged premature rupture of ovular membranes, prolonged labor, Instrumental birth (forceps, vacuum, etc), high risk pregnancies.
   - — Normal clinical surveillance during the first 48 hours postpartum.
   - — Normal white cells count.
3. *Low risk cesarean birth:*
   - — Normal clinical surveillance during the first 48 hours postpartum.
   - — Normal white cells count.
4. *High risk cesarean birth:*
   - — Normal clinical surveillance during the first 72 hours postpartum
   - — Normal white cells count.
5. *Decompensed or nonbalanced disease and vaginal or Cesarean birth:* the patient will be discharged only when her condition can be managed in an ambulatory way. In case of not being sure of the ambulatory follow up, the patient will be treated intrahospitaly until finishing her management.

LATE PUERPERIUM

In this period, the clinical surveillance should continue for puerperium's complications detection, insist in the maternal whole nursing by demand, and begin the contraceptive methods to achieve an appropriate intergenesic period to avoid perinatal complications.

COMPLICATIONS DURING THE PUERPERIUM

There are three kinds of main complications at puerperium:

— *Hemorrhagics:* represented by the postpartum hemorrhage and the perineal and postcesarean hematoms, that may appear mainly up to the first 48 hours.

— *Infectious:* they include postpartum endometritis, surgical site infection and mastitis, they appear mainly from the first 48 hours to the 7th day.

— *Thromboembolics:* it includes deep venous thrombosis and pulmomary thromboembolism; they appear mainly after the 7th day.

POSTPARTUM HEMORRHAGE (PPH) (see also chapter 36)

Blood loss higher than 500 ml in vaginal birth, or 1.000 ml in Cesarean section; severe PPH when is accompanied by hemodynamic unstability, or blood loss higher than 1.500 ml, or there is a fall in the hematocrit of 10% or Hemoglobin level in 4 gr% or more. It can be primary or early (first 24 hours) and secondary or late (after 24 hours). The PPH cause 25% of maternal deaths in the world.

ETIOLOGY

The main causes of PPH can be organized in 4 groups:

1. Contraction anormalities:
   a) Uterine overdistention: polihidramnios, multiple pregnancy and fetal macrosomy.
   b) Uterine muscle fatigue: prolonged labor, precipitate labor, and multiparity.
   c) Intraamniotic infection.
   d) Anatomical or functional distortion of the uterus like myomatosis, previous placenta, mullerian abnormalities, and medication ($MgSO_4$, terbutalin, halogenous anesthetics).
2. Placental remains retention: tear of umbilical cord, placental retention, placental accretism.
3. Birth trauma: from the uterus to the perineum, and it includes:
   a) Uterine rupture: primary or secondary, if a previous uterine surgery was made (Cesarean section, myomectomy or metroplasty).
   b) Uterine inversion.
   c) Histerotomy extension or Caesarean lacerations: they are usually presented when there is fetal advanced descent or malposition.
   d) Trauma in cervix, vagina or perineum: they are frequent in instrumented births, precipitated birth and reveal low quality in birth attention.
4. Clotting abnormalities. These can be primary, such as vonWillebrand disease or thrombocytopenic purple; or secondary, such as HELLP syndrome or Disseminated Intravascular clotting (fetal death, placental abruptio, sepsis or amniotic fluid embolism).

PREVENTION

— Identification of risk factors.

— Prevention and treatment of anaemia during pregnancy.

— Practice the selective use of episiotomy.

— Make a whole physical exam of birth way and placenta to detect lesions or retention of placental remains.

— Make active management of third stage of labor: prophilactic use of uterotonics (oxitocin, metilergometrine, misoprostol), controlled and sustained traction of umbilical cord and uterine massage before and after of childbirth.

TREATMENT

1. **Early diagnosis and timely reanimation:**
   — Assure airway.
   — Assure circulatory access: take two veins with catheters 14F or 16F.
   — Continuous monitorization: arterial pressure, pulse, saturation of oxy-

gen, breathing frecuency and urine production.

— Restore intravascular volume in 20-30 minutes with cristaloid infusions in relationship 3-4:1 according to blood lost.

— Laboratory samples for hemoglobin, hematocrit, hemoclassification, clotting test and crossed tests for transfusion.

— Activate the alarm in the blood bank or transfutional unit.

2. **Management of specific cause:**

a) Contraction abnormalities. If uterus size is increased and not contracted:

— Do a vigorous bimanual uterine massage to stimulate the uterine muscle contraction and evacuate the intrauterine clots that can hinder the contraction.

— *Administer uterotonics.* Oxitocin 10 to 40 units plus Saline solution 500 ml in 20-30 min, if necesary have caution with the hipotention that produce these doses; use metiltilergometrin 0,2 mgs intramuscular every 5 minutes with maximum 5 dose (1 mg), or Misoprostol 600-800 mcgs rectal, if there is hipotention, or oxitoxin is not available.

b) Retention of placental remains.

— Check if the placenta came out complete.

— Uterine manual revision or curetaje with sedation or general anesthesy may be necessary.

c) Trauma of birth way.

— Make a systematic review of the birth way.

— Suture the wounded areas with absorbable sutures and hemostatic points. The uterine rupture should be corrected by laparotomy, and depending of the size could apply an emergency hysterectomy.

— In case of uterine inversion the reduction of the uterus with the placenta in situ should be carried out, to extract it later on.

d) Clotting abnormalities.

Should have been corrected at the best level previous to childbirth, but if they appear again it is necessary to make the respective reinstatement of the altered blood component.

3. **Untractable postpartum hemorrhage. If after 20 minutes with the previous actions the hemorrhage does not stop:**

a) Blood transfusion. Begin with packed red globules (PRG) of the same patient's group and Rh, but in case of no stock use group O and Rh negative. If in the emergency there are no units with compatibility crossed tests, it is necessary to begin with units without crossing, because is higger the probability of complications for hipovolemia and shock are higher than the probability of incompatibility reactions, but test should be carried out for the following blood units. In case of multiple deficiency of clotting factors, disseminated intravascular clotting or 4 units of PRG is to be transfused, frozen cool plasm should begin. In case of thrombocytaemia and need of surgical intervention transfuse platelets to reach 50.000 platelets/mm^3, 1 unit for each 10.000 platelets.

b) Uterine Tamponade. It is a transitory measure for the patient's transport to an other institution or as an option in patients with suitable conservative treatment. It can be used in cases of uterine atony or placenta accreta. It uses gauze or inflated devices (Sengstaken-Blackmore's probe, Rusch's urologic catheter, Condom + bladder catheter), maintained for up to 24 hours and always

with prophilactic antimicrobial therapy and Oxitocin for 12 to 24 hours.

c) Antishock technology. It is used to improve the venous return and includes position changes (elevation of legs), and the use of pneumatic or non pneumatic suits.

d) Surgical Procedures. They should be applied by trained personnel:

— Trauma correction.

— Uterine or Hypogastric arteries ligature: the best result is achieved with the uterine arteries ligature (80-90% Vs 50%).

— Compresive uterine sutures: B-Linch, Hayman (transfixiant points) and Cho (multiple square points).

— Emergency hysterectomy.

— *Abdominal packaging:* Suitable when it cannot be maked hemostasy and clotting anomalies exist.

e) Angiografic embolization. Used in some cases when there is difficult surgical access, or when in spite of the surgical procedures bleding persists.

f) Intensive care units. After surgical procedures and when stabilization and intensive monitorization are required.

POSTPARTUM ENDOMETRITIS (see also chapter 37)

Infection of the uterine cavity present after the childbirth. It can extend to produce endomyometritis, pelvic abscess, septic pelvic tromboflebitis, sepsis and septic shock. It is characterized by polimicrobian aetiology, which comes mainly from the lower genital tract. There are risk factors such as bacterial vaginosis, prolonged premature rupture of ovular membranes (RPMO), Prolonged labor, more than 6 vaginal tacts in labor, Caesarean section and internal fetal monitorization.

PREVENTION

— Treat previous vaginal infections (Bacterial Vaginosis, Streptococcus agalactiae colonization, Trichomoniasis).

— Induction of labour in PROM that does not need expectant management.

— Appropriate control of labour.

— Decrease of Caesarean section index.

DIAGNOSIS

— Fever higher than 38 °C.

— Taquicardy.

— Subinvoluted and painful uterus.

— Odorous and hemopurulents lochias.

— White cells count with leucocitosis and neutrophylia.

— If possible, take samples of endometrial cavity for cultivation of aerobic and anaerobics.

— Differential diagnosis: urinary infection, infected haematome, pelvic abscess, mastitis, viral infection.

TREATMENT

1. **Antimicrobial therapy:** wide spectrum schedules are used by parenteral way, until the patient remains asymtomatic 48 hours.

   a) Clindamicin 900 mg IV every 8 hours plus Gentamicin 5 mg/kg/day IV in single dose.

   b) Ampicilin-Sulbactam 1,5-3 grs IV every 6 hours.

   c) Crystalline G Penicillin 5.000.000 UI IV every 6 hours plus Gentamicin

and Metronidazol 0,5-1 gr IV every 8 hours.

d) Cefoxitin 2 gr IV every 6 hours.

e) Piperacilin/Tazobactam 2-4 gr/0,25-0,5 gr every 6-8 hours IV.

2. **Extraction of placental remains** if there is retention evidence.

3. In case of **Endomyometritis** and/or pelvic abscess, laparotomy and hysterectomy should be done.

4. In case of **septic pelvic tromboflebitis,** heparin begin with a bolus of 5.000-10.000 UI and continue with 1.000 UI/hour with clotting control test every 6 hours. Also it is posible to use low molecular weight heparins such as Enoxaparin or Nadroparin 1 mg/kg every 12 hours, or Dalteparin 200 UI/kg.

MASTITIS (see also chapter 37)

Infection in the breast caused by the incoming of germs into the galactic ducts or nipple fissures, facilitated by bad milk drainage and wrong cleaning of nipple. Generally produced by Staphilococcus or Streptpcoccus.

DIAGNOSIS

— Fever higher than 38 °C.

— Pain, eritema, heat and tenderless of breast.

— In case of mammary abscess, there is a fluctuating and painful mass.

TREATMENT

1. **General measures:**

   — Continue the breast drainage white nursing with the contralateral breast.

   — Apply hot compresses with Epson's or England's salt.

   — Maintain the use of brassière.

   — Pacacetamol 500 mgs VO as needed according to level of pain.

2. **Antimicrobial therapy:**

— Outpatient: Dicloxacilin 500 mgs VO every 6 hours for 7-10 days, or if penicillin allergy give Eritromicin 250 mgs VO every 6 hours.

— Inpatient: is used in case of not response to oral therapy for 72 hours or if there is a mammary abscess, Oxacilin 2gr IV every 4 hours.

3. **Abscess drainage:** it should be done with general anesthesia, asepsis and antisepsis technics, taking samples of pus for Gram tinction and culture; leave a gauze in cavity, to be removed at 24 hours. Wound's cures 2 times a day.

THROMBOEMBOLIC DISEASES

They are Superficial Tromboflebitis, deep venous trombosis (DVT), and pulmonary Thromboembolism (PTE). They take place because pregnancy is a procoagulant state due to increase of clotting factors and decrease of fibrinolitic factors, and venous estasis.

PREVENTION

— Early walking.

— Elevation of lower limbs and active/passive movements.

— Gradient stockings and bandages.

— In patients that can not be strolled use thromboprofilaxis with Enoxaparin or Nadroparin 0,5 mg/kg every 12 hours.

DIAGNOSIS

1. **Superficial Thromboflebitis:**
   - — Pain and eritema along venous lap.
2. **Deep Venous Trombosis:**
   - — Deep pain in legs that improves with the elevation.
   - — Increased leg circumference bigger than 2 cm compared to the contralateral.
   - — Positive Homan sign (muscular pain when foot dorsiflexion with extended leg).
   - — Changes in skin coloration and delayed capillary fullnes.
   - — Increased seric Dimer D.
   - — Venous Doppler shows flow obstruction.
3. **Pulmonary Thromboembolism:**
   - — Taquipnea, dysnea, pleuritic pain, cough and hemoptisis.
   - — Electrocardiogram changes like taquicardia, inverted T wave, depressed ST, right branch blockade.
   - — Hipoxemy and decreased oxigen saturation.
   - — Rx of thorax shows increased heart silhouette, pulmonary condensation, increased pulmonary artery and pleural effusion.
   - — Disbalance in ventilation/perfution gammagraphy.
   - — Arteriography and Angiotomography show pulmonary arterial thrombosis.

TREATMENT

1. **Superficial Thromboflebitis:**
   - — Bed rest and elevation of lower limb, with stockings or pressure bandages.
   - — Hot compresses with of Epson's or England's salt.
   - — Paracetamol 500 mg VO as needed.
   - — Early walking.
2. **Deep venous thrombosis.** The abovementioned plus:
   - — Anticoagulant therapy: Intravenuos Heparin with a bolus of 5.000-10.000 UI and continue with 1.000 UI/hour with clotting control test every 6 hours. Low molecular weight Heparin can also be used such as Enoxaparin or Nadroparin 1 mg/kg every 12 hours, or Dalteparin 200 UI/kg. When confirming the diagnosis continue with low molecular weight heparins or warfarin for maintenance therapy, for 6 weeks to 6 months depending on level of risk.
3. **Pulmonary Thromboembolism.**
   - — Transfer to intensive care unit.
   - — Oxigen therapy for mechanic ventilation according to the clinical condition.
   - — Opiate analgesics for management of pain.
   - — Bed rest.
   - — Anticoagulation therapy according to outline enunciated in point 2.
   - — Inotropic drugs in the event of heart deficiency.

CONTRACEPTION DURING NURSING

The objective is to space pregnancies to allow the complete recovery of the maternal systems and to preserve the quantity and quality of the maternal milk, and this way decreases the infantile mortality and improve women's health.

Lactational amenorrhoea method (LAM). The requirements must be:

— Exclusive or almost exclusive maternal nursing (85 % of the food drinks to be maternal milk), and suckle to free demand (8 to 10 times/24hours).

— Remain without menstrual bleeding (amenorrhoea)

— It can last the first 6 months of baby's life.

This method is very effective (98 %), it doesn't have secondary effects, it does not require insert of any device during the sexual relationship, it can begin immediately after the childbirth, it improves the relationship mother-baby, it is cost less and accepted by all religions. Its disadvantages are lasting for only 6 months, frequent breastfeeding by day and night, and does not protect from sexual transmited infections, including VIH.

Interrupted coitus. It can be used during the maternal nursing because it does not affect it. It is inexpensive and appropriate for even highly motivated.

Methods based on the knowledge of the fertility. There is no contraindication, but there is great difficulty to identify of the signs of fertility and the calculation of the fertile days.

Barrier methods. The condoms, diaphragms, cervical caps, spongy and espermicids do not produce alteration of the nursing in quantity or quality. For the diaphragm the involution of the pelvic organs is required and the condom is ideal to be used with lubricant for the vaginal dryness.

Intra-uterine device (IUD). The copper T is used (TCu-380A) and the intrauterine systems with progestins (SIU) have a effectiveness similar to the surgical sterilization. The postpartum IUD is located in the uterine cavity 10 to 20 minutes after having expelled the placenta, and it is indicated in patient with very difficult follow up for a birth control program. The interval IUD is placed in women with regular menstrual cycles, and during the days 2 or 3 of the menstrual period or between week 6-8 of the postpartum.

Combined hormonal Contraceptives. They are contraindicated during the nursing because of their hipercoagulant effect and since they decrease the maternal milk quantity and quality.

Only Progestins Hormonal contraceptives. It includes pills (Levonorgestrel 30 mcg, Desogestrel 75mcg), Medroxiprogesteron acetate (MPAD) injections of 150 mg, levonorgestrel subdermic implants, intra-uterine systems with levonorgestrel, and vaginal Rings with Progesteron or Nesterone; none of them present problems for the quality of the maternal milk, and they may show a slight increase in the volume and duration of the nursing. It is recommended to begin use after the 28th postpartum day, although in patient of very difficult control it is possible to apply medroxiprogesteron injection before hospital discharge, having scarce effect on the newborn.

Surgical sterilization. It is an effective and safe method in postpartum, and it does not present any adverse effect with the nursing, except when moving away the mother during the time of the procedure; in the immediate or mediate postpartum it is easier and surer a minilaparotomy, and later a laparoscopy.

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CHAPTER 36

PUERPERAL PERIOD

Postpartum haemorrhage

S. Rueda Marín | D. Orós López | E. Fabre González

INTRODUCTION

Postpartum haemorrhage (PPH) is one of the top five causes of maternal mortality in both developed and developing countries. Death from postpartum haemorrhage is eminently preventable. A large percentage of births in the developing world occur at home without a skilled attendant present. Approximately 14 million women suffer postpartum hemorrhage every year worldwide. Without the presence of a skilled provider to recognize and treat the conditions leading to postpartum hemorrhage (uterine atony, uterine rupture, and/or genital lacerations) and to manage postpartum hemorrhage if it occurs, women rapidly experience shock and death, resulting in approximately 125.000 deaths per year due to primary postpartum hemorrhage[1] (see also chapter 35).

DEFINITION

The official World Health Organisation (WHO) definition of primary PPH is *the loss of 500 ml or more of blood from the genital tract within 24 h of the birth of a baby,* while secondary PPH is when it occurs more than 24 h after delivery. A few factors have made this definition somewhat arbitrary:

- Visual estimation of blood loss is subjective and generally underestimated.
- The recognition that the mean blood loss is different in vaginal delivery compared to caesarean section, being 500 and 1.000 ml, respectively.
- A blood loss of more than 500 ml rarely compromises maternal condition; patients cope with blood loss in different ways depending on their pre-existing health, e.g. anaemia or a volume-contracted condition secondary to dehydration or pre-eclampsia.
- New methods for more accurate measurement of blood loss have been devised (e.g. plastic bedpans, linen-savers), however these are only used in trial settings.

Fortunately, due to physiological increases in plasma volume and red cell mass during pregnancy, measured blood loss up to 1.000 ml is fairly well tolerated by healthy pregnant women. A blood loss of more than 1.500 ml is usually accompanied by clinically significant hemodynamic changes and has been associated with severe obstetric morbidity. In obstetrics the volume of blood loss can be difficult to assess as a result of concealed bleeding.

On the basis of these findings, more objective assessment parameters have been advocated for the diagnosis of major PPH-viz:

The patient:

- Is haemodynamically unstable.
- Has a blood loss of >1.000 ml from genital tract.
- Has a >10% change in her haematocrit between admission and the post partum period or requires a transfusion of red blood cells[2].

ETIOLOGY

PPH is a description of an event and not a diagnosis. PPH occurs in 5-15% of deliveries, the wide range reflecting different definitions used. The cause is due to abnormalities on one of four basic processes, or the *'4 T's'* mnemonic, which act individually or in combination: Tone (poor uterine contraction after delivery), Tissue (retained products of conception or blood clots), Trauma (to genital tract) or Thrombin (coagulation abnormalities)[3]. Some of the many risk factors are outlined in table 1[4].

It is impossible to consistently identify women at highest risk of PPH, although several factors have been associated with an increased risk of hemorrhage. Nonetheless, two-thirds of PPH cases occur in women with no identifiable risk factors.

- The most common cause of immediate severe PPH is uterine atony (failure of the uterus to properly contraction after delivery). It is responsible for 50% of PPH and 4% of maternal mortality.
- Lacerations of the vagina and cervix are another common cause of postpartum hemorrhage. In developed countries, these lacerations occur more commonly with operative vaginal deliveries. In the developing world, they tend to happen when unskilled operators perform unnecessary forceps deliveries and when unskilled attendants allow or persuade women to push before the cervix is fully dilated.
- Given the lack of access to facilities and providers, many women who are carrying an undetected retained dead fetus will likewise develop disseminated intravascular coagulation (DIC) with resultant uncontrollable hemorrhage. Inherited disorders of coagulation, which might have been identified in developed countries with the onset of menarche, often are not discovered until the woman develops severe postpartum hemorrhage in developing countries.

PREVENTION OF PPH

Prevention of PPH in developing countries is a critical goal.

ACTIVE MANAGEMENT OF THE THIRD STAGE OF LABOR

Expectant (also known as conservative or physiologic) management of labor involves waiting for signs of placental separation and allowing for spontaneous delivery of the placenta aided by gravity and/or nipple stimulation.

Active management of the third stage of labor[2] consists of interventions designed to speed up the delivery of the placenta by increasing uterine contractions and to prevent PPH by averting uterine atony. The usual components are[5]:

Table 1. Aetiology and risk factors for the «4 T's» processes involved in PPH.

Process	*Aetiology*	*Risk factors*
Tone	Uterus over-distension.	• Multiple pregnancy. • Macrosomia. • Polyhydramnios. • Fetal abnormalities e.g. severe hydrocephalus.
	Uterine muscle fatigue.	• Prolonged/precipitate labour, especially if stimulated. • High parity (20-fold increased risk). • Previous prengancy with PPH.
	Uterine infection/chorioamnionitis.	• Prolonges SROM. • Fever.
	Uterine distortion/abnormality.	• Fibroid uterus. • Placenta praevia.
	Uterine relaxing drugs.	Anaesthetic drugs, nifedipine, NSAIDs, betamimetics, $MgSO_4$.
Tissue	• Retained placenta/membranes. • Abnormal placenta-succituriate/accessory lobe.	• Incomplete placenta at delivery, especially $<$ 24 weeks. • Previous uterine surgery. • Abnormal placenta on ultrasound.
Trauma	Cervical/vaginal/perineal tears.	• Precipitous delivery, manipulations at delivery. • Operative delivery. • Episiotomy especially mediolateral.
	Extended tear at CS	• Malposition • Fetal manipulation e.g. version of second twin. • Deep engagement.
	Uterine rupture.	• Previous uterine surgery.
	Uterine inversion.	• High parity. • Fundal placenta. • Excessive traction of cord.
Thrombin	Pre-existing clotting abnormality e.g. haemoplilia/vWD/hypofibrinogenaemia.	History of coagulopathy/liver disease
	Acquires in pregnancy • ITP. • PET with thrombocytopenia (HELLP). • DIC from PET, IUD, abruption, AFE, severe infection/sepsis. • Dilutiional coagulopathy.	• High blood pressure, bruising. • Fetal death. • Fever, raised WCC • APH, sudden collapse. • Massive transfusions.
	Anticoagulation.	• History of DVT/PE. • Aspirin heparin.

PPH, postpartum haemorrhage; SROM, spontaneous rupture of membranes; NSAIDs, non-steroidal anti-inflamatory drugs; $MgSO_4$, magnesium sulphate; CS, caesarean section; vWD, von Willebrandt's disease; ITP, idiopathic thrombocytopenic purpura; PET, preeclamptic toxaemia; HELLP, haemolysis, elevated liver enzymes and low platelets; DIC, disseminated intravascular coagulation; IUD, intrauterine death; AFE, amniotic fluid embolism; WCC, while cell count; APH, antepartum haemorrhage; DVT/PE, deep vein thrombosis/pulmonary embolism.

- Administration of oxytocin or another uterotonic drug within one minute after the birth of the baby.
- Controlled cord traction (delaying cord clamping by one to three minutes reduces anaemia in the newborn) while applying simultaneous counter-pressure to the uterus through the abdomen (figure 1).
- Uterine massage after delivery of the placenta as appropriate.

Evidence suggests that active management reduces the incidence and severity of PPH, postpartum anaemia and the need for blood transfusion[6].

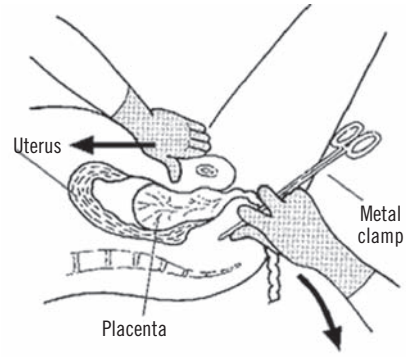

Figure 1. Controlled cord traction while applying simultaneous counter-pressure to the uterus through the abdomen.

UTEROTONICS FOR PREVENTION OF POSTPARTUM HEMORRHAGE

Oxytocin and ergometrine are the traditional first line approach to achieve contraction in case of uterine atony; both are unstable at room temperature and thus require special temperature and light storage conditions to remain effective. Moreover, in many low-resource settings, safe injection is not always possible due to the need for injection skills and training, lack of sterile equipment, and difficulty measuring the correct dose. To overcome some of these barriers to safe injection, the «Program for Appropriate Technology in Health (PATH)» developed the *Uniject* device. The device comes individually in a sterile packet and is a prefilled, non-refillable, sterile, easy to use device with a fixed needle that can be «activated» for use after opening the sterile packet (figure 2).

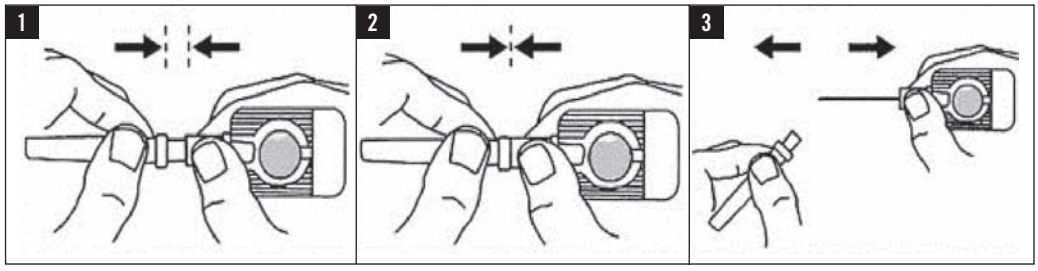

Figure 2. Uniject device.

Misoprostol, an oral preparation of prostaglandin (PGE_1) analogue, is a prime candidate given its uterotonic properties; ease of use as an oral, vaginal, or rectal preparation; relative low cost in some areas; and stability at high temperature[7]. In situations where no oxytocin is available or birth attendants' skills are limited, administering misoprostol soon after the birth of the baby reduces the occurrence of haemorrhage[8]. The most common side effects are transient shivering and pyrexia. Education of women and birth attendants in the proper use of misoprostol is essential. The usual components of giving misoprostol include:

- Administration of 600 micrograms (μg) misoprostol orally or sublingually after the birth of the baby.
- Controlled cord traction ONLY when a skilled attendant is present at the birth.
- Uterine massage after the delivery of the placenta as appropriate.

In the absence of current evidence, FIGO recommend that when no uterotonic drugs are available to either the skilled or nonskilled birth attendant, management of the third stage of labour includes the following components:

- Waiting for signs of separation of the placenta (cord lengthening, small blood loss, uterus firm and globular on palpation at the umbilicus).
- Encouraging maternal effort to bear down with contractions and, if necessary, to encourage an upright position.
- Controlled cord traction is not recommended in the absence of uterotonic drugs**,** or prior to signs of separation of the placenta**,** as this can cause partial placental separation, a ruptured cord, excessive bleeding and uterine inversion.
- Uterine massage after the delivery of the placenta as appropriate.

MANAGEMENT OF PPH

The key to the management of PPH involves rapid recognition and diagnosis of the condition, restoration of circulating blood volume with a simultaneous search for the cause[9]. Delay in initiating appropriate management in severe PPH is the major factor resulting in adverse outcomes. Long transports from home or primary health care facilities, a dearth of skilled providers, and lack of intravenous fluids and/or a safe blood supply often create long delays in instituting appropriate treatment.

Although the presentation of PPH is most often dramatic, bleeding may be slower and clinical signs of hypovolaemia may develop over a longer time frame, especially if secondary to retained tissue or trauma, or if concealed in the form of haematomas.

The practical management of PPH may be considered as having at least four components:

RESUSCITATION

An assessment of vital signs (level of consciousness, pulse, blood pressure and oxygen saturation if available) and amount of blood loss must be made initially and continually throughout resuscitation. Immediate resuscitation measures include:

- Establishment of a large-bore intravenous access.
- Administration of oxygen by mask at 8 litres/minute.
- Crystalloid solutions should be administered through the intravenous site.
- Transfuse blood. Compatible blood (supplied in the form of red cell concentrate) is the best fluid to replace blood loss and should be transfused as soon as available.
- Until blood is available, it is necessary to infuse in turn and as rapidly as required: crystalloid solutions (maximum 2 litres) and colloid solutions (maximum 1,5 litres).
- If X-matched blood is unavailable once 3,5 litres of crystalloid and colloid solutions have been infused: administration of «0» negative blood or un-X-matched own group blood must be considered.
- If bleeding persists and results of coagulation studies are unavailable: 1 litre of Fresh Frozen Plasma and 10 units of cryoprecipitate must be given empirically.

MONITORING AND INVESTIGATION

- Monitoring of vital signs including blood pressure, pulse, respirations and urine output.
- Venepuncture (obtaining 20 ml) for: X-match, full blood count and clotting screen).
- Foley catheter to monitor urine output.
- Continous pulse, blood presure recording and oxygen saturation monitor, if it exists.

ESTABLISH ETIOLOGY

TONE

Assess uterine size and tone. If the uterus is poorly contracted, commence vigorous massage and use therapeutic uterotonic agents. Emptying the bladder may facilitate uterine contraction and aid in ongoing assessment.

TISSUE

Ensure completeness of placenta and membranes. If in doubt, manual exploration should be performed, ideally under anaesthesia. Immediately resume bimanual massage and compression following exploration and evacuation of the uterus. Broad-spectrum antibiotics are commonly advocated following manual removal, manual exploration, or instrumentation of the uterus.

TRAUMA

Genital tract trauma is the most likely cause if bleeding persists despite a well-contracted uterus. Examination under anaesthesia should be performed, in particular looking for extended tears in the cervix or high in the vaginal vault, as these may involve the uterus or lead to broad ligament or retroperitoneal haematomas. Pressure or packing over the repair may be required to achieve haemostasis.

Traumatic haematomas are rare and may be related to lacerations or occur in isolation. Lower genital tract haematomas are usually managed by incision and drainage, although expectant management is acceptable if the lesion is not enlarging.

THROMBIN

If exploration has excluded retained tissue or trauma, bleeding from a well-contracted uterus is most commonly due to a defect in haemostasis. Blood product replacement should be commenced as appropriate. If coagulation test results are abnormal from the onset of PPH, consider an underlying cause.

ARREST THE BLEEDING

The commonest cause of PPH is uterine atony. However, clinical examination must be performed to exclude other causes of bleeding: retained products, lower genital tract lacerations or haematomas, uetrine inversion or rupture, extragenital bleeding... If PPH persists, the following measures should be started until the bleeding stops: *a)* uterine massage and compression to stimulate contraction, *b)* ensure bladder is empty, *c)* use of uterotonic drugs. If conservative measures fail to control haemorrhage, it is necessary to initiate surgical treatment.

The components of management of PPH are presented sequentially, but, in practice, these components must be implemented and progressed simultaneously (figure 3).

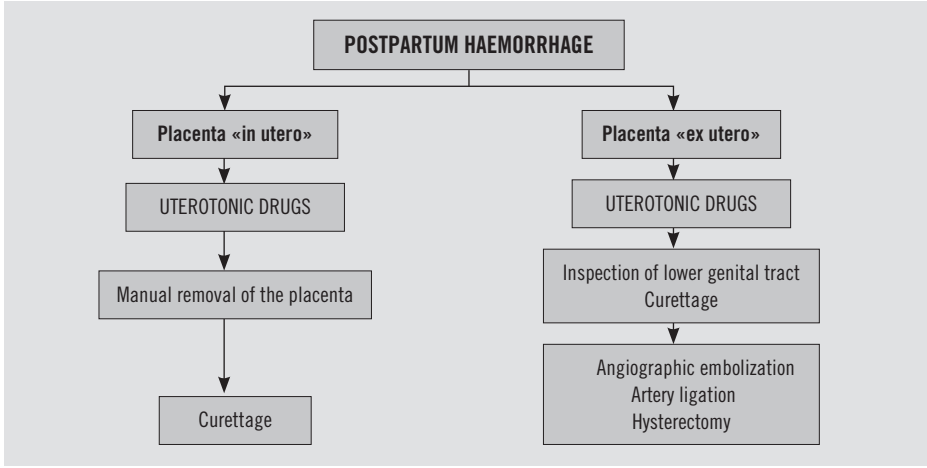

Figure 3. Postpartum haemorrhage treatment algorithm.

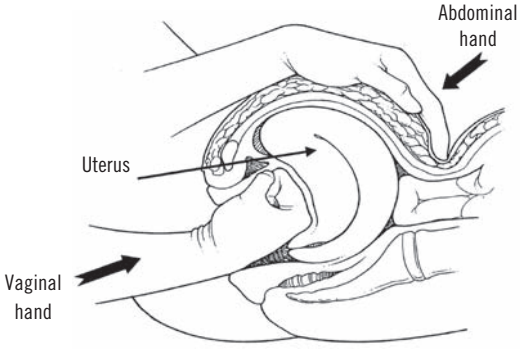

Figure 4. Uterine compression.

UTERINE MASSAGE

Uterine massage should be commenced if the uterus remains atonic, either manually with a hand on the fundus or bimanually with the vaginal hand in the anterior fornix and the abdominal hand on the posterior aspect of the fundus. (figure 4). This compression expels clots and stimulates uterine contraction.

UTEROTONIC DRUGS

Several drugs are available to treat uterine atony (table 2)[10]. Oxytocin infusion (syntocinon 40 units in 500 ml of 0,9 % normal saline, infused at a rate of 125 ml/h) can be used to maintain uterine contraction. Rectal administration of misoprostol (800-1.000 μg has emerged as a valuable agent in the treatment of PPH, especially in developing countries due to its low cost and relatively easier storage. The rectal route may prove advantageous because it could lessen the gastrointestinal side effects, as it can be administered to patients who are vomiting or unable to take oral medications (e.g., patients under general anesthesia).

TAMPONADE (BALLOON) OR UTERINE PACKING

It should be considered in all patients not responding to medical therapy. Balloon tamponade using either a Foley catheter, a Sengstaken-Blakemore tube or a the Rusch urological hydrostatic balloon has been shown to effectively control postpartum bleeding and may be useful in several settings: uterine atony, retained placental tissue, and placenta accreta. These devices have open tips, which permit continuous drainage from the uterus.

The technique is simple. A Foley catheter with a 30-mL balloon capacity is easy to acquire and may routinely be stocked on labor and delivery suites. Using a No. 24F Foley catheter, the tip is guided into the uterine cavity and inflated with 60 to 80 mL of saline. Additional

Table 2. Uterotonic drugs.

Drug	*Dose*	*Side effects*	*Contraindications*
Oxytocin	– 10 units IM/IMM. – 5 units IV bolus. – 10 to 20 units/litre.	– Nausea, vomiting. – Water intoxication (rare).	– Hypersensitivity to drug.
Methylergonovine Maleate	– 0,25mg IM repeat every 5 minutes as needed (maximum 5 doses). – 0,125mg IMM/IV.	– Peripheral vasospasm. – Hypertension. – Nausea, vomiting.	– Hypertension. – Hypersensitivity to drug.
Carboprost	– 0.25 IM/IMM repeat every 15 mins as needed (maximum 8 doses).	– Diarrhea, nausea, vomiting, flushing, bronchospasm, headache, restlessness. – Oxygen desaturation.	– Active cardiac, pulmonary, renal, or hepatic disease. – Hypersensitivity to drug.
Misoprostol	– 400 to 600 micrograms given orally or rectally.	– Infrequent (diarrhea, nausea, abdominal pain).	– Hypersensivity to drug.

IM: Intramuscular; **IV:** Intravenous; **IMM:** intramyometrial.

Foley catheters can be inserted if necessary. If bleeding stops, the patient can be observed with the catheters in place and then removed after 12 to 24 hours.

In the absence of available balloon devices, packing the uterus with sterile gauze could be attempted, with the end of the pack fed through the cervix into the vagina. The hydrostatic condom catheter is a sterile rubber catheter fitted with a condom, placed into the uterus through the vagina, and inflated with 250 to 500 mL of saline. To keep the catheter in place, the vagina (not the uterus) must be packed with gauze.

SURGICAL TECHNIQUES

If conservative measures fail to contol haemorrhage, it is necessry to initiate surgical haemostasis. The following interventions should be undertaken, in turn, until the bleeding stops: *a)* compression sutures, *b)* bilateral ligation of uterine arteries, *c)* bilateral ligation of internal iliac arteries, and *d)* hysterectomy[11].

Compression sutures

The use of multiple vertical compression sutures (B-Lynch suture and modifications) may be needed to approximate the anterior and posterior uterine walls at various points to virtually obliterate the uterine cavity. Compression sutures are easy to perform, less time consuming, require less surgical expertise and may be a rapidly effective alternative to pelvic devascularisation or subtotal or total hysterectomy.

Bilateral ligation of uterine arteries

This surgical technique may be effective in controlling PPH and it should be among the first surgical steps attempted, as it is simple to perform and can be done quickly. Advantages over internal iliac ligation include lower complication rates, more distal occlusion of arterial supply with less potential for rebleeding because of collaterals, and high reported rates of success in controlling haemorrhaging.

Bilateral ligation of iliac arteries

This procedure has been reported for use in PPH, however its effectiveness is not yet proven. This technique requires more extensive surgical skills and the clinician must consider if the patient's haemodynamic status can allow time to use this conservative, but longer, procedure.

Hysterectomy

Peripartum hysterectomy is the most common treatment modality when massive postpartum haemorrhage requires surgical intervention. This procedure can be life saving in PPH. The technique differs little from that in nonpregnant patients and the tissue planes are often more easily developed. Total hysterectomy is preferred to subtotal hysterectomy, although subtotal technique may be performed faster and be effective for bleeding due to uterine atony. Subtotal hysterectomy may not be effective for controlling bleeding from the lower segment, cervix, or vaginal fornices. The disadvantage of hysterectomy may include the loss of uterus in a woman who wishes to continue childbearing.

Post hysterectomy bleeding

Unfortunately hysterectomy does not guarantee control of blood loss in severe PPH. Bleeding may persist from the pelvic surfaces due to decreased coagulation combined with the trauma from prolonged manipulation. These small sites may be difficult or impossible to isolate and coagulate or suture. Bleeding vessels may retract deep into the pelvic retroperitoneal space and be difficult or impossible to isolate surgically.

Intra-abdominal packs have been used for continued bleeding from peritoneal surfaces when hysterectomy has been done, a consumptive coagulopathy exists, and there is continued widespread bleeding.

Disadvantages of angiographic embolization include the time needed to perform a procedure (1-2 hours) and the fact that the necessary facilities and skills may not be available in all centres. Nevertheless, it is a useful technique, particularly in a patient with ongoing bleeding who is stable or when surgical options have been exhausted.

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CHAPTER 37

Postpartum and puerperal infections

PUERPERAL PERIOD

S. Rueda Marín | D. Orós López | E. Fabre González

INTRODUCTION

Infections are among the most prominent puerperal complications. Puerperal febrile morbidity is defined as an oral temperature of 38,0 ºC (100,4 ºF) on 2 separate occasions at least 24 hours apart following the first 24 hours after delivery or a single oral temperature of 38,7 ºC (101,6 ºF) in the first 24 hours.

Overt infections can and do occur in the absence of these criteria, but fever of some degree remains the hallmark of puerperal infection, and the patient with fever can be assumed to have a genital infection until proven otherwise. The source of infection should be identified, the likely cause determined, and the severity assessed. Endometritis is the most frequent infective cause of puerperal fever. Other sources of postpartum infections include urinary tract infections, mastitis, post surgical wound infections, perineal cellulitis, respiratory infections, retained products of conception, and septic pelvic phlebitis. Once infection reaches the bloodstream, puerperal sepsis may develop.

Deaths related to puerperal infection are very rare in developed world. Maternal mortality ratio due to puerperal infection is estimated to be around 3 maternal deaths for each 100.000 live births. However, the death ratio in developing countries may be 100 times higher[1] (see chapter 35).

ENDOMETRITIS

ETIOLOGY

Most cases of endometritis are due to usual bacteria of the bowel, vagina, perineum, and cervix. The uterine cavity is usually sterile until the rupture of the amniotic sac. As a consequence of labor, delivery, and associated manipulations, anaerobic and aerobic bacteria can contaminate the uterus. Caesarean delivery increases the risk of endometritis (10-20% of patients); other factors of risk are membranes ruptured more than 6 hours, multiple pelvic examinations, and indigent status

Infection tends to be polymicrobial; the most common pathogens include gram-positive cocci (group B streptococci, *Staphylococcus epidermidis,* and *Enterococcus* sp), anaerobes (peptostreptococci, *Bacteroides* sp, and *Prevotella* sp), and gram-negative organisms *(Gardnerella vaginalis, Escherichia coli, Klebsiella pneumoniae,* and *Proteus mirabilis).* If these infections are not treated aggressively, the organisms may act synergistically to form complex abscesses or necrotizing infections.

CLINICAL

Endometritis usually develops on the second or third postpartum day. Fever and a soft, tender uterus are the most prominent signs of endometritis. Also there is anorexia, malaise and headache.

- Endometritis results in temperatures ranging from 38 °C to over 40 °C (100,4 °F to over 104 °F), depending on the patient, the causative microorganism, and the extent of infection.
- Early fever (within hours of delivery) and hypotension are almost pathognomonic for infection with beta-hemolytic streptococci.
- A later onset of fever suggests a mixed infection containing aerobic organisms, facultative and obligate aerobes.
- Fever originating more than seven days after delivery suggests the presence of Chlamydia trachomatis.
- In both early- and late-onset endometritis, anaerobes play a significant role.
- Uterine tenderness; the uterus is soft and exquisitely tender. Motion of the cervix and uterus may cause increased pain. Abdominal tenderness is generally limited to the lower abdomen and does not lateralize.
- Lochia may be decreased or profuse and malodorous. Some women have foul-smelling lochia without other evidence of infection. Some infections, most notably caused by group A beta-hemolytic streptococci, are frequently associated with scanty, odorless lochia.

Bowel sounds may be decreased and the abdomen distended and tympanitic. Adnexal masses palpable on abdominal or pelvic examination are not seen in uncomplicated endometritis, but tuboovarian abscess may be a later complication of an infection originally confined to the uterus. When parametria are affected, pain and pyrexia are severe; the large, tender uterus is indurated at the base of the broad ligaments, extending to the pelvic walls or posterior cul-de-sac.

Considerable leukocytosis, a shift to the left of the differential WBC, and markedly increase RBC sedimentation rate are typical of puerperal infections. The result of lochia cultures must be interpreted with great care, even when the intrauterine specimens are obtained transcervically.

TREATMENT

The usual recommendation is to start treatment with clindamycin (900 mg) and gentamicin (1,5 mg/kg) intravenous administered every eight hours. This combination covers anaerobes, group B *Streptococcus* and gramnegative organisms. After initiation of treatment, the patient is observed for 48 to 72 hours. If no response has occurred, despite adequate doses of antibiotics, or no source of the fever is identified, a third antibiotic is added. Usually, ampicillin is added to provide better synergistic coverage for enterococci. The triple antibiotic regimen is tried for up to 72 hours.

Pelvic abscess should be suspected in the patient with persistent spiking fever despite antibiotic coverage. A clinical and ultrasound examination is very helpful in making the diagnosis. Ultrasound may confirm an abscess when fluid and gas collections are associated with shaggy walls and fluid in the cul-de-sac. The treatment of choice is surgical exploration and drainage.

Septic pelvic thrombophlebitis is more common after cesarean section than after vaginal delivery. The mechanism of action involves the presence of a hypercoagulable state and ascent of infection from the myometrium to pelvic and ovarian veins. The diagnosis is suspected when a patient responds poorly to antibiotic treatment of endometritis and a mass is palpable on pelvic examination. When the diagnosis is highly suspected, a trial of anticoagulation therapy with heparin may suggest the diagnosis.

PUERPERAL MASTITIS

ETIOLOGY

Lactation predisposes patients to mastitis. The presence of milk in the duct, combined with nipple cracking from feeding, creates a favourable environment for infection. The process begins with milk stasis. If a heavy bacterial inoculum is introduced into the duct system, infectious mastitis may develop. Whether the bacteria originate from the infant's mouth or mother's skin is unclear, and both are probably potential sources of the offending organisms. *Staphylococcus aureus* is the most common causative agent in patients with puerperal mastitis. Other organisms less frequently isolated include group A and group B b-hemolytic streptococci, *Escherichia coli,* and *Bacteroides* species[2].

CLINICAL

The distinction of mastitis from breast engorgement is based on clinical evaluation. Breast engorgement is characterized by diffuse distended firm and nodular breasts. This condition is a normal precursor to lactation. Engorgement typically occurs in the first few postpartum days and, although it typically causes a brief temperature elevation, the fever is rarely higher than 39 °C and lasts no longer than 24 hours. Treatment for engorgement consists of supporting the breasts with a binder or brassiere, application of ice, and prescribing analgesics.

Puerperal mastitis, however, occurs two to three weeks postpartum and is associated with fever (temperature of 39 °C [102,2 °F]) or higher) and diffuse myalgias, essentially a flu-like illness. The diagnosis is based on identification of a tender, erythematous, wedge-shaped area in the breast.

TREATMENT

EFFECTIVE MILK REMOVAL

Because milk stasis is often the initiating factor in mastitis, the most important management step is frequent and effective milk removal. Mothers should be encouraged to breastfeed more frequently, starting on the affected breast. If pain prohibits letdown, feeding may begin on the unaffected breast, switching to the affected breast as soon as let-down is achieved. Massaging the breast during the feed with an edible oil on the fingers may also be helpful. Massage should be directed from the blocked area moving outward towards the nipple. After the feed, expressing by hand or pump may also augment milk

drainage and hasten resolution of the problem. Patients should be reassured that nursing is not harmful to the infant. Women who are unable to continue breastfeeding should express the breast by hand or pump, as sudden cessation of breastfeeding leads to a greater risk of abscess development than continuing to feed.

SUPPORTIVE MEASURES

Rest, adequate fluids and nutrition, are essential measures. Application of heat —for example, a shower or a hot pack— to the breast prior to feeding may help the milk flow. After feeding or expressing, cold packs can be applied to the breast in order to reduce pain and edema

ANALGESIA

Analgesia may help with the milk ejection reflex and should be encouraged. An antiinflammatory agent such as ibuprofen may be more effective in reducing the symptoms relating to inflammation than a simple analgesic like paracetamol/acetaminophen. Ibuprofen is not detected in breast milk and is regarded as compatible with breastfeeding.

ANTIBIOTICS

If symptoms of mastitis are mild and have been present for less than 24 hours, conservative management (effective milk removal and supportive measures) may be sufficient. If symptoms are not improving within 12 to 24 hours or if the woman is acutely ill, antibiotics should be started. The preferred antibiotics are usually penicillinase resistant penicillins, such as dicloxacillin or flucloxacillin 500 mg every 6 hours for 7-10 days. Cephalexin (250-500 mg every 6 hours) is usually safe in women with suspected penicillin allergy, but clindamycin (300 mg every 6 hours) is suggested for cases of severe penicillin hypersensitivity.

LACTATION ABSCESS

If a well-defined area of the breast remains hard, red, and tender despite appropriate management, then an abscess should be suspected. Diagnosis of an abscess may be difficult when a distinct fluctuant mass is not present. Abscesses tend to be peripherally situated in the breast. The collection can often be drained by needle aspiration, which itself can be diagnostic as well as therapeutic. Surprisingly, axillary lymph node enlargement is not frequently palpable. Patients typically appear ill and have tachycardia and myalgias.

Conventional treatment of abscesses is incision and drainage. Antibiotic regimens must provide broader coverage to include methicillin-resistant staphylococci and anaerobes. Parenteral antibiotics should be initiated. Options include ampicillin 1 g intravenously every 6 hours, methicillin 1-2 g every 6-8 hours, or cefazolin 1 g intravenously every 6-8 hours. Anaerobic coverage with clindamycin 900 mg every 8 hours or metronidazole 500 mg every 6 hours should be added.

The incision to be placed over the site of maximum tenderness and extend radially, from near the areolar margin toward the periphery of the breast. This type of incision avoids injury to the lactiferous ducts and decreases the complication of duct fistulas. Once the cavity is thoroughly opened, it is particularly important to break down all loculi that may have formed.

Nursing should continue as tolerated, but the affected breast may be quite painful for several days. If it is too painful to nurse, the breast should be mechanically emptied and the infant fed from the other breast until nursing can be tolerated. In rare cases, suppression of lactation may be necessary.

EPISIOTOMY INFECTION

ETIOLOGY

Although episiotomy infections are infrequent, they do occur and may be associated with significant complications and even death. It is surprising that infected episiotomies do not occur more often, since contamination at the time of delivery is universal. In general, the more extensive the laceration or episiotomy, the greater the chances for infection and breakdown of the wound. *Staphylococcus* or *Streptococcus* species and gram-negative organisms, are the most often etiologic organisms associated with perineal cellulitis and episiotomy site infections.

CLINICAL FINDINGS

Patients with episiotomy infections have significant perineal pain, erythema, edema, tenderness, and pus-like discharge from the wound or episiotomy site. Spontaneous drainage is frequent, so a mass rarely forms. Inspection of the episiotomy site shows disruption of the wound and gaping of the incision. A necrotic membrane may cover the wound. A rectovaginal examination should be performed to determine wheter a rectovaginal fistula has formed. Pelvic examination may detect the presence of hematomas or abscesses.

TREATMENT

If no abscess or extension is suspected, hip baths are usually sufficient treatment. Treatment consists of exploration of the episiotomy, drainage and debridement. The wound is then allowed to heal secondarily. An opened and infected episiotomy must not be sutured.

CESAREAN SECTION WOUND INFECTION

ETIOLOGY

Infections of abdominal incisions following cesarean section are more common than infections of episiotomy incisions

CLINICAL FINDINGS

Post-cesarean wound infections are usually detected between day 3 and day 7, postoperatively. Swelling, edema, erythema and tenderness of the wound are present. Later, drainage of purulent material is noted.

TREATMENT

Treatment consists of local care; the wound is opened, cleaned and debrided. In wound infections following cesarean section, the wound may be packed with saline-soaked gauze (or, alternatively, modified Dakin's solution-soaked gauze, 0,5 g of sodium hypochlorite per 100 mL) 2-3 times per day, which will remove necrotic debris each time the wound is unpacked. The wound may be left open to heal, or it may be closed secondarily under local or light general anesthesia when granulation tissue has begun to form.

NECROTIC FASCIITIS

Necrotic fasciitis must be considered whenever infection of the fascia is suspected. This is a rare, life-threatening infection. The diagnosis of necrotic fasciitis can be made if the patient has a high fever resistant to antibiotics, with associated systemic toxicity and a hard, «wooden» feel to the infected area.

Necrotic fasciitis requires immediate aggressive treatment to reduce morbidity and mortality. Fundamental to the successful treatment of necrotic fasciitis is early diagnosis, early administration of broad-spectrum (aerobic and anaerobic bacteria) antibiotics, and rapid surgical debridement[3, 4, 5]:

- Surgical excision and drainage to remove all infected, necrotic tissue and fascia until clean, healthy, pearly gray fascia is identified in all margins of the wound should be performed as soon as NF is identified to arrest the infection process[6].
- Frequently used antibiotics include one or a combination of cefazolin, clindamycin, gentamycin, penicillin, and metronidazole. If the causative organism is GABHS, penicillin is the drug of choice.

MISCELLANEOUS CAUSES

As with any patient with fever, the possibility of other causes, such as urinary tract infection, respiratory tract infections, thrombophlebitis, viral infection, connective tissue disease, malignancy, human immunodeficiency virus infection or subacute bacterial endocarditis, should be considered.

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CHAPTER 38

Treatment of obstetric fistulas

N. R. Devesa

INTRODUCTION

- Fistula is a traumatic opening between the urinary tract and the outside. Worldwide, the most common cause of fistulas is obstructed labor. This problem existed in developed countries 200 years ago, but advances in the provision of basic obstetric services and advanced obstetrical intervention have virtually eliminated fistula in these countries. In the rest of the world we are still fighting.
- Obstructed labor often occurs in rural areas where girls are married young (sometimes as early as 9 or 10 years of age) and where transportation is poor and access to medical services is limited. In such circumstances, pregnancy often occurs shortly after menstruation begins and before maternal skeletal growth is complete.When labor begins, cephalopelvic disproportion is common, and little can be done to correct fetal malpresentations.
- Women may be in labor as long as 5-6 days without intervention, and if they survive, they usually give birth to a stillborn infant. In such cases, the soft tissues of the pelvis have been crushed by constant pressure from the fetal head, leading to an ischemic vascular injury and subsequent tissue necrosis. When this tissue sloughs, a vesico-vaginal fistula (VVF) or rectovaginal fistula develops.
- Many of these patients have complex or multiples fisulas, involving total destruction of the urethra and sloughing of the entire bladeer base. Frequently obstetric fistulas are as large as 5-6 cm.
- After such fistulas develop, the lives of these young women (most of whom are younger then 20 years of age) are disrupted unless they can gain access to curative surgical services.
- The constant, uncontrolled dribble of urine makes them offensive to their husbands and family members. They can no loner live with their families. Most of them eventually become destitute social outcasts- and yet these are otherwise healthy functional young women.

- The social and economic costs of this problem are enormous, but the problem has largely been neglected by the world medical community. The morbidity associated with obstetric fistulas remains, along with the related problem of maternal mortality, one of the single most neglected issues in international women's health care.

APPROACHES TO PREVENTIVE CARE

- Currently, there is a shift in health care from a focus on disease to a focus on prevention. Efforts are under way to promote effective screening measures that can have a beneficial effect on public and individual health.
- For patients with whom a primary care relationship has been established, the initial evaluation involves a complete history, physical examination, evaluation and counseling.
- Risk factors should be identified[1].

PRINCIPLES OF INVESTIGATION

- History.
- Physical examination.
  - — The vulva and perineal area sould be carefully inspected.
  - — Speculum examination. The differential diagnosis for the discharge or urine into the vagina includes single or multiple vesicovaginal, urethrovaginal, or ureterovaginal fistulas and fistula formation between the urinary tract and the cervix, uterus, vagina and vagina cuff.
- Lab studies:
  - — Concentration to determine urea, creatinine.
- Imaging Studies:
  - — An intravenous urogram is necessary to exclude ureteral injury or fistula because 10 % of VVFs have associated ureteral fistulas.

URINARY FISTULA TREATMENT

CONSERVATIVE TREATMENT

For very small fistulae, an indwelling Foley catheter to remain in place for about 4 weeks may result in closure.

SURGERY

TRANSVESICAL APPROACH

This approach is usually done when the fistula is located at the level of the ureteral orifices or higher or if the vagina is stenotic. After opening the bladder, ureteral stents are placed to identify the ureters. The fistula is exposed, circumscribed and excised, thus allowing closure of the individual vaginal and bladder layers. Omentum can be useful to interpose between suture lines to improve healing rates.

VAGINAL APPROACH

DECALOGUE OF THE BASIC PRINCIPLES[2-6]

1. TIMING DECISION

If VVF is diagnosed within the first few days of surgery, a catheter sould be placed and maintained for up to 30 days. Small fistulas of 1 cm may resolve or decrease during this period if caution is used to ensure proper continuous drainage of the catheter.

2. PATIENT POSITIONING

The patient is placed in a prone position with the knees spread and ankles raised in the air and supported by stirrups. Combining it with reverse Trendelenburg positioning enhances visualization with this technique. (Lawson position).

3. TECHNIQUES OF REPAIR. INSTRUMENTAL

The best chance for a surgeon to achieve successful repair is by using the type of surgery most familiar. Long instrumental are adequate, blue methilene, Vicry l.000.

4. EXPOSURE VVFS

Exposure and access to a VVF can be facilitated by catheterization of the fistula with a bulb catheter, such as a Fogarty Catheter. An uninflatd catheter may thread the fistula where the bulb is inflated, then traction is placed on the catheter to draw the VVF into the field. A small VVf may be probed first with a lacrimal duct probe and dilated with cervical dilators to permit placement of a pediatric catheter/ureteral bulb catheter.

5. VAGINAL CUFF EXCISION

The vaginal mucosa is denuded circumferentially for a raduis of 3-5 mm from the vaginal cuff, including the fistula. This incision is then extended obliquely to the bladder wall so as to resect the fistula tract and vaginal cuff scar in a funnel-shaped specimen.

6. MOBILIZE THE VAGINA

Dissect the anterior vaginal wall off the underlying pubocervical fascia.

7. CLOSE THE FÍSTULA TRACT (BLADDER AND VAGINA MUCOSA)

Vertically using 3,0-absorbable sutures in a watertight fashion. Close the pubocervical fascia using 3,0-absorbable sutures horizontally. Excise the redundant vaginal mucosa. Approximate the vaginal incision using 2,0-absorbable sutures, without causing an overlapping suture line.

8. CLOSE TENSION-FREE

The bladder and vagina should be mobilized to enable tension-free. The bladder and vagina should be closed separately. The vaginal skin epithelia can be opposed either by minimal suturing to allow for drainage or closed more formally, but in either case haemostasis should be obtained.

9. URETHERAL INTEGRITY

The uretheral inegrity should be observed with cistoscopy or retrograde pyelogram.

10. BLADDER DRAINAGE

The bladder should be drained with a size 16-18 catheter, 14 days.

Postoperative details: Continue intravenous antibiotics until the patient is able to tolerate an oral diet. To prevent bladder spasms, prescribe anticholinergics. Remove pelvic drains when the output becomes minimal, usually prior to discharge.

The cases where closure is difficult or tenuous, a Simonds-Knapstein skin and fat pad (pedicle flap) may be harvested (figure 1) from the labia majora and interposed. A cylindrical bundle of bulbocavernosus (figure 2) and pedicled fat are developed carefully, preserving the superior external pudendal artery. A capacious tunnel under the vaginal mucosa between the labia majora and the fistula site then is developed. The labial pedicle flap is brought through the vaginal mucosal tunnel and sutured to the edges of the fistula repair (figure 3 and 4). The vaginal mucosa then is closed over the labia skin (see pictures).

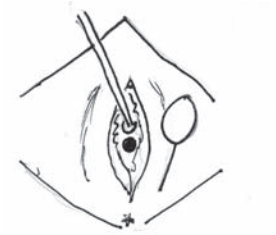

Figure 1. Pedicle flap exposure.

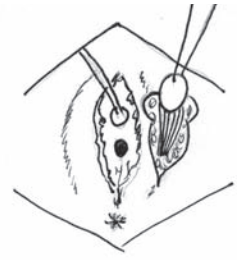

Figure 2. Bulbocavernosus muscle.

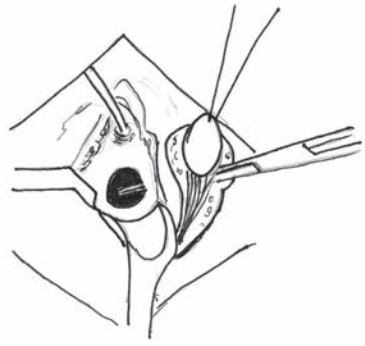

Figure 3. Transposition of pedicle flap.

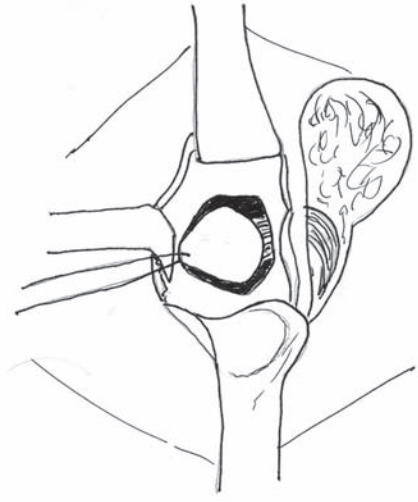

Figure 4. Suture Low-Tension Closure.

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NEWBORN

Care of low-risk newborn

CHAPTER 39

M. R. G. Carrapato | F. Menezes | T. Sotto Maior | S. Ferreira

INTRODUCTION

There is general agreement and consensus regarding the need for special or intensive care for the high risk neonate as well as for little or no intervention for the full term normal delivered baby.

The «low risk» baby is a different matter: does one become unnecessarily aggressive, causing a great deal of discomfort and distress to both the mother and the baby, or does one become permissively tolerant and loose the opportunity for an early and needed intervention?

The first question is how to define «low risk», a hotchpotch of conditions and situations, from family history to maternal underlying disorders and complications of pregnancy, to delivery and the immediate neonatal problems of being born near term and the multitude of small problems arising from an adverse background of whatever nature.

One inference of defining the low risk baby is the time factor: theoretically, the low risk baby becomes a «no risk» baby within a 24 to 72 hour period, as most situations are transient, implying that this baby is merely adjusting to extra-uterine life a little more slowly than «normal» babies. On the contrary, some low risk babies may develop serious and life-threatening diseases, such as congenital heart disorders or inborn errors of metabolism.

The physician is faced, moreover, with the dilemma of separating mother and child, impairing natural bonding, often submitting the baby to regular observations and the inconvenience of blood tests and, frequently, having to reschedule the baby's feeding «timetable».

Although clinical practices may vary from country to country, depending upon both the human and financial resources available, the base line of caring for low risk babies should be *Primum non noccere,* meaning that every attitude must be weighed on the scale of cost-benefit balance instead of being bound to strict protocols.

PRENATAL RISK FACTORS

Assessment of the low risk baby should begin well before delivery, and include the maternal and obstetric history, in order to search for risk factors.

Special attention should be paid to family history, with emphasis on genetic and familial disorders, within their socio-economical environment. The mother's medical history should include occupational exposure, chronic diseases, medications, alcohol, tobacco, illegal drugs and infections, including sexually transmitted diseases, etc.

The past obstetric history must cover spontaneous abortions, terminations and previous pregnancy outcomes. Maternal age, the very young and elderly mothers, especially, are traditionally risk groups. Whether, in the absence of other factors, maternal age alone is an indication for amniocentesis, is open to debate. Blood group incompatibilities are still a major feature in some parts of the world and all steps should be taken for their identification, possible prevention and eventual treatment. Current obstetric history should include estimated gestational age, based upon the date of the last menstrual period confirmed by obstetric evaluation, whenever possible by early ultrasonography (US). Serologies for: hepatitis B, syphilis, human immunodeficiency virus, toxoplasmosis and group B Streptococcus screening should, ideally, be part of national policies and adapted to local epidemiological data. In places where rubella immunization is not done routinely, antibody titles should also be included, although, in the short run, vaccination will be cheaper and more efficient. Universal screening for gestational diabetes is also cheap and cost-efficient for the mother and her offspring, both in the immediate perineonatal period and probably in the long term and should therefore also be included. EPH gestosis, a common complication of pregnancy, especially in under-privileged populations, should not be overlooked, in order to prevent serious maternal complications, fetal and neonatal problems and, quite possibly, adverse future outcomes.

CARE IN THE DELIVERY ROOM

The likelihood of pregnancy-related disorders should be anticipated on the basis of antenatal care (or its lack) and intrapartum monitoring.

Intrapartum pertinent events must also be recognised, particularly clinical and laboratory signs of amnionitis, fetal wellbeing, spontaneous or induced labour, since babies born after induction are potentially less well-equipped for extra-uterine adaptation, whilst the nature of delivery and maternal sedation may also affect immediate neonatal status at birth.

Despite its limitations, Apgar score remains a good tool for evaluation and management of the baby in the delivery room, as well as for prognosis. It is important to understand the metabolic and physiologic changes involved in the transition to extra-uterine life, in order to avoid overly enthusiastic and unnecessary resuscitation. Most babies are born in physiological primary apnea and will therefore need very little help apart from gentle stimulation and suctioning as required, but not necessarily routinely. Importantly, an appropriate room environment should be provided to avoid hypo/hyperthermia and, if resuscitation is needed, room air rather than oxygen supplementation should be used preferentially, with its use limited to non-responders. Equally, although a depressed baby with meconium aspiration will need intubation and suction, this will by no means apply to all vigorous meconium stained babies[1, 2].

Cord blood is collected for blood typing and Coombs testing when indicated.

Ophthalmia neonatorum may be sight-threatening if caused by *N. gonorrhoeae.* The other common agents are *C. trachomatis, Staphylococcal* and other Gram positive cocci. Although detection and treatment of gonococcal and chlamydial infections in pregnancy is the most efficient way to prevent neonatal disease, not all women receive antenatal care or comply to treatment. Neonatal prophylaxis is therefore recommended, with either topical erythromycin ophthalmic ointment 0,5 % or tetracyclin 1 %. Povidone-iodine appears to be an effective and cheap alternative, especially in developing countries. Silver nitrate should be avoided because of both ineffectiveness against *Chlamydia* and the possibility of inducing chemical conjunctivitis[3].

For the prevention of hemorrhagic disease, 1 mg of intramuscular or subcutaneous vitamin K remains standard therapy, in spite of the concerned, but unproven, increased risk of childhood leukaemia or other malignancies. Oral formulations need additional research for efficiency, safety and bioavailability, especially with breast-fed infants[4].

No single cord care practice has proved to be superior. Dry cord care with water and soap without antiseptic agents does not appear to increase the risk of infection, in spite of higher rates of colonization, at least in developed countries. For less developed regions of the world, application of antimicrobial and antiseptic agents is recommended, commonly triple dye, chlorhexidine, 70 % alcohol, and hexachlorophene[5].

First examination in the delivery room should exclude obvious congenital malformations, remembering that minor abnormalities, especially if multiple, may point towards serious underlying disorders, whilst even life-threatening malformations may not be evident at birth.

Placental observation for size, membranes, vessels, infarcts, clots, etc., must also be performed as well as anatomopathological examination in all conditions where the placenta may be a useful marker of maternal/fetal pathologies.

The baby must be given to the mother as soon as possible for early skin-to-skin contact to promote bonding and successful breastfeeding. The father, if present, should also be encouraged to participate.

POSTNATAL CARE

Neonate's condition allowing, baby and mother should stay together, even when certain procedures and treatments might be indicated.

FEEDING

Breastfeeding, besides providing all the necessary nutrients, growth factors and immunological components, is also an important means of maternal/infant bonding and should therefore be encouraged by early onset, on demand. It is debatable whether maternal nutrition will adversely affect milk composition; the recommendation, therefore, is that the mother should have a normal diet, with locally available foodstuffs and specific restrictions will only very rarely be required. Whether fully breast-fed babies will be spared the burden of atopic disease, diabetes and the later onset of many adult diseases remains controversial, but at least it is reassuring that they are certainly not caused by maternal milk.

One of the most frequently asked question is whether maternal infection and medication are contraindications to breastfeeding: in most cases they are not. True contraindications

to breastfeeding are extremely uncommon and include only a very few maternal disorders namely active, untreated tuberculosis, varicella, herpetic lesions on the breast, T cell leukaemia virus type I, anticancer therapy[6, 7].

Neonatal diseases to contradict breastfeeding are equally rare and mostly due to congenital errors of metabolism.

Whilst in the more affluent countries HIV positive mothers are restrained from breastfeeding, in the lesser developed countries the benefits from breastfeeding far outweigh the risk of HIV transmission.

Supplementation or replacement of breast milk should be the exception, especially if medical and nursing staff play their really supportive role. However, when circumstances demand, an adequate formula should be prescribed and the mother not made to feel guilty.

IMPORTANT OR TRIVIAL?

Most of the conditions and situations below are part of the daily routine in every postnatal ward and, more often than not, are either within the limit of normality or of very little significance, although occasionally they may represent a potentially serious disorder. Clinical sense and sensibility will make all the difference and ancillary investigations should be carefully balanced.

REFUSAL TO FEED/THE «VOMITING» BABY

The immediate neonatal period may present a difficult challenge since even the «no risk» baby may have some difficulty in establishing breastfeeding. Antenatal preparation of future mothers could improve their knowledge of the newborn feeding patterns and help with many of these matters, avoiding unnecessary concern and stress. However, feeding refusal, especially in association with vomiting, lethargy and abnormal cry, should be sufficient warning signs that all is not well and requires attention.

NOT PASSING MECONIUM/URINE

Most healthy infants will have their first miction in the first few hours of life, although a few, especially following maternal sedation, may have a delay of up to 24 hours. Similarly, meconium evacuation may be delayed for a couple of days or more, depending on gut motility —a function of gestational age and maturity. In addition, many babies will have eliminated meconium or urine in the delivery room at the time of birth, which went unrecorded…

Besides the failure to pass urine or meconium there will be the presence or absence of any other signs which point to either renal or gut pathologies *per se* or as an expression of major systemic involvement.

JAUNDICE

Physiologic jaundice obeys to the following criteria: onset after 24 hours of age; total bilirubin rising by less than 5 mg/dl per day; peak bilirubin occurs at 3-5 days of age, with a total bilirubin of no more than 15 mg/dl; clinical jaundice is resolved by one week in the full-term infant and by two weeks in the preterm infant. Hyperbilirubinemia outside these parameters or an elevated «direct» bilirubin requires investigation and treatment[8].

HYPOTHERMIA

Babies' chemical and non-shivering thermogenesis is quite incipient whilst heat loss by radiation, conduction, convection and evaporation are overwhelming, with the resulting tendency to hypothermia. The risk is further increased in some babies, namely preterms,

SGA and sick babies in general, due to whatever reason. However, a very common and easily preventable cause is an inadequate thermal environment during the cold months in certain parts of the world and occasionally in the delivery room.

The chance of survival of the neonate is markedly enhanced by the successful prevention of excessive heat loss. Following delivery, healthy term infants should be dried, kept under a preheated radiant warmer and given to the mother for skin-to-skin contact and prevention of heat loss. For that purpose, the newborn infant must be kept under a neutral thermal environment[9].

It remains controversial as to whether established hypothermia should be treated by gradual or rapid re-warming. In general, depending upon temperature, gestational age, birth weight and overall condition, the smaller the baby the slower should be the re-warming. Whatever the situation, careful monitoring and resuscitation should be available[9].

HYPOGLYCAEMIA

Blood glucose screening is performed in neonates at risk of hypoglycaemia (infants of diabetic mothers, preterm, low birth weight, small for gestational age, large for gestational age, hypothermia, sepsis, etc). The questions are 1) what is hypoglycaemia-methodological problems of glucose measurements to storage and transport, all interfering with evaluation and accounting for different definitions; and 2) does it matter? In other words, what low level of blood glucose is harmful and will asymptomatic hypoglycaemia be less damaging? For these reasons it is recommended that blood levels should be kept at $\geq$2,6 mmol/l regardless of gestational and postnatal age, promoting early enteral feeds. If oral feeds are not tolerated, I.V. glucose at 5-6 mg/kg/min, increased to 8-10 mg/kg/min should be given as required. For symptomatic babies with signs of neuroglycopenia a bolus of 0,25-0,5 g/kg should be given followed by glucose infusion at the required rates. Glucagon 200-300 μg/kg may be given on occasions, in an emergency. At the earliest opportunity, enteral feeding should be reinstated with gradual withdrawal of the I.V. infusion[10].

JITTERINESS

Jitteriness is a common occurrence, especially in tiny babies, consisting of symmetric, fine rapid movements of the hands and feet, not affecting the eyes, and that can be stopped by restricting the affected member, an important distinguishing feature from neonatal convulsions. Occasionally it may be due to hypoxic-ischemic encephalopathy, drug withdrawal or metabolic imbalances of hypoglycemia and hypocalcaemia. There are no EEG changes and no specific treatment, only correction of the underlying metabolic alterations[11].

THE HEART MURMUR

At a time of transitional adaptation to extra-uterine life the presence of heart murmurs in the first few days of life is quite common. In the absence of any other clinical manifestations upon an otherwise normal examination, the heart murmur is quite unlikely to be pathological. Conversely, even the most serious congenital heart disease may present without a murmur or any abnormal signs at all in the first week or two of life. Thus, even a low risk baby for congenital heart disease must be re-evaluated, preferably towards the second week of life. Routine ultrasound examination for an asymptomatic heart murmur in the first few days of life is not necessarily recommended, although local expertise and availability may dictate options.

CONGENITAL ANOMALIES

Minor congenital anomalies occur in about 4% of the general population and, if isolated, in an otherwise normal infant, require no diagnostic evaluation. That is the case for instan-

ce, with preauricular pits or tags, sacral dimple without other cutaneous abnormality, a single transverse palmar crease, three or less café-au-lait spots in a white infant or five or less in an Afro-American infant, etc. In these circumstances the best action is no action, saving unnecessary expense and worry. However, some minor abnormalities are markers for occult malformations, particularly if multiple, and a thorough investigation for an underlying major abnormality should then be undertaken[12].

Haemangioma and nevus are a cause of concern for parents, especially if their location or size is troublesome; however, they are generally benign, unless they are part of important syndromes such as Stuge-Weber, Kasabach-Merritt, multiple angiomatosis, etc.

A large spectrum of genitourinary tract abnormalities is often diagnosed antenatally, mostly representing minimal changes or no pathological features at all. In spite of the ongoing controversy, in the absence of severe hydronephrosis, most conditions require no urine tract infection prophylaxis from birth and investigation can be postponed until the first month of life.

IMMUNIZATIONS

Recent experiments and the success of modern vaccination programmes confirm that infants can reproduce significant immune responses. Some passive immunity from maternal antibodies will protect the infant during the first few months of life. In fact, IgG travels across the placental stroma and fetal endothelium by unknown mechanisms entering into fetal circulation; IgA and IgM do not bind to neonatal receptors[13].

All infants should be immunized against hepatitis B, the most effective way to protect against later liver complications. If the mother is HBsAg negative, the first dose can wait until 1-2 months of age; if the mother is HBsAg positive or status is unknown, active immunization and simultaneous immune globulin should be administered, whenever available, soon after birth[1].

Immunization of infants with Bacille Calmette-Guérin vaccine (BCG) can protect against tuberculosis (TB) meningitis and other severe forms of TB in children less than 5 years old. In countries with a high incidence of TB and in less favorable environments, a single dose of BCG vaccine is recommended for all infants as soon as possible after birth[14].

NEONATAL SCREENING

INBORN ERRORS OF METABOLISM

Inborn errors of metabolism are an uncommon group of disorders with non-specific clinical manifestations, often mistaken for sepsis, heart failure or neurological problems when convulsions are the presenting features; this diagnosis should therefore be considered in any baby who is sick for no apparent reason.

Early neonatal screening should be performed and adapted to local epidemiological data in order to include the more common errors and those susceptible to treatment.

Tandem mass spectrometry allows diagnosis of a wide spectrum of disorders.

HEARING

About 1-3 per 1.000 newborns have significant bilateral hearing loss, with deleterious effect on language development. Although populations may be heterogeneous and often with limited resources, wherever possible high risk infants with a family history, adverse

perinatal events and recognised hearing-loss syndromes should be considered for screening at least by evoked otoacoustic emissions. An early detection and intervention in these infants will be critical[15].

FOLLOW UP

Most less-well developed countries will experience difficulty in handling the follow-up of low risk babies. Depending upon local facilities, evaluation should take place regularly in order to assess baby's development, to determine how the family is coping with yet another small addition and the opportunity used to enforce national immunization programmes.

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CHAPTER 40

Clinical care of the preterm infant

NEWBORN

L. McKechnie | M. Levene

This chapter deals with common problems affecting the very premature infant. We describe best evidence based on Cochrane reviews or published meta-analyses. Where results from randomized controlled trials are unavailable the best evidence based on clinical experience is described.

THERMAL CARE OF THE PRETERM INFANT

Preterm infants are susceptible to heat loss because

- Low body weight to surface ratio.
- High transepidermal evaporative water loss due to poorly keratinised stratum corneum.
- Poor glycogen and brown adipose tissue stores (which metabolise to produce thermogenesis).
- Immature behavioural and physiological responses to heat loss.

Temperature can drop by 0,1-0,3° centigrade per minute unless interventions to prevent this are put in place immediately.

Hypothermia in the newborn infant has been shown to:

- Increase the severity of illness.
- Decrease the survival.
- Decrease the rate of growth.

An infant should therefore be nursed in a thermo-neutral environment so that excess energy is not wasted on maintaining body temperature. This is most difficult to achieve around the time of delivery when the infant is wet and the environment is cool and dry.

Interventions at delivery to prevent heat loss:

- Maintain delivery room temperature at 25 °C.
- Pre-warm all contact surfaces.
- Eliminate all drafts.
- Use a pre-warmed radiant heater during resuscitation.
- Dry infants >28weeks gestation thoroughly, especially the head.

- Remove any wet towels/blankets.
- Put hat on baby.
- Infants <28weeks gestation place immediately into plastic bag.
  - Do not dry infant.
  - Place entire body to neck into bag.
  - Auscultation and colour can be assessed though the bag.
  - If access required to umbilical cord vessels, small holes may be made in bag and then occluded when no longer required.
- Infants <28 weeks or <1.500 g to be placed on transwarmer mattress.

INTERVENTIONS FOR HYPOTENSION

Hypotension is a common complication of prematurity. The definition varies in the literature; it may be defined as:

- <30 mmHg.
- <10th centile of a birth weight and age-specific range.
- Mean arterial pressure (MAP) < number of completed weeks of gestation of the infant.

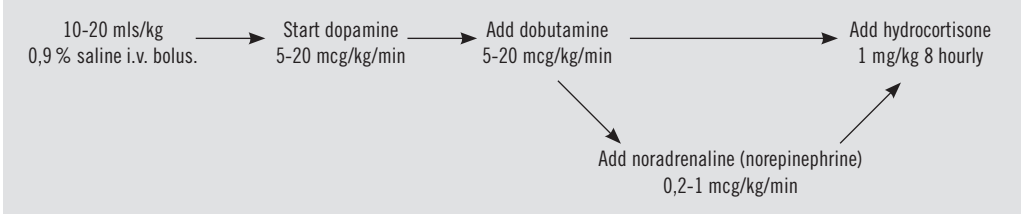
Hypotension is associated with:

- Increased rate of intraventricular haemorrhage.
- Poor long term neurodevelopmental outcome.

There are a number of treatment strategies:

- Volume expansion:
  - The use of intravenous volume expander (normal saline preferred to albumin) is common.
  - There is no evidence to support or refute the routine use of volume expansion in hypotensive newborn infants.
- Inotropes:
  - Dopamine and dobutamine are most commonly used.
  - Other inotropes (adrenaline, noradrenaline and isoprenaline) are less frequently used in severe resistant hypotension.
- Systemic steroids:
  - Meta-analysis shows that a single dose of dexamethasone is effective in treating infants with refractory hypotension.
  - Post-natal dexamethasone used to prevent chronic lung disease suggests it is associated with a poor neurodevelopmental outcome.
  - Subsequently hydrocortisone has been used with no long-term adverse effects yet evident.

TREATMENT OF HYPOTENSION IN NEWBORN



PATENT DUCTUS ARTERIOSUS (PDA)

Patent ductus arteriosus is associated with an increased risk of:

- IVH.
- NEC.
- CLD.
- Death.

Standard treatment has been indomethacin.

Side effects include:

- Decreased cerebral blood flow.
- Decreased cerebral oxygen delivery.
- Transient renal failure.
- Isolated bowel perforation.
- Decreased cerebral blood volume.
- Oliguria.
- Necrotizing enterocolitis.
- Gastrointestinal hemorrhage.

More recently ibuprofen has been used and shown to:

- Close PDA.
- No reduction in cerebral, intestinal or renal circulation.
- Enhance cerebral blood flow auto regulation.
- Protect neurological functions following an oxidative stress in a piglet model.

PROPHYLACTIC TREATMENT OF PDA

Systematic review:

- Prophylactic indomethacin *vs.* placebo.
- 2.872 infants less than 37 weeks at birth.

Indomethacin in the short term	↓ symptomatic PDA. ↓ ligation of PDA. ↓ grade 3 and 4 IVH.
In the long term	No benefit or harm in neurodevelopmental outcome.

Systematic review:

- Prophylactic ibuprofen *vs.* placebo.
- 672 infants less than 37 weeks at birth.

Ibuprofen	↓ PDA at 72 h . ↓ Medical treatment of PDA. ↓ Surgical ligation.
No benefit	IVH, NEC, CLD, mortality, GI haemorrhage

One study stopped early; 3 cases of pulmonary hypertension in the ibuprofen group.

TREATMENT OF ASYMPTOMATIC PDA

Systematic review:

- Treatment of asymptomatic PDA with either indomethacin or ibuprofen.
- 620 infants.

No significant difference in	Treatment success. Most side effects.
Significance	Less oliguria and more oxygen dependence at 28 days or 36 weeks post conceptual age in the ibuprofen group.

Systematic review:

- A prolonged course (>4 days) indomethacin *vs.* short course (≤3days).
- 291 infants.
- 4 studies.

Significant (favouring prolonged course)	↓ Duct re-opening.
	↑ Chronic lung disease less severe IVH and renal impairment.
The dosage regimes varied considerably from a total dose of 0,6 mg/kg-1,6 mg/kg in prolonged course.	

TREATMENT OF SYMPTOMATIC PDA

Treatment has long been established with indomethacin. Because of the side-effect profile of indomethacin, ibuprofen is now being used in some centres. Systematic review looked at surgery *vs.* medical closure of PDA. There was a higher rate of closure but more pneumothorax and ROP in the surgical group. The use of frusemide during indomethacin treatment has not been seen to confer benefit.

FEEDING THE LBW INFANT

Breast milk is the recommended nutritional source for full term infants but for preterm infants human milk supplies insufficient quantities of protein, calcium, phosphorus and sodium to meet demand. Multicomponent human milk fortifiers are available that contain protein, carbohydrate, calcium, phosphorus, vitamins and trace minerals.

Preterm infants fed human milk compared with infants fed term or preterm formulae have:

- ↓ Weight gain.
- ↓ Bone mineralization.
- ↓ Risk of necrotising enterocolitis.
- ↑ Neurodevelopmental outcome.

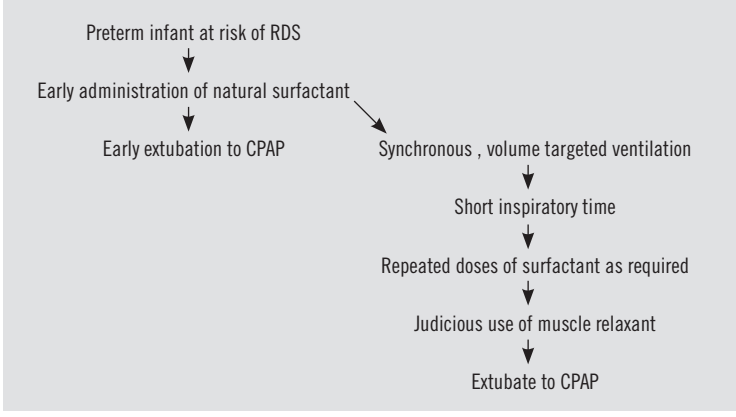
Systematic review	*Significant findings*	*Non significant findings*
Fortification of human milk feeds for preterm infants.	↑ Short term weight gain.	Long term growth (2 studies only).
	↑ Linear length.	Bone mineral content.
	↑ Head growth.	Fractures.
		Feed intolerance.
		NEC.
Fortification of milk post discharge.	No evidence to prove benefit or harm.	

Techniques of feeding:

Systematic review	*Significant findings*	*Non significant findings*
Demand *vs* scheduled feeding.	↓ Wt. Gain in demand fed	Trend to earlier discharge.
Continuous *vs* bolus feeding.	Bolus feeders achieved full feeds 3 days earlier.	No difference in NEC. More apnoeas in continuous feeders.
Early ($\leq$ 4 days) vs. delayed ($>$ 4d) feeds.	↓ PN days, sepsis evaluations, central venous catheters.	NEC, trend to ↓ days of phototherapy. BUT only 2 small studies.
Erythromycin for feed intolerance.		NEC, days to full feeds, length of stay.
Thickeners for GOR.	No studies suitable for inclusion in systematic review but trend to improved symptoms.	
Non-nutritive sucking.	↓ Length of stay (& days)better transition from tube to bottle feeds better performance with sucking feeds.	
Rapid vs slow advancement of feeds.	↓ No. of days to full feeds if rapid.	NEC. Length of stay.
Transpyloric vs gastric feeds.	None.	Transpyloric ↑ mortality, ↑ GI disturbance.

RESPIRATORY DISTRESS SYNDROME

Early administration of surfactant to a preterm infant confers less risk of air leak, oxygen dependence at 36 weeks and mortality. Naturally derived surfactant reduces the risk of air leak, BPD and mortality. Repeated doses of surfactant in severe RDS provide a more sustained improvement in oxygenation and a decreased requirement for ventilatory support. In infants with RDS the use of CPAP reduces the need for IMV. If an infant is ventilated for RDS the use of CPAP helps prevent failure of extubation. Infants ventilated for RDS with volume-targeted rather than pressure-limited strategies are ventilated for shorter times, have fewer air leaks and less severe IVH. When ventilated the inspiratory time should be short and muscle paralysis should be used if the babies efforts are asynchronous (decreased incidence of air leak). There is no evidence to prove benefit of conventional tidal ventilation compared to high frequency oscillatory ventilation.



GERMINAL MATRIX-INTRAVENTRICULAR HAEMORRHAGE (GMH-IVH)

INCIDENCE

- Decreased over the last 30 years.
- About 20% of preterm infants have evidence of GMH-IVH.
- The majority occur in the first 72 hours may extend over 24-48 hours.

PATHOLOGY

- GMH-IVH usually arise form the germinal matrix.
- Fragile, highly vascular capillary bed over the head of caudate nucleus.
- Most abundant at 24-34 weeks; almost entirely involuted by term.
- Venous drainage of deep white matter is through the germinal matrix: If venous drainage is impaired periventricular venous infarction may evolve.

AETIOLOGY

A number of factors interact to increase the likelihood of GMH-IVH:

Prenatal	*Perinatal*	*Postnatal*	
Prematurity. No antenatal steroids.	Birth depression. Birth trauma.	RDS. Pneumothorax. Hypercarbia. Acidosis. Hypoxia.	Pulmonary haemorrhage. Hypotension. Coagulation disorders. PDA.

DIAGNOSIS

- Most frequently the onset of GMH-IVH is asymptomatic.
- Rarely catastrophic deterioration e.g. increased ventilation, hypotension etc.

CONFIRMATION OF THE DIAGNOSIS

- With ultrasound.
- There are classification systems but perhaps more reliable to describe the ultrasound appearances accurately when reporting to avoid confusion.

GMH-IVH may be:

- Small and confined to the GMH.
- Larger with blood filling the ventricle.
- Blood filling the ventricle and ventricular dilatation.
- Large GMH-IVH with periventricular venous infarction.

COMPLICATIONS

Complications may occur, particularly with the larger GMH-IVH.

- Post-haemorrhagic ventricular dilatation (PVHD) may occur causing hydrocephalus.
  - — This may occur 2-3 weeks post GMH-IVH.
  - — Symptoms include apnoea, feed intolerance and seizures.
  - — Assessment is by serial ultrasound measurement of the ventricular size and head circumference.
  - — Measurement of cerebrospinal fluid (CSF) pressure at lumbar puncture should be measured if there is ventriculomegaly.
  - — Drainage should be considered if symptoms are present, CSF pressure is >10 cm or head circumference is rapidly increasing.
  - — Measures to decrease the incidence of PHVD such as fibrinolytic therapy or acetazolamide have been shown to be harmful.

PREVENTION

The following methods have been shown to reduce the incidence of GMH-IVH:

- Antenatal corticosteroids vs control (OR 0,54, CI 0,43 0,69) (Roberts & Dalziel 2007).
- Indomethacin vs control:
  - — All grades of GMH-IVH (RR 0.88, CI 0,80 0,96) (Fowlie & Davis 2003).
  - — Severe GMH-IVH (grade 3 and 4) (RR 0,66, CI 0,53 0,82) (Fowlie & Davis 2003).
  - — Neurodevelopmental outcome (RR 1,02, CI 0,90 1,15) (Fowlie & Davis 2003).

No effect of surfactant, vitamin E, phenobarbitone or plasma expansion.

PROGNOSIS

Uncomplicated GMH-IVH has a good prognosis. PVHD has a high risk of poor neurodevelopmental outcome of about 50 % increasing to 75 % if a shunt is needed.

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CHAPTER 41

Resuscitation and neonatal asphyxia

NEWBORN

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PART I. NEONATAL RESUSCITATION

INTRODUCTION

The majority of deliveries, which occur under normal circumstances, will not require any intervention for the baby will adequately adapt to extra uterine life. However, approximately 10 % will require some type of active resuscitation to attain a normal pattern of respiration. In most cases, very simple maneuvers will suffice, and only in 1 % of the newly born infants more aggressive interventions will be required.

In this chapter guidelines for caregivers attending newly born infants (Nwb) are given in a stepwise manner to guide them along the resuscitation procedure.

GETTING READY FOR INTERVENTION IN THE DELIVERY ROOM

ANTICIPATION

Caregivers should know «risk factors» in every pregnancy and/or delivery that may pose the Nwb at risk of resuscitation. High risk pregnancies should be transferred to an appropriate referral center fulfilling medical and equipment requirements.

ATTENDING PERSONNEL

One attendant, trained to initiating basic neonatal resuscitation including positive pressure ventilation and chest compression, should take immediate care of the infant. Another attendant trained in deep cardio-pulmonary resuscitation including tracheal intubation and drug administration should be easily accessible. Deep resuscitation always requires 2 trained attendants: one for intubation and drug administration and the other for monito-

ring vital signs and, if necessary, to initiate chest compression. The leader of the procedure will always be the most experienced attendant and will assume care of the respiratory airway.

DELIVERY ROOM

Delivery room should be around 25 °C, well illuminated, and include a plane surface under a radiant heater (37 °C) for the newly born infant.

*Basic installations recommended**:

— Oxygen supply (with flow meter).

— Air supply (with flow meter).

— Oxygen-air blender (desirable).

— Negative pressure source (with manometer desirable).

(*) In rural areas, room air will be used initially for ventilation.

*Basic material recommended**:

— Suction catheter (FR 6, 8, 10, 12, 14).

— Self-inflating bag (250-500 mL).

— Facial mask (size for term and preterm).

— Laryngoscope (size 0, 1).

— Tracheal tubes (ETT) (size 2,5; 3; 3,5 and 4 mm).

(*) In rural areas only self-inflating bag and bulb syringe may be requested.

*Basic medication recommended**:

— Adrenaline (diluted 1:10.000 with normal saline).

— Bicarbonate 1 M (diluted 50 % with distilled water).

— Naloxone.

— Normal saline (ClNa 9 %).

(*) In rural areas only normal saline may be requested.

Material and medication should be easily accessible and reviewed daily.

STEPS IN RESUSCITATION

Term infant with vigorous cry and effective respiration, good tone and clear amniotic fluid do not need resuscitation. Dry gently with warm cloth and put to mother's breast.

If one of the previous conditions fails, the following steps should be performed (see figure 1):

a) Initial stabilization.

b) Ventilation.

c) Chest compression.

d) Drug administration.

(allow 30 seconds for each step, re-evaluate respiration, HR and color, and decide to go to the following step).

A. INITIAL STABILIZATION:

— Maintain body temperature keeping the baby under a radiant heater and drying with warm towels.

— Adequate supine position with slightly extended neck (neutral position (figure 2).

— Clean secretions with gauze or gentle aspiration with suction bulb syringe.

— If obstruction of the upper respiratory airway is suspected aspirate with suction catheter and negative pressure mouth (first) and nostrils (max pres. −100 mmHg; 5 sec). Prolonged suction delays spontaneous respiration

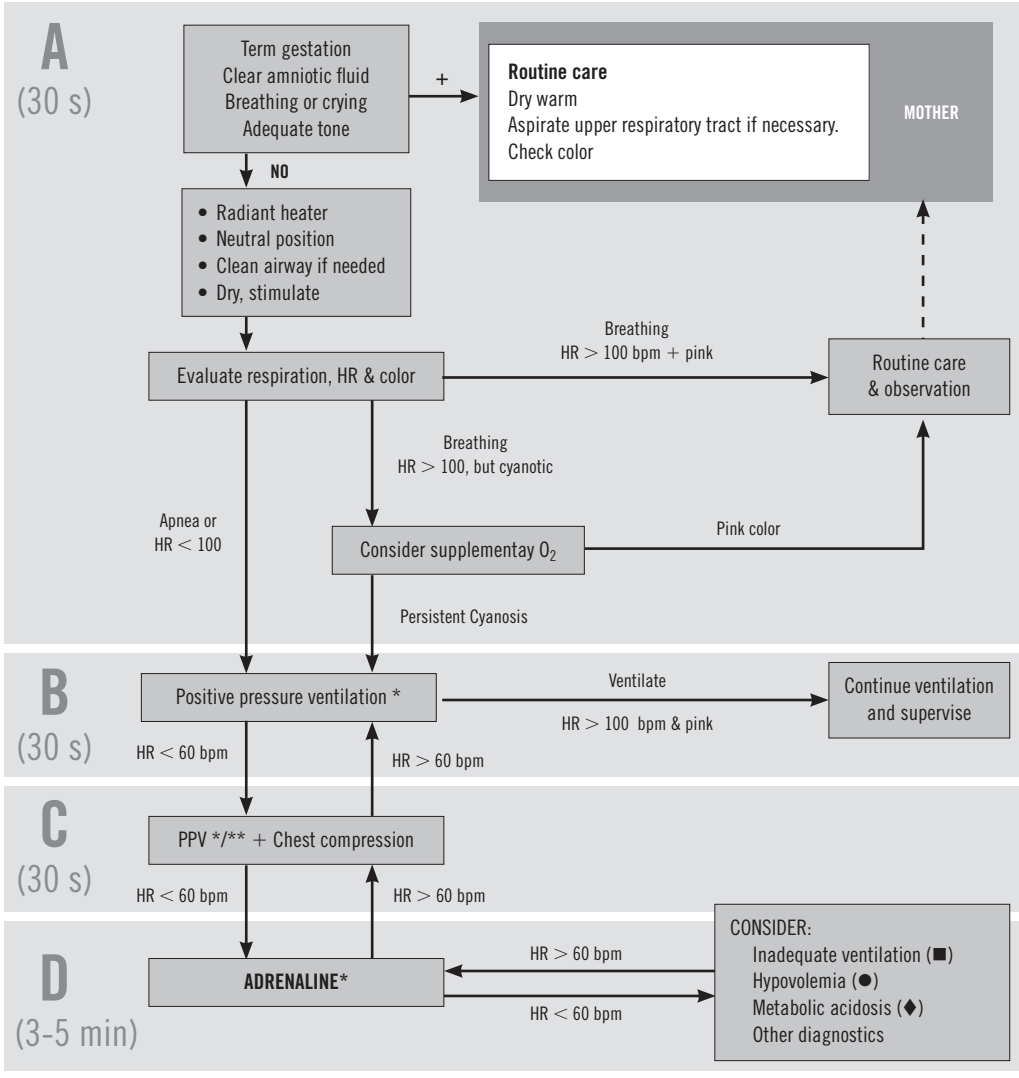
and may cause bradycardia and/or laryngeal spasm.

— Respiration can be stimulated by gently rubbing while drying or stimulating back or feet sole. If unsuccessful initiate ventilation.

— If the baby is not spontaneously breathing oxygen is useless, and positive pressure ventilation should be initiated.

— Positive pressure ventilation can be initiated with room air if oxygen is not available. If oxygen is available and heart

Figure 1. Flow chart for resuscitation of the asphyxiated newly born infant. Modified from Modificado de International Liaison Committee on Resuscitation *(Resuscitation 2005; 67: 293-303)* y de European Resuscitation Council Guidelines for Resuscitation 2005 *(Resuscitation 2005; 67S1: S97-S133).*



* Consider tracheal intubation in difficult clinical situations (PPV: positive pressure ventilation).

(■) (check ETT or pneumothorax → punction)

(●) Normal saline perfusion (10 mL/kg/30 min)

(♦) Evaluate bicarbonate if adequately ventilated

rate does not improve after 30 sec, FiO2 should be increased to 40 % and to 100 % thereafter with 30 sec intervals.

B. VENTILATION

POSITIVE PRESSURE VENTILATION

— Should be promptly initiated if after 30 sec of stabilization the baby exhibits:

- Gasping or apnea.
- Heart rate below 100 beats per minute (bpm).
- Central cyanosis (with supplemental oxygen).

— Technique (figure 3):

- Free upper airway by aspirating secretions
- Put the baby supine with slightly extended head (neutral position see figure 2).
- Choose the adequate facial mask and adjust it to impede leaking.
- Connect mask to self-inflating bag (250 mL or 500 mL (see figure 4).
- Set pressure limit (if possible) around 30- 40 cmH_2O.
- First puffs should be performed using 30-40 cmH_2O and prolonged inspiratory time to achieve an adequate FRC (functional residual capacity). Thereafter 20 cmH_2O should be enough to maintain an adequate ventilation.
- Respiratory rate should be kept between 30 (term) to 60 breaths (preterm) per min.
- Efficacious ventilation will promptly increase heart rate and cause thoracic wall to expand.

TRACHEAL INTUBATION

— It should be always considered when:

- Meconium-stained amniotic fluid is present in lower respiratory tract.

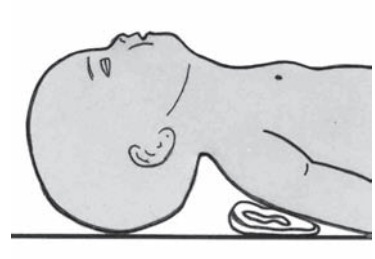


Figure 2. Head in neutral position.

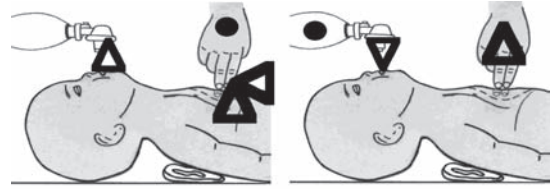


Figure 3. Bag and mask ventilation and chest compression.

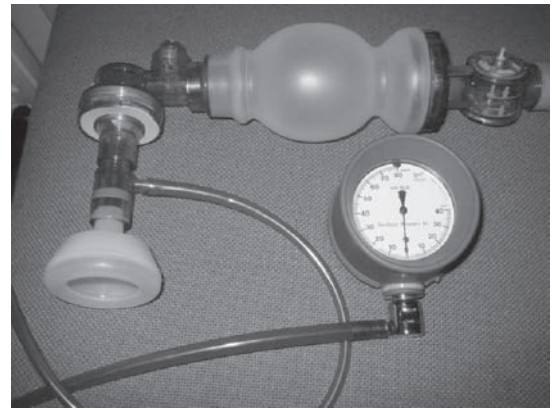


Figure 4. Bag and mask resuscitator with pressure manometer and relief valve.

- Unsuccessful bag and mask ventilation.
- Cardiac massage is needed.
- Need for tracheal administration of drugs.
- Extreme prematurity (< 1.000 g) or diaphragmatic hernia.

— Technique:

- Mouth intubation is preferred in emergency situations.
- Patient is put in neutral position (see figure 2)

- Laryngoscope is introduced through the right side of the mouth and tongue is displaced to the left side.
- Blade is forwarded until its tip is located within the vallecular crease. With a slightly vertical movement of the blade, the epiglottis is folded upwards to allow visualization of the vocal cords (see figure 5).
- ETT in inserted between the vocal cords, and laryngoscope gently retired.
- Adequate ETT size is essential for an adequate ventilation. Internal diameter: <1 kg: 2.5 mm; 1-3 kg: 3.0 mm; >3 kg: 3.5 mm.
- ETT is then connected to positive pressure device.

— Important

- To avoid hypoxemia the baby should be adequately ventilated with bag and mask before the procedure.
- Intubation attempts should not last more than 30 sec.

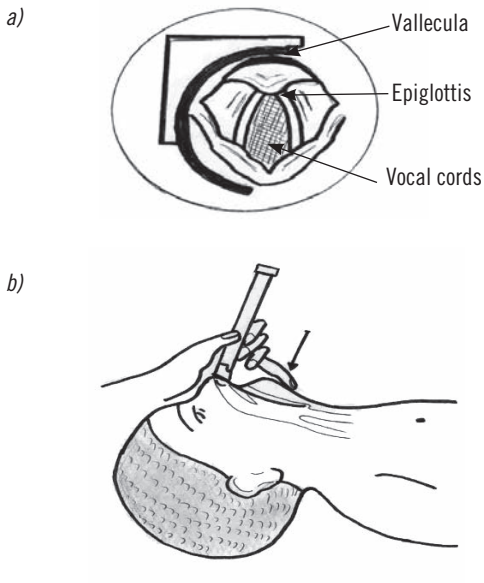


Figure 5. *a)* Anatomic sketch of vallecular, epiglottis and vocal cords. *b)* Technique of intubation as described in text.

- If heart rate goes below 100 bpm procedure should be interrupted and allow baby to recover by bag and mask ventilation.
- Effective ventilation should promptly increase heart rate.

C. CHEST COMPRESSION (figure 3)

— Initiate if after 30 sec of effective tracheal ventilation heart rate stays <60 bpm.

— Technique:

- Compression should be performed with both thumbs with the rest of the fingers encircling the chest and the lower third of the sternum. Avoid compression of the xyphoid process.
- Each compression should depress the sternum by one third of the anterior-posterior diameter of the chest.
- Frequency should be of 90 bpm, with a ventilation interposed between 3 compressions.
- HR and respiration should be continuously checked, and chest compression interrupted if heart rate >60 bpm.
- *In rural areas with only one person present, chest compression should be performed with the index and middle finger of one hand, while the other hand fixes the face in the right position for doing mouth-to-mouth ventilation (figure 3).

D. DRUG ADMINISTRATION

— Drugs are very seldom used in newborn resuscitation.

— Bradycardia is usually a consequence of hypoxemia, thus an adequate ventilation and oxygenation will solve most of the situations.

— *In rural areas drug administration only seldom for no accessible venous route.

- ADRENALINE
  - Indicated in a-systolic infant or non-responsive bradycardia < 60 bpm.
  - Preferred by intravenous route (IV). Umbilical vein (UV) is preferred. Alternative intra-osseous (IO) route. Tracheal route has not been adequately evaluated.
  - Dose: 0,01-0,03 mg/kg/dose of a 1:10.000 solution; every 3-5 min.
- VOLUME EXPANDERS
  - Indicated in fetal hemorrhage or suspicion of hypovolemic shock.
  - Crystalloid solution such as Normal Saline by UV is preferred. Seldom IO.
  - Dose: 10 mL/kg in 5 to 10 min; it may be repeated after 30 min if perfusion does not improve.
  - Very infrequently blood transfusion will be needed.
- SODIUM BICARBONATE
  - Only exceptionally used for prolonged metabolic acidosis.
  - Mandatory: the baby is undergoing an adequate ventilation.
  - Use 1M bicarbonate diluted 1:1 with distilled water.
  - Dose: 1-2 mEq/kg in 2-3 min IV. UV is preferred (seldom IO).
- NALOXONE
  - Very seldom used and only after adequate ventilation and heart rate normalization.
  - Never use in opiate addicted mothers.
  - Dose: 0.1 mg/kg IV (UV preferred) or IM (intramuscular).
  - Short half-life. Repeat every 2-3 min if respiratory depression persists.

RESUSCITATION IN SPECIAL SITUATIONS

PRESENCE OF MECONIUM STAINED AMNIOTIC FLUID (SAF)

— Risk of aspiration pneumonia at birth or during resuscitation.

— Aspiration of pharynx before delivery is no longer recommended.

— In vigorously crying Nwb just observe.

— In depressed Nwb check trachea for the presence of SAF. If present, insert ETT connected to an intermittent suction catheter device. Aspirate while withdrawing ETT. Valid alternative is intubation with FR12-14 suction catheter.

— Repeat procedure until suction catheter appears clean (keep HR >100 bpm).

PREMATURE INFANT

— 80% of Low birth-weight infants (<1.500 g) or premature (<32 wks) will require resuscitation maneuvers.

— Prone to hypothermia, respiratory depression, lung damage and intraventricular hemorrhage thus requiring expert personnel.

— RECOMMENDED: Transfer the mother to the REFERRAL CENTER with Neonatal Intensive Care.

— If ventilation is needed use with low tidal volume with positive inspiratory pressure (PIP) with pressure limitation valve adjusted at 20 cmH_2O, and positive end expiratory pressure (PEEP) adjusted 3-4 cmH_2O. Both of these protect lung and improve compliance and gas exchange.

— If prolonged ventilation is needed add PEEP valve to the self-inflating bag.

— In spontaneously breathing, continuous positive airway pressure (CPAP) prompts respiratory stabilization and reduces oxygen requirements.

— It is highly recommended the use of Pulse Oxymeter with saturations kept within 85-92% range. If not possible keep oxygen as low as possible (check central color and HR frequently).

— Avoid loss of heat (use radiant heater and polyethylene bag if possible).

ETHICAL ASPECTS

— Show the highest respect for religious and cultural background of the parents. They usually want to have an active participation and therefore information should be clear and understandable.

— In extreme cases (<400 g; <23 wks; severe congenital anomalies e.g.: anencephaly, 13 or 18 trisomy) resuscitation may not be initiated.

— If after 10 min no vital signs are present active resuscitation could be interrupted.

PART II. NEONATAL ASPHYXIA

DEFINITION

Failure to perform an adequate fetal to neonatal transition due to absence of an adequate oxygenation and/or perfusion thus leading to:

— bradycardia, hypotonia, hypo-responsiveness to stimuli, respiratory depression and cyanosis as defined by Apgar score ≤3 at 5 min.

— metabolic acidosis as detected in blood gases performed in umbilical artery (pH <7,0; base excess ≥12 mEq/L).

— multiple organ damage (especially brain, kidney and heart).

— In the absence of neurological manifestations the presence of an asphyctic episode cannot be ascertained.

APGAR SCORE (Apgar V Anesth Analg 1953; 32: 260).

Score	*0*	*1*	*2*
Heart rate	Absent	<100 bpm	>100 bpm
Respiratory effort	Absent	Slow (irregular)	Good crying
Muscle tone	Limp	Some flexion extremities	Active motion
Reflex irritability	No response	Grimace	Cough or sneeze
Color	Blue, pale	Pink body, blue extremities	All pink

CRITERIA FOR ORGAN FAILURE

— Central Nervous System:

- Variability in clinical condition moving from inability for arousal, hypotonia, hyporreflexia and seizures in the first 24-72 hrs to hypertonia, hyperreflexia, and difficulty for feeding thereafter.
- Increased S100 protein and neuronal specific enolase in CSF.
- Low voltage base line, burst-suppression, absence of arousal-sleep, seizures present in amplitude integrated EEG (Cerebral Brain Monitor).
- Ultrasound: diffuse increase in ecogenicity in hemispheres and collapsed ventricles due to brain edema.

— Renal:

- Anuria/oliguria (<1 mL/kg/h) for ≥ 24 hr and/or creatinine >125 mmol/L.

— Cardiovascular

- Hypotension treated with an inotrope >24 hr and/or ECG with transient myocardial ischemia.

— Pulmonary:

- Need for respiratory support with oxygen requirement $>40\%$ for at least 4 hours after birth.

— Hepatic

- Aspartate amino-transferase >100 UI/L or alanine amino-transferase >100 UI/L at any time during the first week of life.

TREATMENT

— Adequate maintenance of vital signs and metabolic status.

— Treat seizures initially with Phenobarbital (no prophylactic use).

— Avoid hyperthermia and hypercapnia.

— Close follow-up.

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CHAPTER 42

Respiratory therapy in the newborn

NEWBORN

W. Carlo

Many neonates are ill during the first days after birth and require some level of respiratory support. Infants may have impairment of oxygenation or of CO_2 elimination or a combination of both. Infants with only minimal impairment of oxygenation respond well to oxygen therapy whereas those with severe oxygenation problems and/or severe hypercapnia will require ventilatory support.

OXYGEN THERAPY

Infants with central cyanosis and/or documented low levels of oxygen saturations require oxygen supplementation. Term infants should have saturations ≥ 95 %. In preterm infants, saturations of 85 to 95 % are usually acceptable.

Oxygen can be delivered in several ways:

1. **Hood.** An oxygen hood is a simple and effective way of delivering a precise amount of oxygen supplementation. Oxygen can be appropriately warmed and humidified as necessary.
2. **Nasal cannula.** Oxygen nasal cannula is an acceptable method for delivery of oxygen although the actual inspired oxygen level varies markedly. In low-resource countries, this is the preferred method of delivery of oxygen because of its simplicity and low cost.
3. **Bag and mask.** A bag and mask can be used to delivery oxygen during emergencies with or without positive pressure.
4. **Continuous positive airway pressure (CPAP).** CPAP can be used to delivery oxygen when a constant pressure is also necessary. CPAP can be provided by nasal prongs but also can be provided by nasopharangeal prongs and by other means.
5. **Mechanical ventilation.** Mechanical ventilation is used to deliver oxygen when ventilation is necessary.

VENTILATORY SUPPORT

The ventilatory needs of a patient depend largely on the mechanical properties of the respiratory system and the type of abnormality in gas exchange.

PULMONARY MECHANICS

The mechanical properties of the lungs are major determinants of the interaction between the ventilator and the infant. A pressure gradient between the airway opening and alveoli drives the flow of gases. The pressure gradient necessary for adequate ventilation is largely determined by the compliance and resistance (see below). Compliance describes the elasticity or distensibility of the lungs or respiratory system (lungs plus the chest wall). It is calculated as follows:

$$\text{Compliance} = \frac{\Delta\text{Volume}}{\Delta\text{Pressure}}$$

Compliance in infants with normal lungs ranges from 3-5 mL/cm H_2O/kg. Compliance in infants with respiratory distress syndrome (RDS) is lower and often ranges from 0,1-1 mL/cm H_2O/kg.

Resistance describes the ability of the gas conducting parts of the lungs or respiratory system (lungs plus chest wall) to resist airflow. It is calculated as follows:

$$\text{Resistance} = \frac{\Delta\text{Pressure}}{\Delta\text{Flow}}$$

Resistance in infants with normal lungs ranges from 25-50 cm H_2O/L/sec. Resistance is not markedly altered in infants with respiratory distress syndrome or other acute pulmonary disorders, but can be increased to 100 cm H_2O/L/sec or more by small endotracheal tubes.

The time constant is a measure of the time (expressed in seconds) necessary for the alveolar pressure (or volume) to reach 63% of a change in airway pressure (or volume) (figure 1).

It is calculated as follows:

$$\text{Time constant} = \text{Compliance} \times \text{Resistance}$$

For example, if an infant has lung compliance of 2 mL/cm H_2O (0,002 L/cm H_2O) and a resistance of 40 cm H_2O/L/sec, time constant is calculated as follows:

$$\text{Time constant} = 0{,}002 \text{ L/cm } H_2O \times 40 \text{ cm } H_2O\text{/L/sec.}$$

$$\text{Time constant} = 0{,}080 \text{ sec.}$$

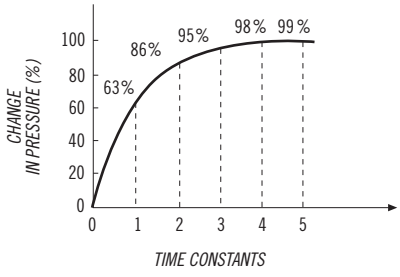


Figure 1. Percentage change in pressure in relation to the time (in time constants) allowed for equilibration. As a longer time is allowed for equilibration, a higher percentage change in pressure will occur. The same rules govern the equilibrium for step changes in volume. Changes in pressure during inspiration and expiration are illustrated. [Modified from Carlo WA, Chatburn RL: Assisted ventilation of the newborn. In Carlo WA, Chatburn RL (Eds.): Neonatal Respiratory Care, 2nd Edition. Chicago, Year Book Medical Publishers, 1988, p. 323, with permission.]

Note that in the calculation of the time constant, compliance is not corrected for unit of weight. A duration of inspiration or expiration equivalent to 3-5 time constants is required for a relatively complete inspiration or expiration, respectively. If inspiratory time is too short (i.e., a duration shorter than approximately 3-5 time constants), there will be a decrease in tidal volume delivery and mean airway pressure (figure 2). If expiratory time is too short (i.e., a duration shorter than approximately 3-5 time constants), there will be gas trapping and inadvertent positive end expiratory pressure (PEEP) (figure 3).

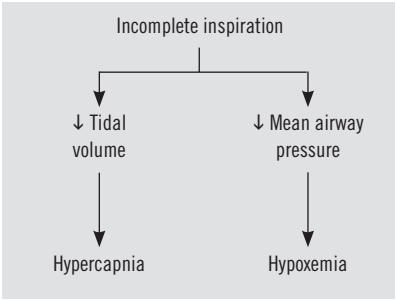


Figure 2. Effect of incomplete inspiration on gas exchange. [From Carlo WA, Greenough A, Chatburn RL: Advances in mechanical ventilation. In Boynton BR, Carlo WA, Jobe AH (eds.): New Therapies for Neonatal Respiratory Failure: A Physiologic Approach. Cambridge, Cambridge University Press, 1994, p. 137, with permission.]

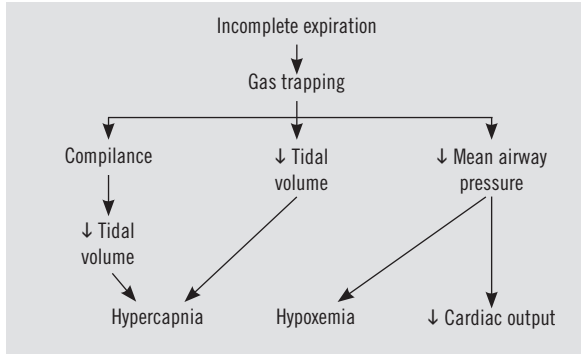


Figure 3. Effect of incomplete expiration on gas exchange. [From Carlo WA, Greenough A, Chatburn RL: Advances in mechanical ventilation. In Boynton BR, Carlo WA, Jobe AH (eds.): New Therapies for Neonatal Respiration Failure: A Physiologic Approach. Cambridge, Cambridge University Press, 1994. p. 137, with permission.]

GAS EXCHANGE

Hypercapnia and/or hypoxemia occur during respiratory failure. Although impairment in CO_2 elimination and oxygen uptake and delivery may coexist, some conditions may affect gas exchange differentially. The pathophysiologic mechanisms responsible for hypoxemia in order of relative importance in neonates are: ventilation-perfusion mismatch, shunt, hypoventilation, and diffusion limitation (figures 4, 5, 6):

- Ventilation-perfusion (V/Q) mismatch is an important cause of hypoxemia in newborns. Supplemental oxygen can largely overcome the hypoxemia resulting from V/Q mismatch.
- Shunt is a common cause of hypoxemia in newborns. A shunt may be physiologic, intracardiac (e.g., PPHN, congenital cyanotic heart disease), or pulmonary (e.g., atelectasis). It can be thought of as a V/Q = 0 and supplemental O_2 cannot reverse the hypoxemia.
- Hypoventilation results from a decrease in tidal volume or respiratory rate. During hypoventilation, the rate of oxygen uptake from the alveoli exceeds its replenishment. Thus, alveolar PO_2 falls and PaO_2 decreases. It can be thought of as low V/Q and supplemental O_2 can overcome the hypoxemia easily. Causes of hypoventilation include: depression of respiratory drive, weakness of the respiratory muscles, restrictive lung disease, and airway obstruction.
- Diffusion limitation is an uncommon cause of hypoxemia, even in the presence of lung disease. Diffusion limitation occurs when mixed venous blood does not equilibrate with alveolar gas. Supplemental O_2 can overcome hypoxemia secondary to diffusion limitation.

Oxygenation may be largely dependent on lung volume, which in turn depends on mean airway pressure (Figure 7). On a pressure ventilator any of the following will increase

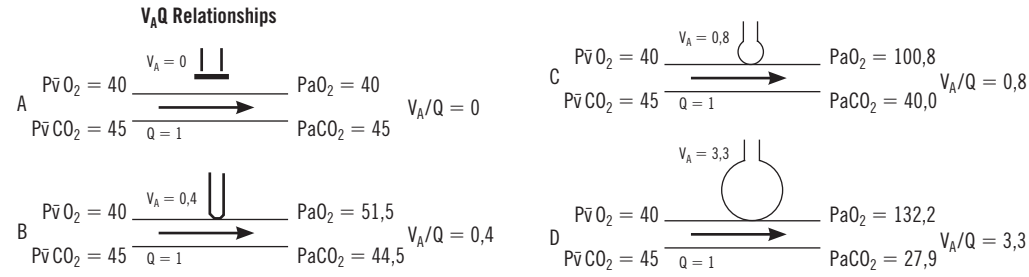


Figure 4. Effects of various ventilation/perfusion ratios on blood gas tensions. A. Direct venoarterial shunting ($V_A/Q = 0$). B. Alveolus with a low V_A/Q ratio. C. Normal alveolus. D. Underperfused alveolus with V_A/Q ratio. [From Krauss AN: Ventilation-perfusion relationships in neonates. In Thibeault DW, Gregory GA (eds.): Neonatal Pulmonary Care, 2nd Edition. Norwalk, CT, Appleton-Century-Crofts, 1986, p. 127, with permission.]

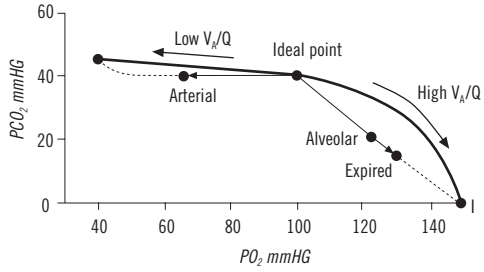


Figure 5. C_2-CO_2 diagram showing the arterial, ideal, alveolar, and expired points. The curved line indicates the PO_2 and PCO_2 of all lung units having different ventilation/perfusion ratios. [From West JB: Gas exchange. In West JB (ed.): Pulmonary Pathophysiology: The Essentials. Baltimore, Williams & Wilkins, 1977, p. 27, with permission.]

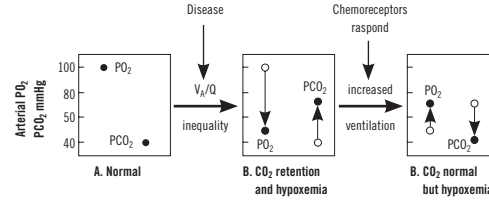


Figure 6. PO_2 and PCO_2 in different stages of ventilation/perfusion inequality. Initially, there must be both a fall in oxygen and a rise in carbon dioxide tensions. However, when the ventilation to the alveoli is increased, the PCO_2 returns to normal, but the PO_2 remains abnormally low. [From West JB: Gas exchange. In West JB (ed.): Pulmonary Pathophysiology: The Essentials. Baltimore, Williams & Wilkins, 1977, p. 30, with permission.]

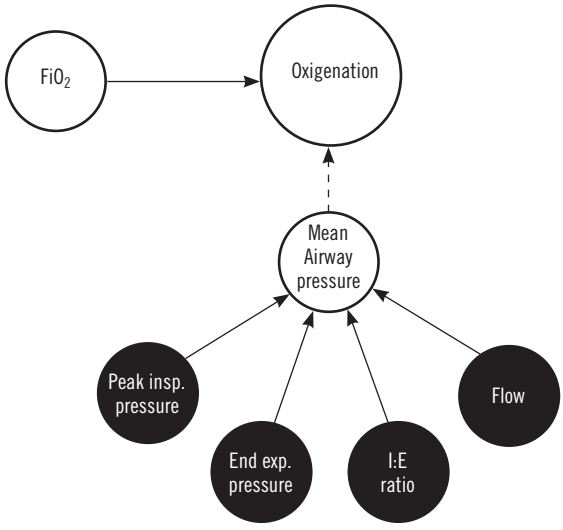


Figure 7. Determinants of oxygenation during pressure-limited, time-cycled ventilation. Shaded circles represent ventilator-controlled variables. Solid lines represent the simple mathematical relationships that determine mean airway pressure and oxygenation, whereas dashed lines represent relationships that cannot be quantified. [From Carlo WA, Greenough A, Chatburn RL: Advances in mechanical ventilation. In Boynton BR, Carlo WA, Jobe AH (eds.): New Therapies for Neonatal Respiration Failure: A Physiologic Approach. Cambridge, Cambridge University Press, 1994, p. 134, with permission.]

mean airway pressure: increasing inspiratory flow, increasing peak inspiratory pressure (PIP), increasing the inspiratory to expiratory (I:E) ration or increasing positive end expiratory pressure (PEEP).

Mean airway pressure maybe calculated as follows:

$$\text{Mean airway pressure} = K(PIP\text{-}PEEP)\,[T_I/(T_I + T_E)] + PEEP$$

where K is a constant that depends on the shape of the early inspiratory part of the airway pressure curve; (K ranges from approximately 0.8 to 0.9 during pressure-limited ventilation): T_I is inspiratory time; T_E is expiratory time. For the same change in mean airway pressure, increases in PIP and PEEP increase oxygenation more. A very high mean airway pressure transmitted to the intrathoracic structures may impair cardiac output and thus decrease oxygen transport despite an adequate PaO_2.

The pathophysiologic mechanisms responsible for hypercapnia are V/Q mismatch, shunt, hypoventilation, and increased physiologic dead space. The physiologic dead space results in part from areas of inefficient gas exchange because of low perfusion (wasted ventilation). Physiologic dead space includes ventilation to conducting airways and alveolar spaces not perfused (i.e., anatomical dead space).

CO_2 diffuses easily into the alveoli and its elimination depends largely on the total amount of gas that comes in contact with the alveoli (alveolar ventilation). Minute alveolar ventilation is calculated from the product of the frequency (per minute) and the alveolar tidal volume (tidal volume minus dead space).

$$\text{Minute alveolar ventilation} = \text{frequency} \times (\text{tidal volume minus dead space})$$

On a volume-cycled ventilator the tidal volume is preset. On a pressure-controlled ventilator, the tidal volume depends on the pressure gradient between the airway opening and the alveoli; this is peak inspiratory pressure (PIP) minus the positive end expiratory pressure (PEEP), or amplitude (ΔP). Depending on the time constant of the respiratory system (and the ventilator) a very short inspiratory time (T_I) may reduce the tidal volume, and a very short expiratory time (T_E) may cause gas trapping and inadvertent PEEP, and consequently may also reduce tidal volume (see above). Figure 8 illustrates the relationships among ventilator controls, pulmonary mechanics, and minute ventilation. Ventilator controls are shown in shaded circles.

VENTILATOR PARAMETERS AND THEIR EFFECTS ON GAS EXCHANGE

PEAK INSPIRATORY PRESSURE (PIP)

PIP in part determines the pressure gradient between the onset and end of inspiration, and thus, affects the tidal volume and minute ventilation. During volume ventilation an increase in tidal volume corresponds to an increase in PIP during pressure ventilation. If tidal volume is not measured, initial PIP can be selected based on observation of the chest wall movement and magnitude of the breath sounds.

An increase in PIP will increase tidal volume, increase CO_2 elimination, and decrease $PaCO_2$. An increase in PIP will increase mean airway pressure, and thus improve oxygenation.

An elevated PIP may increase the risk of barotrauma, volutrauma, and bronchopulmonary dysplasia/chronic lung disease. There is increasing evidence that lung injury is primarily caused by large tidal volume delivery and lung overdistention. Thus, it is important to

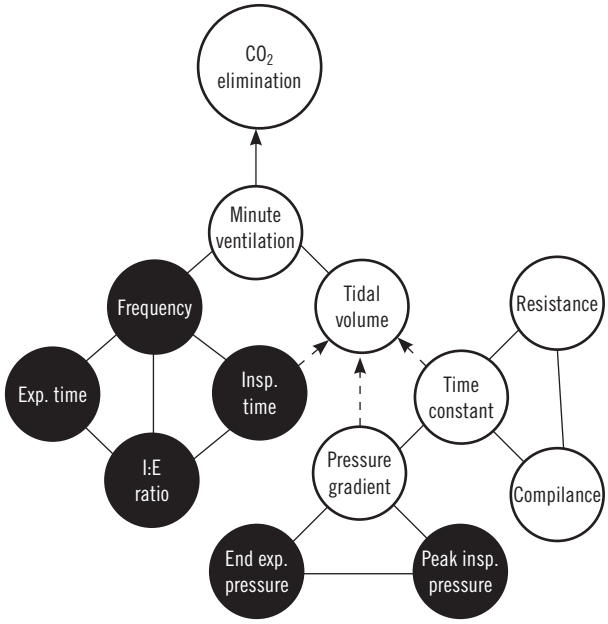


Figure 8. Relationships among ventilator-controlled variables (shaded circles) and pulmonary mechanics (unshaded circles) that determine minute ventilation during time-cycled, pressure-limited ventilation. Relationships between circles joined by solid lines are mathematically derived. The dashed lines represent relationships which cannot be precisely calculated without considering other variables such as pulmonary mechanics. Alveolar ventilation can be calculated from the product of tidal volume and frequency when dead space is subtracted from the former. [From Carlo WA, Greenough A, Chatburn RL: Advances in mechanical ventilation. In Boynton BR, Carlo WA, Jobe AH (eds.): New Therapies for Neonatal Respiration Failure: A Physiologic Approach. Cambridge, Cambridge University Press, 1994. p.133, with permission.]

adjust PIP based on lung compliance, and ventilate with relatively small tidal volumes. (e.g., 3-5 mL/kg).

POSITIVE END EXPIRATORY PRESSURE (PEEP)

PEEP in part determines lung volume during the expiratory phase, improves ventilation/perfusion mismatch, and prevents alveolar collapse. PEEP contributes to the pressure gradient between the onset and end of inspiration, and thus, affects the tidal volume and minute ventilation. A minimum "physiological" PEEP of 2-3 cm H_2O should be used in most newborns.

An increase in PEEP increases expiratory lung volume (functional residual capacity) during the expiratory phase, and thus, improves ventilation/perfusion matching and oxygenation in patients whose disease state reduces expiratory lung volume. An increase in PEEP will increase mean airway pressure, and thus, improve oxygenation in patients with this type of disease. An increase in PEEP will also reduce the pressure gradient during inspiration, and thus, reduce tidal volume, reduce CO_2 elimination, and increase $PaCO_2$.

An elevated PEEP may over distend the lungs and lead to decreased lung compliance, decreased tidal volume, less CO_2 elimination, and an increase in $PaCO_2$. While use of low-to-moderate PEEP may improve lung volume, a very high PEEP may cause over distention and impaired CO_2 elimination secondary to decreased compliance and gas trapping. Furthermore, a very high PEEP may decrease cardiac output and oxygen transport.

FREQUENCY

The ventilator frequency (or rate) in part determines minute ventilation, and thus, CO_2 elimination. Ventilation at high rates (≥ 60/min) frequently facilitates synchronization of the ventilator with spontaneous breaths. Spontaneous breathing rates are inversely related to gestational age and the time constant of the respiratory system. Thus, infants with smaller and less compliant lungs tend to breathe faster.

When very high frequencies are used, the problem of insufficient inspiratory time or insufficient expiratory time may occur (see below).

Use of very high ventilator frequencies may lead to insufficient inspiratory time and decreased tidal volume or insufficient expiratory time and gas trapping.

Inspiratory Time (T_I) Expiratory Time (T_E) and Inspiratory to Expiratory Ratio (I:E Ratio).

The effects of the T_I and T_E are strongly influenced by the relationship of those times to the inspiratory and expiratory time constants. A T_I as long as 3-5 times constants allows relatively complete inspiration. T_I of 0,2-0,5 sec are usually adequate for newborns with respiratory distress syndrome. Use of a longer T_I generally does not improve ventilation or gas exchange. A very prolonged T_I may lead to ventilator asynchrony. A very short T_I will lead to decreased tidal volume. However, infants with a long time constant (e.g., chronic lung disease) may benefit from a longer T_I (up to approximately 0.6-0.8 sec).

Changes in T_I, T_E, and I:E ratio generally have modest effects on gas exchange. A sufficient T_I is necessary for adequate tidal volume delivery and CO_2 elimination. Use of relatively long T_I or high I:E ratio improves oxygenation slightly.

Very short T_I or T_E can lead to insufficient times and decrease tidal volume and increase gas trapping, respectively.

INSPIRED OXYGEN CONCENTRATION (FIO_2)

Changes in FiO_2 alter alveolar oxygen pressure, and thus, oxygenation. Because both FiO_2 and mean airway pressure determine oxygenation, the most effective and less adverse approach should be used to optimize oxygenation. When FiO_2 is above 0.6-0.7, increases in mean airway pressure are generally warranted. When FiO_2 is below 0.3-0.4, decreases in mean airway pressure are generally preferred. FiO_2 directly determines alveolar PO_2 and thus PaO_2. A very high FiO_2 can damage the lung tissue, but the absolute level of FiO_2 that is toxic has not been determined.

Flow

Changes in flow rate have not been well studied in infants, but they probably impact arterial blood gases minimally as long as a sufficient flow is used (which is generally the case with most ventilators).

In summary, depending on the desired change in blood gases, the following ventilator parameter changes can be performed (table 1).

Table 1. Desired Blood Gas Goal and Corresponding Ventilator Parameter Changes.

Desired Goal	*PIP*	*PEEP*	*Frequency*	*I:E Ratio*	*Flow*
To decrease $PaCO_2$	↑	↓	↑	—	±↑
To increase $PaCO_2$	↓	↑	↓	—	±↓
To decrease PaO_2	↓	↓	—	↓	±↓
To increase PaO_2	↑	↑	—	↑	±↑

Neonatal jaundice

CHAPTER 43

M. J. Maisels

NEWBORN

About 2 of every 3 term and near term newborns will appear jaundiced at some time during the first week of life and virtually every premature baby will develop some degree of hyperbilirubinemia. Almost all of these infants remain healthy but, in rare cases, the serum bilirubin rises to a level that can be toxic to the central nervous system[1, 2].

KERNICTERUS

Kernicterus is the result of bilirubin toxicity to the basal ganglia and various brain stem nuclei and results in a choreoathetoid type of cerebral palsy, hearing loss, gaze palsy and dental dysplasia. Although a rare event, kernicterus is one cause of cerebral palsy that should be largely preventable through a relatively straightforward process of identification, monitoring, follow-up and treatment of the jaundiced newborn. We are obliged to monitor and treat many jaundiced infants —most of whom will be perfectly normal— to prevent substantial harm to a few. The clinical features of acute bilirubin encephalopathy are shown in table 1 and those of classical kernicterus or chronic bilirubin encephalopathy in table 2.

Table 1. Major Clinical Features of Acute Bilirubin Encephalopathy.

Initial Phase	*Intermediate Phase*	*Advanced Phase*
• Slight stupor («lethargic», «sleepy»). • Slight hypotonia, paucity of movement. • Poor sucking; slightly high-pitched cry.	• Moderate stupor-irritable. • Tone variable-usually increased; some with retrocollis-opisthotonos. • Minimal feeding; high-pitched cry.	• Deep stupor to coma. • Tone usually increased; some with retrocollis-opisthotonos. • No feeding; shrill cry.

From Volpe JJ. Neurology of the newborn. 4th ed. Philadelphia: WB Saunders, 2001, with permission.

Table 2. Major Clinical Features of Chronic Postkernicteric Bilirubin Encephalopathy.

- Extrapyramidal abnormalities, especially athetosis.
- Gaze abnormalities, especially of upward gaze.
- Auditory disturbance, especially sensorineural hearing loss.
- Intellectual deficits, but minority in mentally retarded range.

From Volpe JJ. Neurology of the newborn. 4th ed. Philadelphia: WB Saunders, 2001, with permission.

NORMAL SERUM BILIRUBIN LEVELS AND THE NATURAL HISTORY OF NEONATAL JAUNDICE

Hyperbilirubinemia occurs when the liver cannot clear enough bilirubin from the plasma and the mechanisms responsible for this are shown in table 3[1]. Figure 1 illustrates the natural history of neonatal jaundice. These data are smoothed curves from diverse populations and the values will differ in different parts of the world. Nevertheless, the curves illustrate the fact that the total serum bilirubin (TSB) generally peaks at 3-5 days of age. This means that infants should be seen between the 3rd and the 5th day if significant hyperbilirubinemia is to be identified. The curves in figure 1 and figure 2, also illustrate that, because the TSB is constantly changing in the hours to days after birth, it is important to *interpret all TSB levels in terms of the infant's age in hours and not days*[3]. When plotted on the nomogram in figure 2, the TSB levels provide guidance for when a TSB level should be investigated and for the risk of an infant developing, or not developing, significant hyperbilirubinemia. A protocol for monitoring infants for jaundice in the newborn nursery is provided in table 4 and the laboratory tests that should be performed are listed in table 5[2]. The causes of indirect hyperbilirubinemia are listed in table 6[1].

Table 3. Physiologic Mechanisms of Neonatal Jaundice[1].

Increased bilirubin load on liver cell: • Increased erythrocyte volume. • Decreased erythrocyte survival. • Increased early-labeled bilirubin. • Increased enterohepatic circulation of bilirubin. **Decreased hepatic uptake of bilirubin from plasma:** • Decreased ligandin.	**Decreased bilirubin conjugation:** • Decreased uridine diphosphoglucuronosyl transferase activity. **Defective bilirubin excretion:** • Excretion impaired but not rate limiting.

Table 4. A jaundice protocol for the nursery.

- Assess infants for jaundice at least every 8 to 12 hours.
- Measure TcB and/or TSB in any infant who is jaundiced in the first 24 hours after birth*.
- Measure TcB and/or TSB if jaundice appears excessive for the infant's age.
- Measure TSB or TcB if there is any doubt about the degree of jaundice.
- Remember: Visual estimation of the bilirubin level from the degree of jaundice can lead to errors, particularly in darkly pigmented infants.
- Interpret all TSB and TcB levels according to the infant's age in hours.

TcB: Transcutaneous Bilirubin.

From Maisels MJ. Jaundice in a newborn. Answers to questions about a common clinical problem. Contemp Pediatr 2005;22:34-40. (with permission).

Table 5. Laboratory tests for the jaundiced infant.

When there is a finding of...	*Then obtain...*
Jaundice in first 24 hours.	Total serum bilirubin (TSB).
Jaundice that appears excessive for the infant's age.	TSB.
An infant receiving phototherapy or having a TSB that is above the 75th percentile or rising rapidly (i.e., crossing percentiles) and unexplained by history or findings on physical examination.	• Blood type; also, perform a Coombs test, if not obtained with cord blood. • Complete blood count, smear, and reticulocyte count. • Direct (or conjugated) bilirubin. • (Repeat TSB in 4 to 24 hours depending on infant's age and TSB level). • Consider the possibility of G6PD deficiency.
A TSB approaching exchange level or not responding to phototherapy.	Reticulocyte count, G6PD test, albumin.
An elevated direct (or conjugated) bilirubin level.	Urinalysis and urine culture; evaluate for sepsis if indicated by history and physical examination.
Jaundice present at or beyond age 3 weeks, or the infant is sick.	• Total and direct bilirubin level; if direct bilirubin is elevated, evaluate for causes of cholestasis. • (Also check results of newborn thyroid and galactosemia screen, and evaluate infant for signs or symptoms of hypothyroidism).

From Maisels MJ. Jaundice in a newborn. Answers to questions about a common clinical problem. Contemp Pediatr 2005; 22: 34-40. (with permission).

Table 6. Causes of a indirect hyperbilirubinemia in newborn infants[1].

Increased production or bilirubin load on the liver	**Hemolytic Disease** • Immune mediated. – Rh alloimmunization, ABO and other blood group incompatibilities. • Heritable. – *Red cell membrane defects.* Hereditary spherocytosis, elliptocytosis, pyropoikilocytosis, stomatocytosis. – *Red cell enzyme deficiencies.* Glucose-6-phosphate dehydrogenase deficiencya pyruvate kinase deficiency, and other erythrocyte enzyme deficiencies. – *Hemoglobinopathies.* Alpha thalassemia, beta-thalassemia. – *Unstable hemoglobins.* Congenital Heinz body hemolytic anemia.	**Other causes of increased production** • Sepsis[a, b]. • Disseminated intravascular coagulation. • Extravasation of blood-hematomas, pulmonary, abdominal, cerebral, or other occult hemorrhage. • Polycythemia. • Macrosomic infants of diabetic mothers. **Increased enterohepatic circulation of bilirubin** • Breast-milk jaundice. • Pyloric stenosis[a]. • Small or large bowel obstruction or ileus.
Decreased Clearance	• Prematurity. • Glucose-6-phosphate dehydrogenase deficiency. **Inborn errors of metabolism** • Crigler-Najjar syndrome, types I and II. • Gilbert's syndrome. • Galactosemia[b]. • Tyrosinemia[b]. • Hypermethioninemia[b].	**Metabolic** • Hypothyroidism. • Hypopituitarism[b].

a Decreased clearance also part of pathogenesis.
b Elevation of direct-reading bilirubin also occurs.

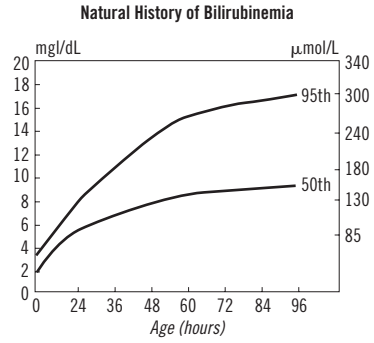


Figure 1. Smoothed curves from studies in different populations illustrating the expected velocity of total serum bilirubin (TSB) levels and approximate values for the 50th and 95th percentiles. Note that values must be plotted according to the infant's age in hours and not days[1].

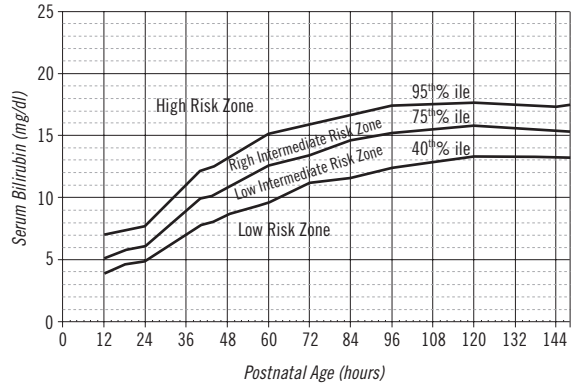


Figure 2. Nomogram for designation of risk in 2.840 well newborns. The serum bilirubin level was obtained before discharge and the zone in which the value fell predicted the likelihood of a subsequent bilirubin level exceeding the 95th percentile[3].

VISUAL IDENTIFICATION OF JAUNDICE

Jaundice is detected by blanching the skin with digital pressure, thus revealing the color of the skin underlying and subcutaneous tissue. This should be done in a well-lit room or, ideally, in daylight by a window. The ability to estimate a bilirubin level from the degree of jaundice, however, varies widely and can lead to errors[2]. Recently, handheld electronic devices have been developed that provide a noninvasive means of measuring the bilirubin in the skin and subcutaneous tissues[4]. Transcutaneous bilirubin (TcB) measurement is not a substitute for TSB, but a TcB measurement can be very helpful as a screening tool.

The American Academy of Pediatrics guidelines[2] for the management of hyperbilirubinemia in the newborn infant 35 or more weeks of gestation, emphasize certain key elements for the identification and management of jaundiced newborns and these are shown in table 7. Some factors increase, or decrease, the risk of severe hyperbilirubinemia[2] and these are shown in table 8. Combining these risk factors, prior to discharge, with a serum or transcutaneous bilirubin measurement can improve the ability to predict which infants might or might not develop significant hyperbilirubinemia[2].

TREATMENT

Hyperbilirubinemia can be treated in three ways[1].

a) Exchange transfusion removes bilirubin mechanically.

b) Phototherapy converts bilirubin to products that can bypass the liver's conjugating system and be excreted in the bile or in the urine without further metabolism.

c) Pharmacologic agents that interfere with heme degradation and bilirubin production, accelerate the normal metabolic pathways for bilirubin clearance or inhibit the enterohepatic circulation of bilirubin.

Table 7. The Ten Commandments for preventing and managing hyperbilirubinemia*.

1. Promote and support successful breastfeeding.
2. Establish nursery protocols for the jaundiced newborn.
3. Measure the TSB or TcB level on infants jaundiced in the first 24 hours.
4. Recognize that visual diagnosis of jaundice is unreliable, particularly in darkly pigmented infants.
5. Interpret all TSB levels according to the infant's age in hours, not days.
6. Don't treat a near-term (35-38 week) infant as you would a term infant —a near-term infant is at much higher risk of hyperbilirubinemia.
7. Perform a predischarge, systematic assessment on all infants for the risk of severe hyperbilirubinemia.
8. Provide parents with information about newborn jaundice.
9. Provide follow-up based on the time of discharge and the risk assessment.
10. When indicated, treat the newborn with phototherapy or exchange transfusion.

* Adapted from the American Academy of Pediatrics guidelines on hyperbilirubinemia.

From Maisels, MJ. Jaundice in a newborn. How to head off an urgent situation. Contemp Pediatr 2005; 22: 41-54 with permission.

Table 8. Risk factors* for development of severe hyperbilirubinemia in infants >35 weeks gestation (in approximate order of importance)[2].

Major risk factors	• Predischarge TSB or TcB level in the high risk zone (fig. 2). • Jaundice observed in the first 24 hours. • Blood group incompatibility with positive direct antiglobulin test, other known hemolytic disease (e.g. G-6PD deficiency), elevated ETCOc. • Gestational age 35-36 weeks. • Previous sibling received phototherapy. • Cephalhematoma or significant bruising. • Exclusive breastfeeding particularly if nursing is not going well and weight loss is excessive. • East Asian race*.
Minor risk factors	• Predischarge TSB or TcB in the high-intermediate risk zone (fig. 2). • Gestational age 37-38 weeks. • Jaundice observed before discharge. • Previous sibling with jaundice. • Macrosomic infant of a diabetic mother. • Maternal age ≥ 25 years. • Male gender.
Decreased risk (these factors are associated with decreased risk of significant jaundice, listed in order of decreasing importance).	• TSB or TcB in the low risk zone (fig. 2). • Gestational age ≥ 41 weeks. • Exclusive bottle feeding. • Black race †. • Discharge from hospital after 72 hours.

* Note that these are the factors that increase the risk of developing hyperbilirubinemia. They are different from the risk levels used in figures 4 and 5 which relate to the risk of brain damage.

† Race as defined by mother's description.

PHOTOTHERAPY

Phototherapy works by infusing discrete photons of energy, similar to the molecules of a drug[5]. These photons are absorbed by bilirubin molecules in the skin and subcutaneous tissue just as drug molecules bind to a receptor. The bilirubin then undergoes photochemical reactions to form excretable isomers and breakdown products that can bypass the liver's conjugating system and be excreted without further metabolism. Some photoproducts are also excreted in the urine. Figure 3 depicts the mechanism of action of phototherapy.

Definitions used in phototherapy and factors affecting the dosage and the efficacy of phototherapy are listed in tables 9, 10 and 11[2, 6].

Guidelines for the use of phototherapy and exchange transfusion in term and near term infants are provided in figures 4 and 5[2] and for low birth weight infants in tables 12 and 13[1].

Table 9. Radiometric quantities used[5].

Quantity	*Dimensions*	*Usual units of measure*
Irradiance (radiant power incident on a surface per unit area of the surface).	W/m^2	W/cm^2
Spectral irradiance (irradiance in a certain wavelength band).	W/m^2 per nm (or W/m^2)	$\mu W/cm^2$ per nm

Table 10. Controlling the dosage of phototherapy.

Factor	*Technical terminology*	*Rationale*	*Clinical application*
Type of light source.	Spectrum of light (nanometers).	Blue-green spectrum is most effective at lowering total serum bilirubin (TSB); light at this wavelength penetrates skin well and is absorbed strongly by bilirubin.	Use special blue fluorescent tubes or light-emitting diodes (LED) or another light source with output in blue-green spectrum for intensive phototherapy (PT).
Distance of light source from patient.	Spectral irradiance (a function of both distance and light source) delivered to surface of infant.	↑ irradiance leads to ↑ rate of decline in TSB. Standard PT units deliver 8-10 $\mu W/cm^2/nm$; intensive PT delivers ≥ 30 $\mu W/cm^2/nm$.	If special blue fluorescent tubes are used, bring tubes as close as possible to infant to increase irradiance. (Do NOT do this with halogen lamps because of danger of burn.) Positioning special blue tubes 10-15 cm above infant will produce an irradiance of at least 35 $\mu W/cm^2/nm$.
Surface area exposed.	Spectral power (a function of spectral irradiance and surface area).	↑ surface area exposed leads to ↑ rate of decline in TSB.	For intensive PT, expose maximum surface area of infant to PT. Place lights above and fiberoptic pad or special blue fluorescent tubes* below infant. For maximum exposure, line sides of bassinet, warmer bed, or incubator with aluminum foil or white reflecting material.

* Available in the Bili-Bassinet (Olympic Medical).

From Maisels MJ. A primer on phototherapy for the jaundiced newborn. Contemp Pediatr 2005;22:38-57.

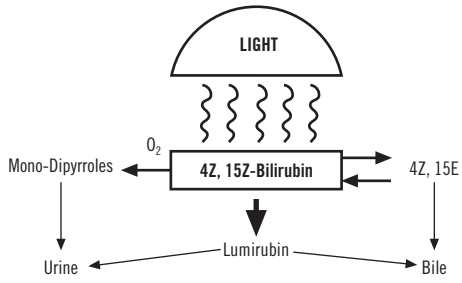
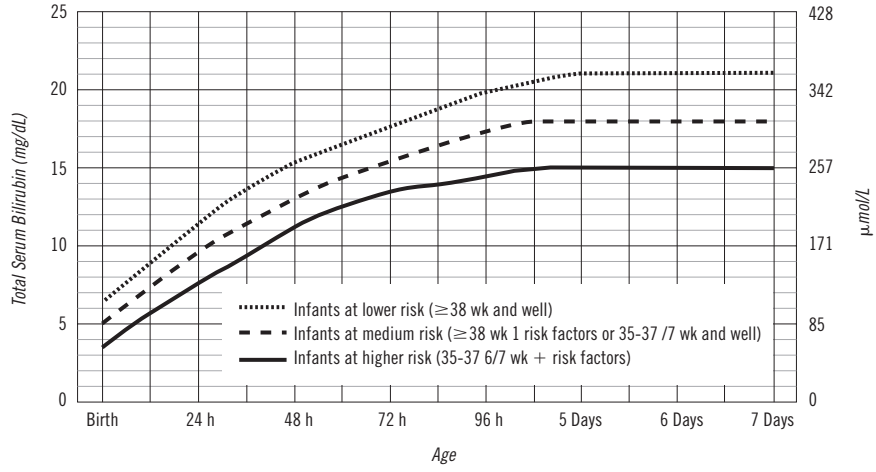


Figure 3. Mechanisms of action of phototherapy.

Figure 4. AAP guidelines for phototherapy in hospitalized infants of 35 or more weeks' gestation[2].



- Use total bilirubin. Do not subtract direct reacting or conjugated bilirubin.
- Risk factors = isoimmune hemolytic disease, G6PD deficiency, asphyxia, significant lethargy, temperature instability, sepsis, acidosis, or albumin <3,0 g/dL (if mesuared).
- For well infants 35-37 6/7 wk can adjust TSB levels for intervention around the medium risk line. It is an option to intervene at lower TSB levers for infants closer to 35 wks and at higher TSB levels for those closer to 37 6/7 wk.
- It is an option to provide conventional phototherapy in hospital or at home at TSB levels 2-3 mg/dL (35-50 mmol/L) below those shown but home phototherapy should not be used in any infant with risk factors.

Note: These guidelines are based on limited evidence and the levels shown are approximations. The guidelines refer to the use of intensive phototherapy which should be used when the TSB exceeds the line indicated for each category. Designation of «risk» refers to the increased risk of brain damage because of the potential negative effects of the conditions listed on albumin binding of bilirubin, the blood-brain barrier, and the susceptibility of the brain cells to damage by bilirubin.

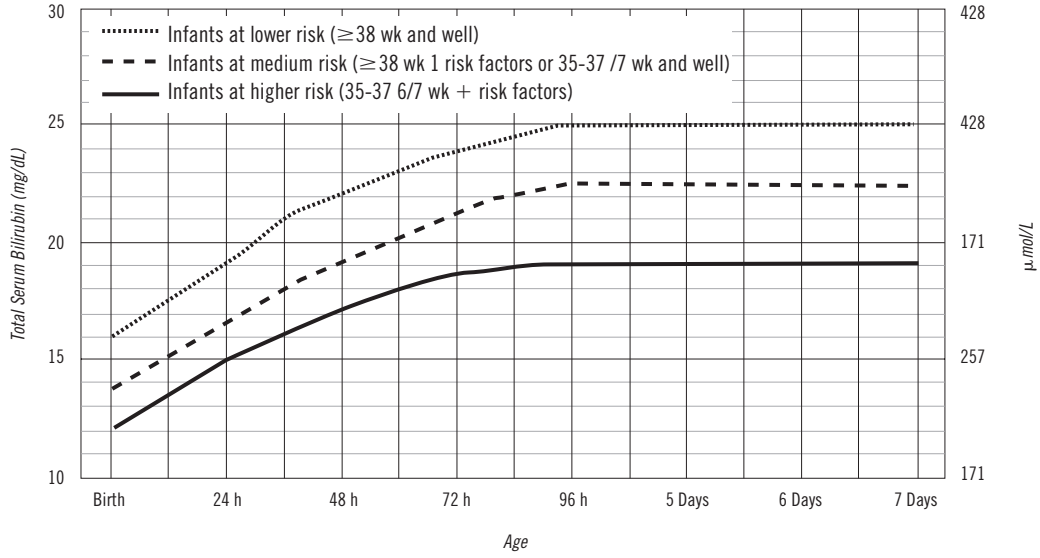
«Intensive phototherapy» implies irradiance in the blue-green spectrum (wavelengths of approximately 430-490 nm) of at least 30 $\mu W/cm^2$ per nm (measured at the infant's skin directly below the center of the phototherapy unit) and delivered to as much of the infant's surface area as possible. Note that irradiance measured below the center of the light source is much greater than that measured at the periphery. Measurements should be made with a radiometer specified by the manufacturer of the phototherapy system.

If total serum bilirubin levels approach or exceed the exchange transfusion line (figure 5) the sides of the bassinet, incubator, or warmer should be lined with aluminum foil or white material. This will increase the surface area of the infant exposed and increase the efficacy of phototherapy.

If the total serum bilirubin does not decrease or continues to rise in an infant who is receiving intensive phototherapy, this strongly suggests the presence of hemolysis.

Infants who receive phototherapy and have an elevated direct-reacting or conjugated bilirubin level (cholestatic jaundice) may develop the bronze-baby syndrome.

Figure 5. AAP guidelines for exchange transfusion in infants 35 or more weeks' gestation[2].



- The dashed lines for the first 24 hours indicate uncertainty due to a wide range of clinical circumstances and a range of responses to phtotherapy.
- Immediate exchange transfusion is recommended if infant shows signs of acute bilirubin encephalopathy (hypertonia, arching, retrocollis, opisthotonos, fever, high pitched cry) or if TSB is ≥5mg/dL (85 μmol/L) above these lines.
- Risk factors - isoimmune hemolytic disease, G6PD deficiency, asphyxia, significant lethargy, temperature instability, sepsis, acidosis.
- Mesure serum albumin and calculate B/A ratio (see legend).
- Use total bilirubin. Do not subtract direct reacting or conjugated bilirubin.
- If infant is well and 35-37 6/7 wk (median risk) can individualize TSB levels for exchange based on actual gestational age.

Note: these guidelines are based on limited evidence and the levels shown are approximatiions. During birth hospitalization exchange transfusions is recommended if TSB rises to these levels despite intensive phototheraphy. For readmitted infants, if TSB is above levels indicated after intensive phototherapy for 6 hours.

Designation of «risk» refers to the increased risk of brain damage because of the potential negative effects of the conditions listed on albumin binding of bilirubin, the blood-brain barrier, and the susceptibility of the brain cells to damage by bilirubin.

The following bilirubin-to-albumin (B:A) ratios can be used together with, but in not in lieu of the TSB level, as an additional factor in determining the need for exchange transfusion.

Risk Category	*B:A Ratio at Which Exchange Transfusion Should be Considered*	
	TSB mg/dL/Alb,/dL	*TSB μmol/L/Alb, μmol/L*
Infants ≥ 38 0/7 wk.	8,0	0,94
Infants 35 07-36 6/7 wk and well or ≥ 38 0/7 wk if higher risk or isoimmune hemolytic disease or G6PD deficiency.	7,2	0,84
Infants 35 0/7 to 37 6/7 wk if higher risk or isoimmune hemolytic disease or G6PD deficiency.	6,8	0,80
If the TSB is at or approaching the exchange level, send blood for immediate type and crossmatch. Blood for exchange transfusion is modified whole blood (red cells and plasma) crossmatched against the mother and compatible with the infant.		

Table 11. Factors that influence the efficacy of phototherapy.

Factor	*Explanation*	*Clinical action*
Dosage.	See Table 12.	See Table 12.
Cause of jaundice.	Phototherapy (PT) is likely to be less effective if jaundice is caused by hemolysis or if cholestasis is present (direct bilirubin is increased).	When hemolysis is present, start PT at a lower TSB level and use intensive PT. Failure of PT suggests hemolysis is cause of the jaundice. When direct bilirubin is elevated, watch for bronze baby syndrome or blistering.
TSB level at start of PT.	The higher the TSB, the more rapid the decline in TSB with PT.	Use intensive PT for higher TSB levels. Anticipate a more rapid decrease in TSB when TSB $>$ 20 mg/dL. (340 μmol/L).

From Maisels MJ. A primer on phototherapy for the jaundiced newborn. Contemp Pediatr 2005; 22: 38-57.

Table 12. Guidelines for the use of phototherapy and exchange transfusion in low birth-weight infants based on birth weight[1].

Total bilirubin level (mg/dl [μmol/l][a])		
Birth weights (g)	*Phototherapy[b]*	*Exchange Transfusion[c]*
$\leq$ 1.500	5-8 (85-140)	13-16 (220-275)
1.500-1.999	8-12 (140-200)	16-18 (275-300)
2.000-2.499	11-14 (190-240)	18-20 (300-340)

Note that these guidelines reflect ranges used in neonatal intensive care units. They cannot take into account all possible situations. Lower bilirubin concentrations should be used for infants who are sick (e.g., sepsis, acidosis, hypoalbuminemia) or have hemolytic disease.

a Consider initiating therapy at these levels. Range allows discretion based on clinical conditions or other circumstances. Note that bilirubin levels refer to total serum bilirubin concentrations. Direct-reacting or conjugated bilirubin levels should not be subtracted from the total.

b Used at these levels and in therapeutic doses, phototherapy should, with few exceptions, eliminate the need for exchange transfusions.

c Levels for exchange transfusion assume that bilirubin continues to rise or remains at these levels despite intensive phototherapy.

Table 13. Guidelines for use of phototherapy and exchange transfusion in preterm infants based on gestational age.

Total bilirubin level (mg/dl [μmol/l])			
Gestational Age (weeks)	*Phototherapy*	*Exchange Transfusion*	
		*Sick**	*Well*
36	14,6 (250)	17,5 (300)	20,5 (350)
32	8,8 (150)	14,6 (250)	17,5 (300)
28	5,8 (100)	11,7 (200)	14,6 (250)
24	4,7 (80)	8,8 (150)	11,7 (200)

* Rhesus disease, perinatal asphyxia, hypoxia, acidosis, hypercapnia.

From Ives NK. Neonatal jaundice. In: Rennie JM, Roberton NRC, eds. Textbook of neonatology, New York: Churchill Livingston, 1999:715-732, with permission.

EXCHANGE TRANSFUSION

The introduction of Rh immune globulin for the prevention of erythroblastosis fetalis and the use of phototherapy have dramatically reduced the need for exchange transfusions. Phototherapy, if used appropriately, can control bilirubin levels in virtually all preterm and term infants with the exception of those with severe hemolytic disease or marked bruis-

ing. Nevertheless, exchange transfusion remains an important mechanism for preventing hyperbilirubinemia[7], particularly in immune-mediated hemolytic disease where exchange transfusion 1) lowers the bilirubin level rapidly, 2) removes the antibody-coated red blood cells and 3) corrects anemia (if present). Exchange transfusions are usually performed via the umbilical vein using a catheter inserted just far enough to obtain free flow of blood. Fresh citrate-phosphate-dextrose blood (<72 hours old and devoid of the offending antigen in the case of immune-mediated hemolytic disease) cross-matched to the infant should be used. If possible, blood for exchange transfusion should be irradiated to avoid the rare possibility of graft-versus-host disease. The blood should be warmed to body temperature and the exchange is performed slowly in aliquots of 5-10 ml/kg body weight with each withdrawal-infusion cycle approximating 3 minutes duration[7]. Some of the potential complications of exchange transfusion are listed in table 14. Sick, preterm infants are much more likely than term infants to experience a serious complication of exchange transfusion[7].

Table 14. Potential complications of exchange transfusion.

Cardiovascular	Arrhythmias. Cardiac arrest. Volume overload.	Embolization with air or clots. Thrombosis. Vasospasm.
Hematologic	Sickling (donor blood). Thrombocytopenia. Bleeding (overheparinization of donor blood).	Graft-versus-host disease. Mechanical of thermal injury to donor cells.
Gastrointestinal	Necrotizing enterocolitis.	Bowel perforation.
Biochemical	Hyperkalemia. Hypernatremia. Hypocalcemia.	Hypomagnesemia. Acidosis. Hypoglycemia.
Infectious	Bacteremia. Virus infection (hepatitis cytomegalovirus).	Malaria.
Miscellaneous	Hypothermia. Perforation of umbilical vein.	Drug loss. Apnea.

From Watchko JF. Exchange transfusion in the management of neonatal hyperbilirubinemia. In: Maisels MJ, Watchko JF, eds. Neonatal jaundice. London, UK: Harwood Academic, 2000: 169-176, with permission.

PHARMACOLOGIC TREATMENT

Pharmacologic agents used in the management of hyperbilirubinemia can accelerate the normal metabolic pathways for bilirubin clearance, inhibit the enterohepatic circulation of bilirubin, and interfere with bilirubin formation by blocking the degradation of heme or inhibiting hemolysis[1]. Phenobarbital is an inducer of microsomal enzymes; it increases bilirubin conjugation and excretion and increases bile flow. Ursodeoxycholic acid (10-18 mg/kg/d divided into 2 or 3 doses) also stimulates bile flow and can be helpful both in unconjugated hyperbilirubinemia as well as in cholestatic liver disease. An oral liquid form is not commercially available but a suspension can be compounded by the pharmacist.

Tin mesoporphyrin (SnMP) is a drug that will inhibit the action of heme oxygenase and suppress the formation of bilirubin[8]. This drug has been tested extensively in studies in

Greece and Argentina but is not yet approved for use in the USA. A single dose of 6 μmol/kg was more effective than special blue light phototherapy in the treatment of term and near term neonates with established hyperbilirubinemia. It was also effective in controlling hyperbilirubinemia in infants with G6PD deficiency[8].

Intravenous immunoglobulin (IVIG) will help to control hyperbilirubinemia in infants with isoimmune hemolytic disease[9]. The doses used have ranged from 500 mg/kg given over 3-4 hours soon after birth to 800 mg/kg given daily for 3 days. The mechanism of action of IVIG is unknown but it is possible that it might alter the course of Rh hemolytic disease by blocking Fc receptors, thereby inhibiting hemolysis.

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CHAPTER
44

Neonatal care of newborns of mothers affected with diseases with neonatal repercussion

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Maternal diseases appropriately treated do not usually prevent a woman from being fertile. Some of these conditions may affect the normal course of pregnancy and will require greater attention to the mother and the newborn.

INFANTS BORN TO DIABETIC MOTHERS

Pregestational diabetes always requiring insulin treatment should be distinguished from gestational diabetes associated with pregnancy that may respond to dietary measures only or require insulin doses. Repercussion on the fetus is similar because it mainly depends on the control of serum glucose levels. From a clinical point of view, the newborn usually has a high birth weight and functional immaturity. Phenotype is characteristic, with round face and intense redness, obesity, marked skin folds mostly in the arms and thighs, and wide neck. During the first hours after delivery, infants adopt a hypotonic appearance with adduction of the lower limbs, relaxed upper limbs, and semi-opened hands. Cardiomegaly, hepatomegaly and splenomegaly of variable magnitude are present. As a consequence of macrosomy, intrapartum traumatisms (particularly of the brachial plexus and clavicle) are more common. Congenital anomalies are 10 times more frequent than expected, including congenital heart diseases (transposition of great arteries, ventricular septal defect, and coarctation of the aorta), caudal regression syndrome with femoral agenesis or hypoplasia, vertebral anomalies (sacrococcygeal agenesis type), situs inversus, spina bifida, anomalies of the central nervous system (such as holoprosencephalia or anencephalia), renal anomalies (agenesis, cysts), urological anomalies (hypospadias, duplication of the ureter), rectal and/or anal atresia, and hypoplasia of the left colon. Increased thickness of the myocardium at the level of the interventricular septum (>5 mm) is observed in all infants, and about 30% of newborns develop hypertrophic miocardiopathy, with heart failure and murmur, which disappears after some months. The frequent association of prematurity with pulmonary immaturity, characteristic of these infants, increases the incidence of hyaline membrane disease. More frequently, respiratory distress is secondary to retention of extravascular fluid in the lungs leading to the wet lung syndrome.

Hypoglycemia is the most common metabolic finding, which is present in 50% of infants, peaking between the first and second hours of life, in relation to fetal hyperinsulinism and

drop of exogenous glucose intake. Hypoglycemia usually disappears in about 1 to 3 days. Hypocalcemia is also a common finding between the second and third days of life, and hypomagnesemia is present in one third of infants.

Patients may present polyglobulia with an excessive number of erythroblasts and abundant extramedullary foci of hematopoiesis, contributing to hepatomegaly. Secondary findings include jaundice and renal venous thrombosis, favored by increased blood viscosity.

Management of these neonates is directed to the prevention and treatment of hypoglycemia (see figure 1 for treatment of hypoglycemia, defined according to hours of life and starting of feeding). In gestational diabetes, measures applied orally may be sufficient to prevent hypoglycemia. In the other cases, hypoglycemia should be prevented by iv continuous infusion of 10 % glucose solution (75 mL/kg/day). Hypoglycemia should be treated with intravenous administration of glucose, bolus injection of 10 % glucose solution, 2-5 mL/kg during 2-5 minutes. Occasionally, the bolus injection should be repeated. This is followed by a maintenance infusion at a rate of 4-8 mg/kg/min, with frequent controls of serum glucose levels until stabilization of normal concentrations. When serum glucose concentrations are repeatedly greater than 90 mg/dL and as oral feeding increases, intravenous administration of glucose can be reduced (rate and concentration) until withdrawal. The use of glucagon at doses of 0,025-0,3 mg/kg is an emergency measure while waiting to establish an intravenous route.

Hypocalcemia is treated with the intravenous administration of calcium gluconate 10 %, at doses of 1-2 mL/kg, slowly injected (< 1 mL/min) with simultaneous control of the heart rate (infusion should be stopped if heart rate < 100 beats/min) and possible extravasation of the agent. A dose of 6-8 mg/kg/day should be given as maintenance treatment.

Polyglobulia should be treated with partial exsanguinations with physiological saline when central hematocrit at 6 hours of life is higher than 70 %. With regard to hypertrophic miocardiopathy with heart failure, treatment includes fluid restriction and furosemide, adding propranolol when necessary.

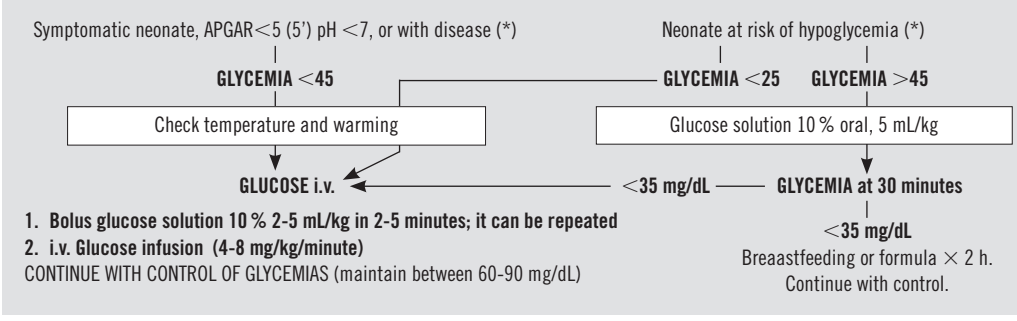

Figure 1. (*) Values of glycemia with the reactive strip. Add 15 % for glycemia measured in the laboratory.

INFANTS BORN TO TOXEMIC MOTHERS OR PREGNANCY-INDUCED HYPERTENSION

Hypertension is found in 5-7 % of pregnancies. Pregnancy-induced hypertension should be differentiated from previous hypertensive states, although this distinction is sometimes difficult when the pregnant woman is visited beyond 20 weeks' gestation. Pregnancy-in-

duced hypertension, —toxemia or preeclampsia—, is a disease characterized by the triad of high blood pressure, edema, and the presence of protein in the urine. In a random sample, proteinuria is higher than 500 mg/mL, although the isolated occurrence of this finding does not allow establishing a diagnosis of preeclampsia and the absence of this finding does not exclude the diagnosis. Preeclampsia is generally classified as mild when blood pressure is lower than 160/110 mmHg, or increase of baseline values is lower than 30 mmHg for systolic blood pressure or lower than 25 mmHg for diastolic blood pressure, and proteinuria is lower than 5 g/24 h. In the presence of higher values or when general clinical manifestations appear (renal dysfunction with oliguria, cyanosis, pulmonary edema, etc.), preeclampsia is considered severe. When neurological symptoms are present (headache, seizures or coma), a diagnosis of eclampsia is established. HELLP syndrome (**H**emolysis, **E**levated **L**iver enzymes, **L**ow platelet count) is characterized by hemolytic jaundice, increase of serum aminotransferases, thrombopenia, hepatomegaly, increase of serum creatinine, and hypoglycemia. Hypertension is usually treated with beta-blockers (labetalol) and calcium antagonists (nefedipine). Diuretics are not recommended as they may cause depletion of intravascular volume, with a decrease of placental perfusion and fetal compromise.

Maternal hypertension reduces uteroplacental blood flow up to 60-65% in the last weeks of gestation. Consequently, hypoxia, malnutrition, and hydroelectrolytic disorders may appear. Chronic hypoxia predisposes to loss of fetal wellbeing at the time of delivery. The newborn infant can present intrauterine growth restriction, hyponatremia (due to administration of hypotonic solutions to the mother), hypothermia, hypoglycemia, hypocalcemia, polyglobulia, hyperbilirubinemia, acidosis, edemas, amniotic aspiration syndrome, bradycardia (by beta-blockers), and respiratory depression due to drugs given to the mother (magnesium sulfate or diazepam) or anesthesia. A preterm delivery is frequently necessary, and newborns may present thrombopenia and neutropenia. Treatment is based on correct resuscitation after delivery and on the control of hyponatremia and aspiration syndromes. The administration of antihypertensive medication and magnesium sulfate to the mothers does not contraindicate breastfeeding.

INFANTS BORN TO MOTHERS WITH RENAL DISEASE

If renal failure is severe (serum creatinine concentration >2,0 mg/dL), there are a few possibilities to become pregnant. Pregnancies in women with moderate or severe renal failure are usually complicated by chronic hypertension, preeclampsia, and anemia. The incidence of abortion, preterm delivery and low birth weight infants is high. Hypertension is probably the main prognostic factor for outcome. Some particular circumstances should be considered:

Infants born to mothers on dialysis therapy. Menses are irregular or absent, contributing to a delayed diagnosis of pregnancy. If a decision is taken to continue with gestation, the fetus is at high risk of hydroelectrolytic disequilibrium and hypotension during dialysis session, with a 20-40% survival. In case of pregnancy, hemodialysis sessions should start earlier, have shorter duration, and be scheduled more frequently in order to maintain blood urea nitrogen between 50 and 60 mg/dL. The accompanying anemia is corrected with packed red cell transfusion and administration of erythropoietin. Peritoneal dialysis reduces the risk of vascular volume exchange and does not require maternal anticoagula-

tion; for this reason, peritoneal dialysis should be recommended when a dialysis program me has to be initiated in a pregnant woman. Uterine contractions that may appear during the sessions disappear with the addition of magnesium sulfate to the dialysate.

Infants born to renal transplantation recipient mothers. About 8 % of renal transplant recipient women will become pregnant. If the first trimester of pregnancy is surpassed, gestation will finish successfully in 90 % of cases. These gestations are especially complicated by hypertension. Preeclampsia develops in 30 % of women who had been transplanted and may cause rejection of the graft. Graft rejection, which is confirmed by renal biopsy, should be suspected in the presence of fever, oliguria, nephromegaly or lumbar pain. Bacterial or viral infections (herpes virus, cytomegalovirus, hepatitis B virus, etc.) can be more frequent due to treatment with immunosuppressants and corticosteroids. Intrauterine growth restriction is frequent (20-35 %) in relation to hypertension, renal failure, and treatment with cyclosporine or similar drugs (tacrolimus). There is also a high incidence of spontaneous preterm delivery (45-60 %). Physical examination of the newborn may reveal congenital anomalies due to treatment with corticosteroids and immunosuppressants. Initial laboratory values in the newborn are similar to those in the mother. If the mother had an increased serum creatinine concentration, the same finding will be observed in the newborn, requiring 2 to 3 days until normal values are restored.

INFANTS BORN TO MOTHERS WITH EPILEPSY

Pathologic conditions present in these newborn infants are probably related to maternal use of antiepileptic medication (barbiturates, hydantoin, valproic acid, carbamazepine), although the relationship between underlying illness and neonatal disorders should be considered. There is a twofold incidence of congenital anomalies compared with the general population. Clinical picture of the neonate may be highly variable, ranging from normal findings to intrauterine growth restriction potentially associated with anomalous traits and mental retardation. From a prophylactic point of view, all pregnant women receiving antiepileptic drugs should be treated with oral vitamin K_1 (20 mg/day) and vitamin D_3 (3.000 IU/day) during the last 15 days of gestation in order to prevent hemorrhagic diathesis mostly due to hydantoin medication as well as the anti-vitamin D effect associated with phenobarbital. Infants born to mothers treated with phenobarbital usually present a withdrawal syndrome, which should be treated with decreasing doses of the drug according to the infant's clinical course. At a later time, early treatment with vitamin D_3 for the prophylaxis of vitamin D deficiency is needed. If the mother has received hydantoin medication, injection of vitamin K_1 2 mg is indicated.

INFANTS BORN TO MOTHERS WITH ASTHMA

A higher incidence of preterm delivery and low birth weight in relation to severe and poorly controlled maternal asthma have been reported. There is no contraindication for breastfeeding. Drugs, such as theophylline are found in the breast milk but no important effects on the neonate are produced. Sodium cromoglycate and beclomethasone are undetectable in breast milk when therapeutic doses are used. By contrast, breast milk has a protective effect in children with family history of atopy as breastfeeding may delay the development of asthma and other allergic diseases. Therefore, breastfeeding is recommended, in particular if increased IgE levels in the cord blood are detected.

INFANTS BORN TO MOTHERS WITH AUTOIMMUNE DISORDERS

Maternal IgG antibodies cross the human placenta and are associated with transient alterations in the infant, particularly in newborns at term, since the half life of these antibodies is about 20 to 30 days. Transplacental passage of IgG antibodies is reduced in both premature and postmature infants. The following conditions deserve to be mentioned:

Transient neonatal hyperthyroidism. The occurrence of transient neonatal hyperthyroidism is related to the presence of maternal hyperthyroidism (Graves' disease), either treated or untreated, and transplancental passage of long-acting thyroid stimulator (LATS) or LATS protector (LATS-P). Symptoms may initially appear at the time of birth, although some times develop after one month of life. Clinical manifestations include weight loss, goiter, bilateral exophthalmia, neurological signs (irritability, continuous crying, hyperactivity, distal tremors of the extremities) and cardiac symptoms (tachycardia, heart failure) in some cases, whereas other patients may present voracious appetite, diarrhea, tachypnea, jaundice, hyperthermia, and thrombocytopenia. Craniosynostoses may be rarely observed. The diagnosis is made by increased serum concentrations of T_4 and LATS-P in the absence of TSH. Infants with mild hyperthyroidism can be treated with Lugol's solution (1 drop, 4-6 times daily) and those with more severe disease may require treatment with propylthiouracil 10 mg/kg/day, carbimazol 2,5 mg/kg/day or metimazol 0,5-1 mg/kg/day, divided into three doses. In infants with very severe hyperthyroidism, treatment with prednisone 1-2 mg/kg/day may be useful. Associated symptomatic management includes sedation with phenobarbital or diazepam, oxygen therapy, and digoxin treatment. Breastfeeding is allowed even if the mother is receiving propranolol, propylthiouracil or metimazol.

Transient neonatal myasthenia. This condition is found in 10 to 15% of infants born to mothers with myasthenia gravis and is due to passive transfer of maternal IgG anti- acetylcholine receptor (AChR) antibodies. AChR antibodies are detected in 85-90% of patients with myasthenia gravis, although a direct correlation between serum levels of AChR antibodies and clinical severity of the disease is not observed. In general, after a period of normal appearance following delivery, neonates present peculiar masklike facies, ptosis, and generalized hypotonia. During the first days of life, there is an alarming clinical picture of respiratory distress and weakened crying, poor suck and impaired deglutition. Symptoms usually disappeared after the first week or along the first 3 months. The diagnosis is established by maternal history and total reversal of symptoms after 10 to 30 min of the intravenous administration of edrophonium chloride (Tensilon^R test) or intramuscular administration of 0,1-0,2 mg of neostigmine (Prostigmine®). The electromyogram shows an almost normal recording but of low potential after repeated nerve stimuli. The detection of AChR antibodies is pathognomonic of this condition. Treatment is based on insertion of a feeding tube, respiratory support, and pharmacological therapy, including the administration every 3-4 hours and especially 30 min before feeding, of neostigmine 0,03-0,1 mg/kg intramuscularly or 0,3 mg/ kg orally, or oral piridostigmine (Mestinon®) 1 mg/kg. Piridostigmine is currently preferred due to a more prolonged pharmacological effect and lower rate of muscarinic side effects (nausea/vomiting, diarrhea, abdominal colic, sialorrhea, bronchorrhea, myosis, sweating), which can be treated with atropine (0,01 mg/kg subcutaneously). All these drugs can also induce nicotinic reactions (muscle cramps, fasciculation, weakness).

Transient thrombocytopenia in infants born to mothers with idiopathic thrombocytopenic purpura (Werlhof's disease). Transient thrombocytopenia due to transplacental transfer of anti-platelet IgG antibodies resolves spontaneously in 90% of cases in about 2 to 3 weeks.

Clinically, there are petechiae and possible hemorrhages. This condition rarely occurs during the intrauterine fetal life. In relation to the type of delivery, if funiculocentesis at week 37 or a sample from fetal scalp show a platelet count $<50.000/mm^3$, an elective caesarean section may be performed to reduce labor-associated trauma. Infusion of compatible washed platelets to the fetus are also useful and may allow vaginal delivery without risk of bleeding. If the platelet cell count in the newborn infant is $<30.000/mm^3$, platelet concentrate (compatible) should be administered (0,3 units/kg dose), which is followed by an increase of platelet count to $75.000/mm^3$. When this platelet cell count is not maintained for an expected 7-day period, corticoids (due to the beneficial effect on blood vessels) or high doses of intravenous IgG can be used. Massive doses of IgG seems to block the reticuloendothelial system avoiding destruction of platelets bound to anti-platelet IgG, and an increase in the platelet blood count occurs after 24 hours of treatment. This measure is especially useful in case of intracranial hemorrhage. IgG is administered at a dose of 400 mg/kg/day diluted in glucose serum over a 6-hour infusion for 5 days, or only 3 days in case of favorable response.

Transient neonatal lupus in infants born to mothers with systemic lupus erythematosus. Systemic lupus erythematosus is a multisystem disorder, more frequent in young women but not exceptionally diagnosed during pregnancy. It may be the cause of late spontaneous abortion (20-40%). Hypertension and renal failure are potential complications for the mother. Maternal treatment with prednisone (60 mg/day) and aspirin (75 mg/day) improves neonatal outcome. Infants born to mothers with systemic lupus erythematosus may present, in addition to congenital heart block, neonatal lupus erythematosus, which appears early and resolves spontaneously during the first 6 months of life. It is more common in female than in male neonates (2/1). Clinical manifestations include discoid exanthema of the face, particularly in the periorbital areas, trunk and upper limbs. Residual lesions with atrophy and telangiectasis may persist after clearance of exanthema. Hemolytic anemia, leukopenia and thrombocytopenia may occur in association with cutaneous rash. The diagnosis is based on detection of antinuclear, anti-Ro and anti-La antibodies, and LE cells in the newborn infant, although the absence of these findings does not exclude the diagnosis. Lesions are usually transient and last for a few weeks to months. The skin should be protected from UV light (sun, fluorescent lamp) and active lesions can be treated with topical corticoids. Systemic corticoids should be administered only in case of abnormal hematological findings.

INFANTS BORN TO MOTHERS WITH CARDIAC DISEASES

Maternal mortality increases considerably in those cases in which pulmonary blood flow cannot be increased, and is lower in cases of tetralogy of Fallot and rheumatic heart disease. Fetal and neonatal mortality is higher in cyanotic congenital heart diseases. Neonatal morbidity results from intrauterine growth retardation. Regarding pharmacological treatment to women with cardiac disease, beta-adrenergic blockers can be safely used in pregnant patients, and in large clinical series, congenital anomalies or other side effects related to the use of these drugs have not been reported. There is a possibility that the administration of these drugs may occult changes of fetal heart rate usually considered in the diagnosis of loss of fetal wellbeing. Inotropic agents and digoxin can be safely used in pregnant women. Digoxin crosses the placental barrier but has no effect on fetal cardiac function; it is also found in minimum amounts in the breast milk, so that breastfeeding is not contraindicated. Anticoagulants cross the placenta. An embryofetopathy in relation to the admi-

nistration of warfarin is well established. Fetal warfarin syndrome results in chrondrodystrophy punctata, nasal hypoplasia, optic atrophy, and mental retardation. Although warfarin might be used between weeks 16 and 37 of gestation, cautious administration of the drug is mandatory. Fetal coagulation abnormalities may persist even for one week after withdrawal of treatment. Heparin is a possible alternative because the high molecule of this compound does not cross the placenta. Heparin would be the treatment of choice during the last weeks of gestation to avoid coagulation-related problems in the newborn and because of heparin reversal with protamine if maternal bleeding occurs at labor. The use of coumarins does not contraindicate breastfeeding.

INFANTS BORN TO MOTHERS WITH CANCER

This occurs in less than 1 per 1.000 gestations. Breast and cervical cancer are the most common malignancies. Pathologic conditions in the newborn infant are related to the teratogenic effect on intrauterine exposure to cytostatic drugs or radiotherapy. The incidence of congenital anomalies secondary to chemotherapy is higher if chemotherapy is used during the first trimester of pregnancy. In late stages of gestation chemotherapy may cause intrauterine growth retardation, prematurity and antenatal fetal death. Radiation therapy is particularly dangerous, with a dose-dependent effect, also in relation to the gestational age at the time of therapy. Fetal metastases are exceptional. If the mother has been treated with corticosteroids, the possibility of adrenal insufficiency in the fetus should be considered. In case of pancytopenia secondary to maternal treatment, supportive measures until spontaneous recovery should be applied. When the mother receives chemotherapy, artificial feedings is recommended.

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CHAPTER 45

Screening of surgical disease in neonatal period

M. Castañón

CHOANAL ATRESIA

Due to the lack of communication between the nasal fossa and nasopharynx; the malformation might be uni or bilateral.

DIAGNOSIS

Clinic. The unilateral shape is normally asymptomatic; the bilateral produces a severe cyanosis and respiratory difficulty. It gets better when the baby opens his mouth and cries. Etiologic: Due to a membrane or septum.

Complementary studies. The clinic gives us the diagnosis in most cases. In the unilateral type, the alternative compression of the nasal fosses with the mouth closed shows the lack of ventilation on the damaged side. Through direct visual inspection by otoscopy or through the failed probe, we can verify this malformation.

TREATMENT

Immediately. Placement of a Mayo Tube. Once the patient has recovered, the atresia is perforated a with a trocar or laser via nasal.

GLOSSOPTOSIS

The most characteristic is the Pierre Robin syndrome. This is characterized by glossoptosis, microrretrognatia, and cleft palate (in the less severe cases ojival palate). The tongue lies posteriorly and obstructs the air entrance.

DIAGNOSIS

Clinic. Distress respiratory syndrome, cyanosis and apnea that get better in upside down.

TREATMENT

Prone position in the mild cases. In severe condition, placement of a Mayo tube, traqueal intubation or surgical techniques (glosopexias). The feeding will be given orally or by nasogastric tube.

CONGENITAL DIAPHRAGMATIC HERNIA

Congenital diaphragmatic hernia (CDH) is a malformation characterized by a defect in the posterolateral diaphragm, the foramen of Bochdalek, through which the abdominal viscera migrate into the chest during fetal life. Congenital diaphragmatic hernia occurs in approximately 1 in every 2.400 to 5.000 babies. In most series, 80% of posterolateral diaphragmatic hernias have been reported to occur on the left side. The mortality rate of infants born with CDH remains high, despite optimal perinatal care.

DIAGNOSIS

Clinic. Widespread use of obstetric sonography has led to an increase in the frequency of antenatal diagnosis of CDH, which is established by demonstration of the abdominal viscera in the chest. The symptoms of a CDH appear soon after the baby is born and include: dyspnea, fast breathing, tachycardia, cyanosis, abnormal chest development, with one side being larger than the other, abnormal abdominal shape (concave) Complementary studies: chest x-ray shows the abnormalities of the lungs, diaphragm and intestine.

TREATMENT

The surgery to repair the diaphragm is not an emergency and the baby should be as stable as possible before it; this may take days to weeks. At the time of surgery the stomach, intestine and other abdominal organs are moved from the chest cavity back to the abdominal cavity. The diaphragmatic defect is repaired by direct suture (stitches); sometimes it may require the use of plastic piece or mesh. Many babies will need to remain in the NICU for a while after surgery.

CONGENITAL CYSTIC ADENOMATOID MALFORMATION (CCAM)

CCAM is a developmental hamartomatous abnormality of the lung with adenomatoid proliferation of cysts resembling bronchioles. CCAM represents approximately 25% of all congenital lung lesions. Incidence of CCAM is 1 case per 25.000-35.000 pregnancies.

Types of CCAM: CCAM is subdivided into 3 major types. Type I lesions, the most common, are composed of 1 or more large cysts measuring 2-10 cm in diameter. Type II lesions are characterized by small relatively uniform cysts resembling bronchioles. The cysts generally measure 0,5-2 cm in diameter. Type III lesions consist of microscopic, adenomatoid cysts, and are grossly a solid mass without obvious cyst formation. Microscopic adenomatoid cysts are present. Type II and III lesions can occasionally coexist with extralobar sequestration.

DIAGNOSIS

Clinic. In the newborn, 80 % of CCAMs present with some degree of respiratory distress secondary to mass effect and pulmonary compression or hypoplasia. Complementary studies: CCAM may be initially detected during prenatal ultrasonography. After birth, chest radiography should be performed first. Although lesions remain filled with fluid, postnatal sonography can be used for a more detailed assessment, particularly in type III lesions. Once lesions are air-filled, CT scanning is necessary for determination of the type and extent of the lesions.

CONGENITAL LOBAR EMPHYSEMA (CLE)

Congenital lobar emphysema presents with overexpansion of a pulmonary lobe and compression of the remaining ipsilateral lung. The abnormality is related to intrinsic bronchial narrowing. In these cases, there is weakened or absent bronchial cartilage. During inspiratory air entry but collapse of the narrow bronchial lumen during expiration. This bronchial defect results in lobar air trapping. CLE almost always involves one lobe (Left upper lobe 41 %).

DIAGNOSIS

Clinic. Approximately half of patients develop respiratory distress within the newborn period while the remainder is delayed till 4 to 6 months of age or later. Presenting sings are those of respiratory embarrassment, including dyspnea, tachypnea, agitation and wheezing.

Complementary studies. Usually, chest X-rayadiography shows marked overdistention of an upper lobe with mediastinal shift to the other side. Computed tomography scanning can provide details about the involved lobe and its vascularity, as well as information about the remaining lung.

TREATMENT

Emergency surgical lobectomy was once considered the only treatment for CLE, but appropriate care may be nonsurgical in infants with only moderate respiratory distress.

OESOPHAGEAL ATRESIA

Oesophageal atresia is defined as an interruption in the continuity of the oesophagus with or without fistula to the trachea. The most frequent type is the form with a distal tracheoesophageal fistula (85 %). The incidence is 1:4500 live births. Oesophageal atresia is associated frequently with other anomalies, such as imperforate anus, skeletal abnormalities or cardiac malformations that can be evident on physical examination. Up to 10 percent of infants with esophageal atresia have the VATER syndrome. The acronym VATER, or VACTERL (vertebral defect, anorectal malformation, cardiac defect, tracheoesophageal fistula, renal anomaly, radial dysplasia and limb defects), has been used to describe the condition of multiple anomalies in these infants.

DIAGNOSIS

Clinic. Postnatal presentation is characterized by drooling of saliva and cyanotic attack. If a fistula between the esophagus and the trachea is present, abdominal distention develops as air builds up in the stomach. The abdomen will be scaphoid if no fistula exists. If passage of 12 F feeding tube into the stomach is not possible, oesophageal atresia is almost certain.

Complementary studies. The prenatal ecography may show polyhydramnios in the second half of pregnancy. The chest radiograph provides information about the cardiac silhouette, the location of the aortic arch and the presence of vertebral and rib anomalies. Contrast studies are seldom necessary to confirm the diagnosis. Such studies increase the risk of aspiration pneumonitis and reactive pulmonary edema, and usually add little information to plain film radiographs.

TREATMENT

Once a diagnosis of esophageal atresia is established, preparations should be made for surgical correction. The oral pharynx should be cleared, and an 8 French sump tube placed to allow for continuous suctioning of the upper pouch. Gastrostomy for gastric decompression is reserved to patients with great operatory risk.

DUODENAL OBSTRUCTION

Congenital duodenal atresia is one of the more common intestinal anomalies treated by pediatric surgeons, occurring 1:5000-10.000 live births. In approximately 40% of cases, the anomaly is encountered in an infant with trisomy 21 (Down syndrome). Duodenal obstruction may be complete or incomplete. Duodenal atresia is a complete intrinsic obstruction. Duodenal stenosis is an incomplete intrinsic abnormality; however, duodenal extrinsic stenosis can occur in association with malrotation, annular pancreas or a preduodenal portal vein. Etiology: the underlying cause of duodenal atresia remains unknown.

DIAGNOSIS

Clinic. Prenatal diagnosis can be suspected by polyhydramnios and the distension of the stomach and the first portion of the duodenum with swallowed amniotic fluid. In the postnatal period, duodenal atresia is typically characterized by onset of vomiting within hours of birth. While vomits are most often bilious, it may be nonbilious because 15% of defects occur proximal to the ampulla of Vater.

Complementary studies. RX a characteristic finding of duodenal obstruction is the double bubble image of an air-filled stomach proximal to an air-filled first portion of the duodenum. Absence of gas in the remaining small and large bowel suggests atresia, whereas scattered amounts of gas distal to the obstruction suggests stenosis or malrotation.

TREATMENT

The definitive intervention to correct the anomaly is surgical and consists of duodenoduodenostomy in the newborn period.

JEJUNO-ILEAL ATRESIA

Defects in the continuity of the small bowel can morphologically be divided into the stenosis or atresia and represent one of the most common causes of neonatal intestinal obstruction. The most accepted theory regarding the etiology is that of an intrauterine vascular accident resulting in necrosis of the affected segment, with subsequent resorption. The prevalence rate is approximately 1:1.000 live births. One third is premature or small-for-date. Four types of jejunoileal atresias are described. The different types represent a spectrum of severity, from a simple web to multiple atresias with loss of bowel length.

DIAGNOSIS

Clinically, the neonates with a proximal atresia develop bilious emesis within hours, whereas the patients with more distal lesions may take longer to begin vomiting. A normal or scaphoid like abdomen in a neonate with bilious emesis should be considered indicative of a proximal obstruction until proven otherwise. Abdominal distension is more pronounced with distal lesions.

Complementary studies. Radiography is helpful to confirm the diagnosis. The more proximal the atresia develops, the fewer air-fluid levels are evident, with no apparent gas in the lower part of the abdomen. Distal lesions demonstrate more air-fluid levels, although the distal intestine remains gasless. A barium enema may be used to define a microcolon indicative of a distal small-bowel obstruction; it is also capable of establishing the diagnosis of other causes of lower obstruction, such as Hirschsprung disease or a meconium plug.

TREATMENT

Gastric decompression and fluid resuscitation. The dilated proximal bulb generally does not have normal function and, as a result, should be resected up to a more suitable size to avoid problems with abnormal peristalsis postoperatively. If the bowel length is limited, a tapering enteroplasty should be considered rather than resection. An end-to-end anastomosis can then be performed

ANORECTAL MALFORMATIONS (MAR)

Anorectal malformations are a complex group of malformations diagnosed at the time of birth because of the absence or an ectopic location of the anus. The incidence is approximately 1:4.000 live births and they are more often seen in males than in females (5/1). 85 % of MAR present with fistulas: genitourinary tract, vagina or perineum.

Classification MARS (Krieckenbeck): perineal fistula, rectourethal fistula (bulbar, prostatic), rectovesical fistula, vestibular fistula and cloaca. No fistula. Anal estenosis.

The cases without fistula are associated to Down syndrome in 50 % of the cases.

DIAGNOSIS

Clinic. Absence of meconium evacuation or meconium emission throughout the fistula, abdominal distention. Physical exploration: Absence or abnormal position of the anus. Proper classification of most MAR can be usualy made.

Complementary studies. A lateral pelvis radiograph obtained with the baby in prone position (between 18 and 24 hours to allow time for gas or meconium to appear in the perineum) and the hips raised usually suffice. A gap of 1 cm or greater between gas shadow and skin usually represents a significant anomaly. Ultrasonography can provide the same type of information.

The rest of physical examination is directed toward detecting associated malformations the are present up to in 70 percent of patients (digestive, cardiac, vertebral, genitourinary, chromosomic...).

Urinary fistula diagnosis by urinary sediment.

TREATMENT

Terminal colostomy in descending colon in case of insufficient fistula.

Posterior surgical anorectoplasty (ARPS) according to Peña (from the 4th month of life on)

MECONIUM ILEUS

Meconium ileus (MI) is one of the most common causes of intestinal obstruction in the newborn. MI could be the first clinical manifestation of cystic fibrosis (CF) and occurs as either simple or complicated in approximately 8-10% of patients who have CF, although MI may also occurs in patients without this disease.

DIAGNOSIS

Clinic. Prenatally, it could determine the development of atresias, perforation or peritonitis. Patients with simple MI usually present with abdominal distension at birth, eventually leading to failure to pass meconium, bilious vomiting, and progressive abdominal distension. Often, examination reveals dilated loops of bowel with a doughy character. The rectum and anus usually are narrow; a finding possibly misinterpreted as anal stenosis. Patients with complicated MI present more dramatically at birth with severe abdominal distension, sometimes accompanied by abdominal wall erythema and edema. Diagnosing CF during the neonatal period is difficult, since the sweat test can only give us relevelant information from the 3rd or 4th month of life on. Altered levels of trypsinogen, a pancreatic enzyme, can identify patients with CF in an early age.

Complementary studies. Abdominal radiographs may reveal a distended bowel, few air-fluid levels and, in the right lower abdomen, meconium mixed with air, which has a ground-glass appearance on plain film. The presence of calcifications, free air or very large air-fluid levels suggests complications. Contrast enema radiographic examination demonstrates a microcolon, often with no bowel contents. Reflux of contrast into the small bowel reveals the plugs. The small bowel is of narrow caliber below the plug and dilated above the plug.

TREATMENT

Simple meconium ileus may be successfully treated by administration of a diatrizoate meglumine (Gastrografin) enema with fluoroscopic control and plenty of intravenous fluids. If the Gastrografin enema is unsuccessful, operative evacuation of the obstructing

meconium by irrigation will be necessary. Complications such as atresia, perforation and meconium peritonitis always require immediate surgery, including resection, intestinal anastomosis and ileostomy.

SERIOUS DEFECTS OF THE ABDOMINAL WALL: GASTROSCHISIS AND OMPHALOCELE

Fortunately, the frequency of important defects of the abdominal wall is low (1: 5.000-10.000 alive newborns). There are two great groups: The defects related to development and closure of the umbilical cord and ring (Omphalocele) and the defects related to evolutionary accidents of the body stalk and the base of the umbilical ring (Gastroschisis). Although both defects may have similar aspects, their different embryonic origin grants differential characteristics:

GASTROSCHISIS. The defect usually occurs on the right side of the umbilical cord, with a healthy piece of skin between both; the herniated bowel loops are not covered by peritoneum, and they are swollen, matted, adhered themselves and covered with a thick fibrinous peel around the intestine. Zones of infarction and one or more zones of atresia or stenosis may be found as a result of intrauterine intestinal infarcts, with a high risk of obstruction and intestinal perforation.

OMPHALOCELE. It may be associated with other congenital anomalies as a polimalformative syndrome in more than 50 % of the cases (cardiopathies, trisomies 13 or 18, etc.). The size of the defect can vary from a simple umbilical hernia to great defects that even affect the anterior region of the thorax and the pelvis. An amniotic sac covers the abdominal content. When the defect is large, the peritoneal cavity usually is too small to contain the herniated visceral organs.

The primary closing of all the layers of the abdominal wall is the objective of the surgical treatment of both abnormalities, but it is not always possible, at least at the first time. In big omphaloceles, when peritoneal cavity is too small to contain the herniated organs, the Schuster technique may be used; organs are covered with a coat of silastic mesh, as a temporary housing for the intestine. Later, the intestines can be returned to the abdomen gradually by gentle pressure and placing the string that ties off the top of the silastic coat lower. Once the intestines are almost back inside, the silastic sac is removed and the abdominal defect closed. In gastroschisis, a direct closing is usually possible but when the intestine could not be completely placed back into the abdomen, the technique of Schuster can be also used.

HIRSCHSPRUNG DISEASE

Hirschsprung disease, also called congenital megacolon, was described by this author in 1887. The disease result from the absence of parasympathetic ganglion cells in the myenteric and submucosal plexus of a segment of the intestine, usually rectum and/or sigmoid colon (75 % of cases). This segment is spastic and noncontractile. The proximal intestine becomes partially or completely functionally obstructed, and begins to dilate. Hirschsprung disease affects 1/5.000 alive newborn; 70-80 % cases are men.

DIAGNOSIS

Clinical. In half of the cases manifestations begins in the neonatal period with intestinal obstruction or chronic constipation since birth. The main symptoms are delayed passage of meconium, abdominal distension and vomiting. In the unweaned baby, disease is usually manifested by a persistent constipation, mostly related to a nourishing change like substitution of breastfeeding for bottle-feeding or introduction of a complementary feeding.

Complementary examinations. Plain abdominal radiography of abdomen shows important bowel distension with a speckled aspect of the bowel content because of trapped air inside of retained meconium. Upright abdomen X-ray film may show fluid levels.

Findings of single-contrast barium or gastrografin enema in newborns can be difficult to interprete. A delayed evacuation of barium and a transition zone between a narrowed aganglionic segment and a dilated and normally innervated segment may be observed.

Accuracy of rectal manometry can be of 85%. Children with Hirschsprung disease fail to demonstrate the reflex relaxation of the internal anal sphincter in response to inflation of a rectal balloon. However, this reflex is not developed in newborn, so the test is not helpful in this age.

The definitive diagnosis of Hirschsprung disease has to be done with the on histological review of rectal biopsies. Specimens are carefully examined for the presence or absence of ganglion cells in the myenteric plexuses and for increased acetylcholinesterase activity by histochemical study.

Differential diagnosis: It should be considered with other problems that manifest neonatal intestinal obstruction: meconium plug syndrome, left colon hypoplasia syndrome, septic problems and cerebral palsy.

TREATMENT

Nursing. Normal saline irrigations through a rectal tube placed beyond the aganglionic segment.

Colostomy. If the nursing management is not helpful, a loop colostomy, performed over healthy colon, proximal to aganglionic zone, is indicated.

A surgical pull-through procedure is the definitive treatment.

PERFORATION OF HOLLOW VISCUS (PNEUMOPERITONEUM)

The pneumoperitoneum is due to an intestinal or gastric perforation.

DIAGNOSIS

Clinical course. Severe abdominal distention, tenderness, shock and respiratory distress. Tympanic abdominal percussion.

Etiology. Gastric perforation can be spontaneous during reanimation maneuvers in perinatal hypoxia or while introducing a nasogastric tube improperly. Duodenal perforation can be because of a stress ulcer or gastroduodenal tube maintained during a long period.

Other perforations along the rest of the bowels might be due to previous pathology (NEC, Hirschsprung disease, meconium ileus).

Complementary studies. Erected plain films show the free air in abdominal cavity located between the diaphragm and the liver. If the patient is supine, plain films with horizontal ray show free air under umbilicus.

Peritoneal lavage can help to determine the presence of enzymes and germs. Differential diagnosis: pneumoperitoneum could be originated in the thorax when there is an air migration through lymphatic vessels.

TREATMENT

Emergency laparotomy in other to close the perforation, excision of an extended area affected and ostomies if necessary.

SOLID ORGANS INJURY (HEMOPERITONEUM)

Solid organs injury can occur during delivery and can cause hemoperitoneum. The most frequent affected organ is the liver followed by the spleen.

HEPATIC RUPTURE

It is a severe lesion with a high mortality rate (60-70 %) due to the hypovolemic shock.

DIAGNOSIS

Clinical course. Acute anemia and hypovolemic shock. The newborn presents pallor, deficient peripheric vascularization with hypothermia, tachycardia with progress to bradycardia, hypotension with a decrease of central venous pressure. The onset of hepatic rupture can be critic or slow in case of integrity of Glisson capsule, causing hepatomegaly and chronic anemia.

Etiology. Obstetric procedures. Immaturity, breech presentation, perinatal asphyxia and fetal macrosomia are predisposing factors. Postnatal, reanimation maneuvers, cardiac massage, etc.

Complementary studies. Progressive anemia. Ultrasonography can show a subcapsular hemorrhage of the liver and later an intra-abdominal hemorrhage.

The goal of the peritoneal lavage is to determine if there is blood in the free peritoneal cavity.

Abdominal plain films provide valuable information such as hepatomegaly and intra-abdominal hemorrhage signs (generalized ground-glass appearance to a largely gassless abdomen, blur the liver edges).

TREATMENT

Fluid resuscitation sufficient to restore promptly and maintain adequate circulatory volume is an absolute priority. Surgery is indicated in case there is an ongoing blood loss that is not controlled.

SPLEEN RUPTURE

It normally occurs in pathologic spleens due to a blunt trauma during delivery or after an exanguintransfusion. Mortality rate is high.

PNEUMOTHORAX AND PNEUMOMEDIASTINUM

Accumulation of air or gas in the pleural cavity or mediastinum occurring as a result of alveolar breakage mainly because of interstitial pulmonary emphysema. The air infiltrates the broncho vascular spaces and then arrives at the mediastinum, pleural cavity and subcutaneously (subcutaneous emphysema).

DIAGNOSIS

In laminary pneumothorax symptoms are very slight and many are asymptomatic. Tension pneumothorax starts abruptly with acute severe respiratory insufficiency, cyanosis, tachypnea, and tachycardia with low response to oxygen therapy. Bilateral pneumothorax is a very severe situation that presents with interstitial and subcutaneous emphysema, pneumomediastinum, pneumopericardium and pneumoperitoneum.

Etiology. Iatrogenic cardiopulmonary resuscitation, obstructions (foreign bodies, mucus, etc), meconial aspiration, neonatal respiratory distress, congenital lobar emphysema, etc.

Complementary exams. X-Ray is diagnostic. Pneumothorax: Lung collapse with peripheral air image without pulmonary density. Pneumomediastinum: Air density along the cardiac silhouette and great vessels. Subcutaneous emphysema: air bubbles in the subcutaneous tissue with smooth bulging of the skin. Pneumopericardium: hyperclarity only along de cardiac silhouette.

TREATMENT

Pneumothorax. Needle puncture and aspiration only in emergency situations. Catheter place in the medial axilar line, not involving the mammary gland, with continuous aspiration (10-15 H20 cm) or just water seal. Catheter is removed when the underlying disease is controlled. First, the catheter has to be closed for 24 h and a new X-Ray done in order to verify that no pneumothorax is formed again. Pneumomediastinum: some severe cases may need drainage.

Pneumopericardium. if cardiac tamponade is associated, immediate pericardiocentesis, needle evacuation of the fluid and lowering of the pericardial pressure, and then treatment of the underlying cause, has to be done. If possible, echocardiography may be helpful.

Pneumoperitoneum originated in the thorax it is usually resolved spontaneously with no need of external intervention.

INGUINAL HERNIA

Congenital indirect inguinal hernias develop because the processes vaginalis remains patent after birth. The incidence of congenital indirect inguinal hernia in full-term neonates is 3-5 % in preterm infants is higher and ranges from 9-11 % . Inguinal hernia is more com-

mon in males than is females 5:1. Of all inguinal hernias, 60% occurs on the right side, 25-30% on the left, and 10-15% is bilateral.

DIAGNOSIS

Clinic. The most common presentation of inguinal hernia in a child is a groin bulge, extending towards the top of the scrotum. Complication: Sometimes a portion of the intestine is trapped in the scrotum (incarceration); this can cut off the intestine's blood supply (strangulation). Strangulated intestines may become gangrenous within hours.

Diagnosis difference. Cyst in the high cord, the transparency by translumination, in front of the strangulated hernia opacity will help us for the diagnosis. The adenitis or inguinal adenophlegmon of the ganglion inguinal packages

TREATMENT

The main treatment for inguinal hernia is surgery to repair the opening in the muscle wall.

TESTICULAR TORSION

The spermatic cord that provides the blood supply to a testicle is twisted, cutting off the blood supply, often causing orchalgia. Prolonged testicular torsion will result in the death of the testicle and surrounding tissues.

It is also believed that torsion occurring during fetal development can lead to the so-called neonatal torsion. Left testicle is more commonly affected. Testicular torsion can be extra or intravaginal (in between the testicle and the epididymis). Extravaginal torsion is the most common form among neonates.

DIAGNOSIS

In the newborn we can found swelling within one side of the scrotum, a blackish testicular mass associated with fever and in some cases nausea or vomiting.

Differential diagnosis has to be done with inguinal hernia. Doppler shows normal blood flux in the normal testicle with low or absence in the torsionated one.

HYDRONEPHROSIS

Pelvi-ureteric junction obstruction (PUJ) is the most common cause of hydronephrosis detected antenatally. Controversy continues on the optimal timing of surgical intervention in children with antenatal detected hydronephrosis. The recognition is important to prevent irreversible damage to the kidneys.

DIAGNOSTIC

Clinic. Before the routine fetal ultrasonography, the commonest presentation was with abdominal flank mass. Some patients present with urinary tract infection, irritability, vomiting and failure to thrive.

Complementary examinations: Radionuclide studies (diethylenetriaminepentaacetic acid DTPA and mercaptocetyltriglycine MAG_3) are undertaken when the child is 6-8 weeks old in order to asses renal function and rule out obstruction.

TREATMENT

The decision of surgical intervention is complex because spontaneous resolution of antenatal and neonatal upper urinary tract dilatations is well known. Currently surgery is undertaken only in infants with deteriorating renal function

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Neonatal Sepsis

CHAPTER 46

NEWBORN

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INTRODUCTION

Although at the present time the concept of neonatal sepsis is under revision and an international consensus regarding the definition of this syndrome is lacking[1], most studies refer to neonatal sepsis as the clinical syndrome resulting from invasion and proliferation of bacteria, fungi or viruses in the bloodstream of the newborn infant. These infecting microorganisms initially contaminate the infant's skin and/or mucous membranes, reaching the circulating blood after penetration through the cutaneous-mucosal barrier[2].

According to the mechanisms involved in the colonization of pathogens, sepsis of vertical transmission, nosocomial sepsis and community-acquired sepsis should be distinguished. Sepsis of vertical transmission[2] is caused by pathogens found in the maternal genital canal, contaminating the fetus by an ascending mechanism (progressing through the birth canal to reach the amniotic fluid) or by direct contact of the fetus with contaminated secretions during labor. Nosocomial (hospital-acquired) sepsis[3] is caused by microorganisms found in Neonatology Services (primarily in neonatal intensive care units [NICUs]), contaminating babies through the health care personnel (e.g., hands) and/or equipment used for diagnostic or therapeutic purposes (e.g., thermometers, catheters, tubes, electrodes, stethoscopes, etc.). Community-acquired sepsis is caused by microorganisms contaminating infants at home, and is very infrequent.

Neonatal sepsis usually presents with non-specific clinical manifestations, including decrease in spontaneous activity, instability of temperature (hypothermia or fever), feeding difficulties (gastric retention, regurgitation, diminished or abolished suck reflex), and in the preterm newborn, episodes of bradycardia, tachycardia and/or apnea. As infection progresses, gastrointestinal symptoms are more pronounced (vomiting, abdominal distention, diarrhea) and frequently cardiorespiratory symptoms (tachycardia, tachypnea, apneas, signs of respiratory distress) and neurological symptoms (apathy, irritability, convulsions) develop. In later stages, signs of severity of infection are apparent, such as reduced spontaneous mobility, hypotonia and jaundice: «septic appearance». At this stage, manifestations of disseminated intravascular coagulation (petechia, ecchymosis, mucosal bleeding) or shock (tachycardia, weak pulse, slow capillary filling, hypotension, etc.) may be present.

SEPSIS OF VERTICAL TRANSMISSION

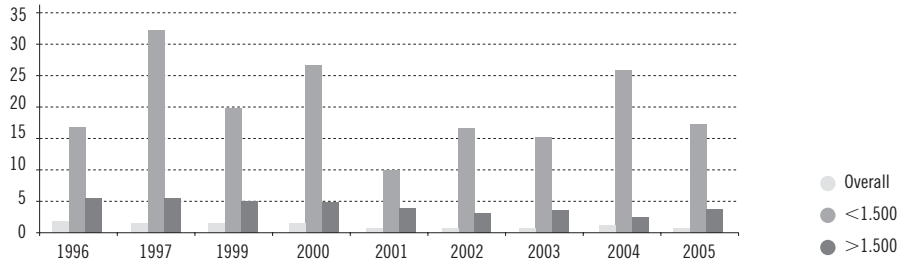
Neonatal sepsis of vertical transmission occurs as a result of colonization of the fetus before (ascending route) or during labor by microorganisms from the maternal genital tract. Therefore, the presence of pathogens in the genital tract of pregnant woman is the main risk factor for infection[4]. Maternal genital colonization is also related to premature rupture of amniotic membranes, chorioamnionitis, and preterm delivery[5]. In pregnant women, the detection of pathogens in the vagina has shown a variable prevalence, ranging from 10 to 30 % in the United States[6] and from 10 to 18 % in Spain[7], and the best method for predicting the status of vaginal colonization at the time of labor is to analyze recto-vaginal exudates at 5 weeks before delivery (between 35-37 weeks' gestation).

Symptoms of sepsis of vertical transmission usually appear at, 3–7 days of life and for this reason, many authors have defined sepsis according to the onset of disease, that is, early-onset infection (<3-7 days of age) for sepsis of vertical transmission and late-onset infection (occurring after 3-7 days of life) for nosocomial-acquired neonatal sepsis[8]. However, on the basis of this criterion it may be possible to exclude vertical transmission sepsis of late onset and to include nosocomial sepsis of early onset. Therefore, it seems more appropriate to classify neonatal sepsis according to the mechanism of transmission rather than according to the time of onset of disease, avoiding mixing infections of different pathogenesis, etiology, and treatment[4].

The **epidemiology** of sepsis of vertical transmission in Spain is the objective of an ongoing multicenter surveillance study *(«Grupo de Hospitales Castrillo»).* The project started in 1996 and more than 800.000 newborns have been included[2]. Along the study years, a significant decrease in the overall incidence of sepsis of vertical transmission has been observed, from 2,4 per 1.000 live births in 1996 to 0,99 per 1.000 live births in 2005 (odds ratio [OR] = = 0,40, 95% confidence interval [CI] 0,3-0,5, $P < 0{,}0001$) (figure 1). This trend has been associated with the implementation of intrapartum antibiotic prophylaxis following guidelines for the prevention of neonatal infection caused by group B *Streptococcus* (GBS)[9]. The incidence of these infections showed significant variations according to the birthweight, being more frequent in neonates weighing <1.500 g than in those weighing ≥1.500 g (17,2 per 1.000 live births *vs* 0,7 per 1.000 live births for 2005; data from *«Grupo de Hospitales Castrillo»),* and this difference was consistently recorded throughout the study (figure 1).

The **etiology** of sepsis of vertical transmission is mostly bacterial; sepsis caused by fungi and viruses account for less than 1 % of cases. *Streptococcus agalactiae* or GBS and *Escherichia coli* are the most common causative pathogens. Sepsis caused by GBS is more frequent in newborns weighing 1.500 g and *E. coli* in infants weighing, >1.500 g. Other less frequent causative pathogens include *E. faecalis,* other streptococci and *Lysteria monocyto-*

Figure 1. Incidence (per 1.000 live births) of sepsis of vertical transmission: overall and according to weight at birth, from 1996 to 2005. «Grupo de Hospitales Castrillo».



genes among the group of Gram positive organisms, and *Klebsiella* spp., *Haemophilus influenzae* and *Enterobacter* among the group of Gram negative pathogens (table 1).

In accordance with changes in the incidence of sepsis of vertical transmission associated with the use of intrapartum antibiotic prophylaxis against GBS colonization, variations in the etiology of infections in recent years have been also observed. The percentage of 75% of cases caused by Gram positive bacteria in the 80's and 90's has decreased to around 50% at the present time[9–11]. In our country, GBS infections showed an incidence of 1,25 per 1.000 live births in 1996 compared with 0,29 per 1.000 live births in 2005, in the clinical series of «*Grupo de Hospitales Castrillo*» (OR = 0,23, 95% CI 0,15-0,36, $P < 0,0001$) (figure 2). On the other hand, in our study in agreement with data reported by others, des-

Figure 2. Trends of GBS and *E. Coli* vertical sepsis in the «Grupo de Hospitales Castrillo».

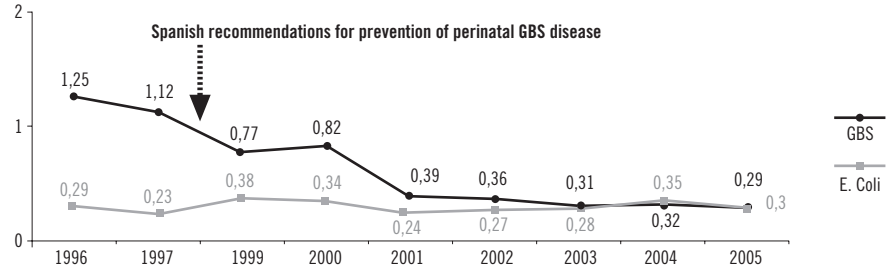


Table 1. Distribution of causative pathogens in sepsis of vertical transmission from 1996 to 2005.

PATHOGEN	*Years 96-97 (N = 367)*		*Years 99-2000 (N = 324)*		*Years 01-02 (N = 211)*		*Year 2005 (N = 91)*	
	Cases	*%*	*Cases*	*%*	*Cases*	*%*	*Cases*	*%*
GRAM-POSITIVE	**293**	**79,8**	**232**	**71,6**	**134**	**63,5**	**53**	**58,2**
GBS *(S. agalactiae)*	**186**	**50,7**	**129**	**39,8**	**78**	**37,0**	**27**	**29,7**
Enterococcus faecalis	33	**9,0**	35	**10,8**	21	**9,9**	7	**7,7**
Other Streptococci	32	**8,7**	19	**5,9**	13	**6,1**	—	**—**
L. monocytogenes	5	**1,3**	12	**3,7**	7	**3,3**	9	**9,9**
Other	37	**10,1**	37	**11,4**	15	**7,1**	10	**11,0**
GRAM-NEGATIVE	**74**	**20,1**	**88**	**27,1**	**73**	**34,6**	**38**	**41,6**
E. coli	**41**	**11,2**	**58**	**17,9**	**55**	**26,1**	**28**	**30,8**
Klebsiella	10	**2,7**	7	**2,1**	7	**3,3**	4	**4,4**
H. influenzae	**3**	**0,82**	6	**1,8**	4	**1,9**	1	**1,1**
Enterobacter	3	**0,82**	3	**0,9**	3	**1,4**	2	**2,2**
Other	17	**4,6**	14	**4,3**	4	**1,9**	3	**3,2**
Candida sp	—	**—**	3	**0,9**	3	**1,4**	—	**—**
Ureaplasma U.	—	**—**	—	**—**	1	**0,5**	—	**—**
Enterovirus	—	**—**	1	**0,3**	—	**—**	—	**—**

pite prophylaxis against GBS infection, sepsis caused by *E. coli* has remained stable[12] with an incidence of 0,3 per 1.000 live births[9] (figure 2).

Because neonatal sepsis presents with non-specific clinical manifestations, particularly in preterm newborns that may be asymptomatic, **diagnostic suspicion** may be based on the presence of risk factors for *infection of vertical transmission*. The presence of bacterial pathogens in the maternal genital tract is the main risk factor, with other indirect risk factors, such as spontaneous premature labor, premature and/or prolonged rupture of membranes (more than 18 hours before delivery) and/or chorioamnionitis (maternal fever, pain in the lower abdomen and/or foul-smelling amniotic fluid). Moreover, history of maternal bacteriuria (symptomatic or asymptomatic) caused by GBS during pregnancy (probably as an expression of intense maternal colonization), as well as a previous offspring with GBS neonatal sepsis are also risk factors for infection of vertical transmission, because in both circumstances it is interpreted that there is a deficiency of maternal antibodies against GBS, so that decreased specific immune defenses in the newborn will make neonates more susceptible to this type of infections[2].

Diagnostic confirmation of sepsis of vertical transmission requires the following criteria:[2] clinical signs of sepsis, laboratory abnormalities with altered hemogram (leukopenia or leukocytosis, immature to mature leukocyte ratio >0,2, immature to total neutrophil ratio >0,16, thrombocytopenia, etc.) and C-reactive protein >10 mg/L, and positive blood culture. For infection episodes occurring after 3 days of life, diagnostic confirmation requires positive blood culture of traditional pathogens of vertical transmission of infection (GBS, *E. coli)* and isolation of the same pathogen in maternal vaginal exudates or in peripheral exudates of the newborn taken during the first day of life. *Vertical clinical sepsis* is defined in the presence of clinical signs, abnormal hemogram and C-reactive protein, isolation of traditional pathogens of vertical transmission in the maternal vaginal exudates and peripheral exudates from the newborn, and negative blood culture[2].

If sepsis of vertical transmission is suspected, empirical **treatment** with ampicillin and gentamicin, the antimicrobial spectrum of which covers the main causative pathogens, should be started[2]. In case of suspicion of associated meningitis, treatment with ampicillin and cefotaxime at the doses shown in table 2 should be administered. After confirmation of sepsis by culture growth, antibiotic treatment should be based on results of antimicrobial susceptibility testing. In addition to antimicrobial therapy, supportive measures are needed (mechanical ventilation, vasoactive drugs, diuretics and/or hemofiltration procedures, etc.). The duration of treatment should not be shorter than 10 days; however, in our experience, length of treatment may be reduced according to the time course of serum C-reactive protein, so that the administration of antibiotics could be discontinued when two normal values (<10 mg/L) are obtained with an interval of at least 48 h.

In our experience, **mortality** has remained stable with a decreasing trend (between 8,7% in 1996 and 5,3% in 2003) and significant differences in relation to birthweight (mortality rate, >25% in newborn babies weighing <1.500 g)[2, 8]. In general, sepsis of vertical transmission caused by Gram negative pathogens have a higher mortality[1]. Mortality of GBS neonatal sepsis is currently lower than 5%[9, 11].

Clinical trials carried out in the 80's have demonstrated that intrapartum administration of antibiotics in a GBS colonized mother prevented invasive neonatal disease, and that culture of rectovaginal exudates between 35 and 37 weeks of gestation was able to identify women susceptible to receive antibiotic **prophylaxis**[13]. In 1996, consensus guidelines for the prevention of perinatal GBS disease were issued by the American College of Obstetricians and Gynecologists, and the American Academy of Pediatrics and the Centers for Disease Control (CDC), which have been recently revised[14]. In the United States, wider use of

Table 2. Dosage schedule for antibiotics frequently used in newborn infants.

Dosage schedules (mg/kg/dose)					
		Birth weight < 2000 g		*Birth weight >2000 g*	
ANTIBIOTIC	*Route*	*Age: 0-7 days*	*>7 days*	*0-7 days*	*>7 days*
Penicillin G*	IV	250.000 U/12 h	Igual/8 h	Igual/8 h	Igual/6 h
Ampicillin*	IV, IM	25/12 h	25/8 h	25/8 h	25/6 h
Oxacillin	IV, IM	25/12 h	25/8 h	25/8 h	25/6 h
Mezlocillin	IV, IM	75/12 h	75/8 h	75/12 h	75/8 h
Nafcillin	IV, IM	25/12 h	25/8 h	25/8 h	25/6 h
Cephalotin	IV	20/12 h	20/8 h	20/8 h	20/6 h
Cefazolin	IV, IM	20/12 h	20/8 h	20/8 h	20/6 h
Cefotaxime	IV, IM	50/12 h	50/8 h	50/12 h	50/8 h
Moxalactam	IV, IM	50/12 h	50/8 h	50/12 h	50/8 h
Ceftriaxone	IV	50/24 h	50/24 h	50/24 h	75/24 h
Ceftazidime	IV, IM	50/12 h	50/8 h	50/8 h	50/8 h
Gentamicin**	IV, IM	2,5/12 h	2,5/8 h	2,5/12 h	2,5/8 h
Tobramycin**	IV, IM	2/12 h	2/8 h	2/12 h	2/8 h
Amikacin**	IV, IM	7,5/12 h	7,5/8 h	10/12 h	10/8 h
Netilmicin**	IV, IM	2,5/12 h	2,5/8 h	2,5/12 h	2,5/8 h
Erythromycin	PO	10/12 h	10/8 h	10/12 h	10/8 h
Ticarcillin	IV, IM	75/12 h	75/8 h	75/8 h	75/6 h
Vancomycin	IV	10/12 h	10/8 h	15/12 h	10/8 h
Clindamycin	IV, IM, PO	5/12 h	5/8 h	5/8 h	5/6 h
Metronidazole	IV, PO	7,5/24 h	7,5/12 h	7,5/12 h	15/12 h
Aztreonam	IV, IM	30/12 h	30/8 h	30/8 h	30/6 h
Imipenem	IV	25/12 h	25/8 h	25/12 h	25/8 h

IV: intravenous. **IM:** intramuscular. **PO:** oral. * In meningitis double dose. ** In <1.200 gr. every 18-24 hours. Appropriate dosage schedule should be based on serum concentration measurements.

prophylactic intrapartum antibiotics resulted by a significant decrease of 65% in the incidence of early-onset GBS neonatal infection (from 1,7 per 1.000 live births in 1993 to 0,6 per 1.000 births in 1998)[11]. In Spain, recommendations for the prevention of perinatal GBS disease were published in 1998, and the implementation of these guidelines has been followed by a significant decrease of 55% in overall sepsis of vertical transmission and 75% for GBS neonatal sepsis[9]. These guidelines have been also recently revised[15] and are summarized in table 3.

The first-choice antibiotic for intrapartum prophylaxis is intravenous penicillin G 5 million units as initial dose at the beginning of labor, and to repeat 2,5 million units every 4 h until

Table 3. Spanish recommendations for prevention of perinatal GBS disease.

Recommendation of universal prenatal screening for vaginal and rectal GBS colonization of all pregnant women at 35-37 weeks' gestation.
Intrapartum prophylaxis is indicated:
1. Positive GBS screening culture during current pregnancy (≤5 weeks previous delivery)
2. GBS bacteriuria during current pregnancy regardless of the colonization status of the mother (vaginal and rectal screening is not necessary).
3. Women who have previously gave birth to an infant with invasive GBS disease (vaginal and rectal screening is not necessary).
4. If the result of GBS culture is not known the onset of labour, intrapartum prophylaxis should be administered to women with any of the following risk factors: gestation <37 weeks, duration of membrane rupture ≥18 hours, or a temperature ≥38 ºC.
Intrapartum prophylaxis is not indicated:
1. Women with negative vaginal and rectal GBS screening cultures within 5 weeks of delivery even if obstetric risk factors develop.
2. Women with not Known vaginal and rectal GBS screening and without obstetric risk factors.
3. Women undergoing planned cesarean deliberéis in the absence of labour or amniotic membrane rupture, regardless of the colonization status of the mother.

the end of delivery. When penicillin is not available, intravenous ampicillin, 2 g at the beginning of labor with 1 g every 4 h thereafter is the second-choice treatment. In case of *allergy to beta-lactam antibiotics,* intravenous clindamycin, 900 mg every 8 h or intravenous erythromycin 500 mg every 6 h until the end of delivery is recommended.

NOSOCOMIAL NEONATAL SEPSIS

Nosocomial (hospital-acquired) sepsis are caused by pathogens found in the Neonatology Services especially in NICUs and, therefore, risk factors favoring the development of these infections[4] are as follows:

1. Overuse of antibiotics and the shortage of health care personnel resulting in difficulties to adhere to cleaning protocols, which determines permanence and diffusion of bacterial pathogens.
2. Insufficient hand washing and disinfection is the main cause of contamination, although the use of insufficiently disinfected material (thermometers, stethoscopes, catheters, incubators, etc.) used for diagnostic or treatment purposes is also an important route of infection. Contamination of respiratory mucosa is frequently secondary to intratracheal intubation, intratracheal aspiration, and mechanical ventilation. Risk factors for the contamination of the gastrointestinal mucosa include the use of inadequately disinfected nasogastric tubes, contaminated feeding-bottle nipples and/or nutritional formulas prepared without adequate cleaning measures.
3. When the newborn becomes contaminated, bacterial pathogens proliferate, cross the cutaneous-mucosal barrier and enter the circulating blood. In this respect, arterial and venous punctures and, particularly the use of invasive catheters for intravenous feeding, are major risk factors for bloodstream infection.
4. Once in the blood, bacterial proliferation follows a logarithmic growth and the development of infection will depend on the infecting organism (more easy in case of *Sta-*

phylococcus epidermidis, E. coli, Candida spp.) and the infant's defense mechanisms, which are impaired in case of prematurity (less IgG, complement and cytokines, lesser capacity of neutrophil and macrophage mobilization, etc.).

The **frequency** of nosocomial sepsis reported in different clinical series is variable. Some studies refer only to the incidence of nosocomial sepsis in neonates weighing, <1.500 g, others to sepsis in neonates admitted to the NICU, most studies exclude nosocomial sepsis in infants older than 1 month of age[16, 17], and finally the identification of nosocomial sepsis witn late-onset sepsis (>3 days or >7 days of life)[16] accounts for the exclusion of early-onset nosocomial sepsis (disease onset at <3-7 days of life) and the inclusion of late-onset sepsis of vertical transmission[3]. Taking into account these differences and in order to assess the real incidence of these infections, a study of the «*Grupo de Hospitales Castrillo*» analyzed the frequency of sepsis including all episodes in infants admitted to the participating hospitals independently of the birthweight, site of care (NIUC, intermediate care units, etc.) and age at the onset of symptoms (sepsis in infants older than 28 days of life were included). In this study, nosocomial sepsis was defined as onset of disease after the 3rd day of life, although early-onset nosocomial sepsis (before the 3rd day of life) was also included and late-onset sepsis of vertical transmission excluded. According to this criteria and in a total of 30.993 newborn infants admitted to the participating hospitals, 730 cases of nosocomial sepsis (2,3 %) in 663 infants (2,1 %) were diagnosed (0,89 per 1.000 days of hospital stay) (table 4). It should be noted that the frequency of nosocomial sepsis was higher in newborn infants weighing <1.500 g than in those with a birthweight ≥1.500 g (15,5 % *vs* 1,16 %) and in infants admitted to tertiary care hospitals (table 4).

It is well established that low birthweight is the main **risk factor** for nosocomial sepsis. In different series published in the literature, frequencies higher than 20 % in neonates weighing <1.500 g have been reported[16, 18, 19]. Risk factors include immaturity of the immune system, greater use of invasive procedures (table 4), increase of pathogens in NICUs, and longer stay in the hospital increasing the risk per patient/day.

The overall **etiology** of nosocomial sepsis in the study of «*Grupo de Hospitales Castrillo*»[3] was similar to that reported in other series[17] with *S. epidermidis* (42 %) as the most frequent causative organism followed by *Candida* spp. (11,5 %), *E. coli* (7,8 %), *Enterococcus* (7,7 %) and *Klebsiella* spp. (7 %) (table 5). Sepsis caused by *Candida* sp. were more common in infants weighing <1.500 g ($P < 0,001$) and sepsis caused by *E. coli* and *Enterobacter* in infants weighing ≥1.500 g ($P < 0,05$)[3] (table 5).

Clinical features of nosocomial neonatal sepsis are similar to those described for sepsis of vertical transmission, although it should be noted that bloodstream infections caused by *Candida* spp. have a slower progression and more insidious clinical course, and sepsis caused by *S. epidermidis* are more frequent in preterm babies carriers of invasive catheters[3].

The **diagnosis** is based on clinical signs and symptoms, abnormal hemogram, serum C-reactive protein concentration >10 mg/mL and positive blood culture (it is recommended to drawn a minimum of 1 mL of blood). In case of *S. epidermidis,* —an ubiquitous commensal of the human skin that may contaminate the blood at the time of blood sampling—, two consecutive positive cultures in different blood samples, or a positive culture of peripheral blood and catheter tip at the time of catheter removal are required for the diagnosis of sepsis. In preterm babies in whom two blood samples are very difficult to obtained, a single peripheral puncture with blood sampling using two different extraction equipments and seeding of samples in two bottles, with isolation of the same *S. epidermidis* strain (similar antibiotic susceptibility pattern) can be accepted. In doubtful cases between contamination and infection, identification of pathogens can be performed using molecular techniques.

Table 4. Incidence of nosocomial sepsis in neonates according to weight at birth, type of hospital, and presence of risk factors.

Data	*N.º admissions**	*Infants with sepsis (%)*	*Sepsis per 1.000 patient days*	*<1.500 g n = 362 n*	*≥1.500 g = 368*
N.º patients	30,993	662 (2,1)♦	0,89	—	—
Birth weight					
<1500 g	2,088	326 (15,6)◉	2,5	—	—
≥1500 g	28,905	336 (1,16)	0,55	—	—
Type of hospital					
Tertiary care	25,538	604 (2,36)◉	—	—	—
Non-referral	5,455	58 (1,06)	—	—	—
Risk factors					
Percutaneous venous catheter	—	—	—	330 (91,2)	257 (69,8) ◉
Intravenous feeding	—	—	—	300 (82,9)	217 (59,0)◉
Previous antibiotics	—	—	—	281 (77,6)	237 (64,4) ◉
Mechanical ventilation	—	—	—	276 (76,2)	187 (50,8) ◉
Intravenous lipid therapy	—	—	—	211 (58,3)	130 (35,3) ◉
Previous surgery	—	—	—	35 (9,7)	125 (34,4) ◉
Two or more risk factors	—	—	—	348 (96,1)	290 (78,8) ◉

* Infants admitted to neonatal units of the participating hospitals including neonatal intensive care units or special care nurseries.
♦ There were 730 episodes of sepsis in 662 neonates.
◉ $P < 0,001$.

Treatment is based on the immediate administration of antibiotics as soon as sepsis is suspected (empirical treatment) followed by directed antimicrobial agents according to results of antibiotic susceptibility testing for pathogens isolated from the blood cultures. Recommended empirical therapy includes combined treatment with ampicillin and an aminoglycoside or a third-generation cephalosporin (depending on the epidemiology of each particular Neonatal Service), and in neonates with invasive catheters, ampicillin should be substituted by vancomycin or teicoplanin at doses shown in table 2, although CDC guidelines recommends avoiding empirical vancomycin to prevent the development of vancomycin-resistant *Enterococcus* strains and, for this reason, cloxacillin associated with an aminoglycoside could be an alternative[21]. Another controversial issue is the removal of the catheter in the presence of sepsis. Although in sepsis caused by *Candida* spp. it is accepted to remove the catheter and to wait until at least 4 days of antifungal treatment have been completed before insertion of another catheter[22], there is more variability in the recommendations for patients with bacteremia[23]. As in case of neonatal sepsis of vertical transmission, complex supportive measures may be required (vasoactive drugs, mechanical ventilation, hemofiltration procedures, etc.) and regarding other therapeutic possibilities, treatment with intravenous immunoglobulins is not effective[24] and granulocyte colony stimulating factor (G-CSF) or granulocyte-macrophage colony stimulating factor (GM-CSF) although contributes to decrease mortality in patients with leukopenia, further clinical trials are needed before recommendation of their use can be generalized[25].

Table 5. Distribution of causative pathogens in 730 cases of neonatal sepsis.

Organism	*Total (%)*	*< 1500 g n = 362*	*≥ 1500 g n = 368*	*< 28 days n = 646*	*≥ 28 days n = 84*
Gram-positive	432 (58,4)	205 (55,5)	227 (61,3)	386 (59,0)	46 (54,7)
S. epidermidis	310 (42,0)	156 (42,3)	154 (41,6)	277 (42,3)	33 (39,3)
Enterococcus	57 (7,7)	28 (7,6)	29 (7,8)	49 (7,5)	8 (9,5)
S. aureus	31 (4,2)	11 (3,0)	20 (5,4)	29 (4,4)	2 (2,4)
Other CON	9 (1,2)	4 (1,1)	5 (1,3)	8 (1,2)	1 (1,2)
S. viridans	14 (1,9)	1 (0,3)	13 (3,5)*	14 (2,1)	
Other	11 (1,5)	5 (1,3)	6 (1,6)	9 (1,4)	2 (2,4)
Gram-negative	218 (29,5)	105 (28,5)	113 (30,5)	192 (29,3)	26 (31,0)
E. coli	58 (7,8)	21 (5,7)	37 (10,0)♦	53 (8,1)	5 (6,0)
Klebsiella	51 (7,0)	28 (7,6)	23 (6,2)	45 (6,9)	6 (7,1)
Pseudomonas	36 (4,8)	21 (5,7)	15 (4,0)	30 (4,6)	6 (7,1)
Enterobacter	28 (3,8)	8 (2,2)	20 (5,4)♦	24 (3,6)	4 (4,8)
Serratia	14 (1.9)	9 (2,4)	5 (1,3)	11 (1,7)	3 (3,5)
Other	31 (4,2)	18 (4,9)	13 (3,5)	29 (4,4)	2 (2,4)
Fungus					
Candida spp.	85 (11,5)	57 (15,4)◉	28 (7,5)	74 (11.3)	11 (13,1)
Other	4 (0,5)	2 (0,5)	2 (0,5)	3 (0.4)	1 (1,2)

CON: coagulase-negative staphylococci. Dual pathogens in 9 cases.
Absolute numbers with percentages in parenthesis.
*$P < 0{,}001$; ♦$P < 0{,}05$; ◉$P < 0{,}01$ between <1.500 g and ≥1.500 groups.

Currently, nosocomial infections are the leading cause of **mortality** in Neonatology Services[4]. In the study of «*Grupo de Hospitales Castrillo*», 78 deaths in 662 newborns with nosocomial sepsis (11,8%) were recorded. Mortality was significantly higher in neonates weighing <1.500 g than in those weighing ≥1.500 g (17,3% *vs* 6,5%, $P < 0{,}001$) and in sepsis caused by *Pseudomonas* compared with other pathogens (33% *vs* 9,4%, $P < 0{,}001$), whereas sepsis caused by *S. epidermidis* showed a lower mortality (5,5% *vs* 14,2%, $P < 0{,}001$).

Considering the frequency and mortality of nosocomial infections, maximal efforts should be directed to **prophylaxis** and in this respect, a large number of preventive strategies have been recommended, including early withdrawal of antibiotic treatment when infection is not confirmed, implementation and surveillance of cleaning and/or sterilization protocols of diagnostic and/or therapeutic material, achievement of an adequate number of health care personnel, and large enough facilities to prevent overgrowth and permanence of pathogen organisms[26-28]. However, *adequate washing of the hands before manipulation of neonates*[26-28] and the use of clean and sterile material are the most effective measure to prevent contamination of the infant by pathogen organisms. Other additional measures include favoring early enteral feeding[26, 27], reduction of days of parental feeding, length of

time with catheters in place, and use of sterile techniques for the insertion of invasive lines and manipulation of catheter connections[29]. Although all these measures are very important, they would not be sufficiently effective if the health care personnel is not convinced through periodic informative session that nosocomial infections can be and should be avoided as well as how to prevent them.[4] It is also important to develop prospective surveillance systems of the infection rates, causative microorganisms and possible antibiotic resistance in episodes of sepsis diagnosed in the last months, making this information available to all personnel of the unit in informative sessions in order to discuss possible epidemiological factors involved and to facilitate the implementation of effective «good medical practices»[4]. Applying these criteria, Kilbride et al.[24] in a prospective multicenter study, achieved a reduction of the rates of nosocomial neonatal sepsis from 24,6% to 16,4%.

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CHAPTER
47

Anemia and coagulation disorders in neonatal period

NEWBORN

M. Stanojevic

INTRODUCTION

Newborn infant lives in Mount Everest conditions in utero. The PO_2 in blood delivered to the tissues is only one-third to one-fourth the value in adults. This relative hypoxia may be responsible for the increased erythropoietin content with resultant increased number of reticulocytes in newborns at birth. The compensatory mechanisms of such hypoxic condition are increased number of erythrocytes, increased concentration of fetal hemoglobin with decreased oxygen affinity, and relative tachycardia. Within 72 hours of birth erythropoietin is undetectable, while reticulocytes count decreases significantly. Normal hemoglobin, hematocrit, mean corpuscular volume (MCV) and reticulocyte values in newborns of different gestations and different postnatal ages are given in the table 1[1, 2, 3].

The placenta contains approximately 100 mL of fetal blood 25% of which enters the newborn in 15 s of birth if newborn when delivered is placed bellow the level of placenta, while 50% of placental blood riches the newborn by one minute[1, 2, 3]. Therefore umbilical cord clumping affects the blood volume in newborns, which can be increased by up to 15%. Delay in cord clamping of 2 minutes could help prevent iron deficiency at 6 months of age, when iron-fortified complementary foods could be introduced[4, 5, 6]. Delaying cord clamping by 30 to 120 seconds, rather than early clamping, seems to be associated with less need for transfusion and less intraventricular haemorrhage[6]. It is estimated that blood volume in term infants is around 50 to 100 ml/kg, mean 85 ml/kg[1, 2, 3]. The blood volume in preterm infants is slightly greater than in term newborns due to an increased plasma volume, while the erythrocyte mass expressed in ml/kg is the same as in term newborns[1, 2, 3].

Although there is a general believe that newborn is more prone to thrombosis than to hemorrhage, hemorrhagic disorders are very common in neonatal period[7]. The separation process of the newborn and the mother is connected with many risks, among which impaired hemostasis in newborns is significant[7]. In term newborns vascular phase of hemostasis is very similar to that in adults, while function of platelets and coagulation factors is

Table 1. Norma hemoglobin and hematocrit values in newborns of different gestational and postanatal age (changed and adapted from 2).

Age	*Hemoglobin (g/dL)*	*Hematocrit (%)*	*MCV (μ^3)*	*Reticulocytes (%)*
Gestational weeks				
26-27	19,0 ± 2,5	62 ± 8	132 ± 14,4	9,6 ± 3,2
28-29	19,3 ± 1,8	60 ± 7	131 ± 13,5	7,5 ± 2,5
30-31	19,1 ± 2,2	60 ± 8	123 ± 15,7	5,0 ± 1,9
32-33	18,5 ± 2,0	60 ± 8	123 ± 15,7	5,0 ± 1,9
34-35	19,6 ± 2,1	61 ± 7	122 ± 10	3,9 ± 1,6
36-37	19,2 ± 1,7	64 ± 7	121 ± 12,5	4,2 ± 1,8
38-40	19,3 ± 2,2	61 ± 7	119 ± 9,4	3,2 ± 1,4
Postnatal (days)				
1	1,0 ± 2,2	61 ± 7	119 ± 9,4	3,2 ± 1,4
3	18,7 ± 3,4	62 ± 9	116 ± 5,3	2,8 ± 1,7
5	17,6 ± 1,1	57 ± 7	114 ± 7,5	1,8 ± 1,1
7	17,9 ± 2,5	56 ± 9	118 ± 11,2	0,5 ± 0,4
Postnatal (weeks)				
1-2	17,3 ± 2,3	54 ± 8	112 ± 19,0	0,5 ± 0,3
2-3	15,6 ± 2,6	46 ± 7	111 ± 8,2	0,8 ± 0,6
3-4	14,2 ± 2,1	43 ± 6	105 ± 7,5	0,6 ± 0,3

impaired. Coagulation is the most sensitive part of hemostatic process, because most of coagulation and anticoagulation factors do not cross the placenta, which means that newborn is dependent on intrinsic synthesis of coagulation as well as anticoagulation factors[7]. On the other hand newborns are vitamin K deficient, which means that vitamin K dependent coagulation factors (II, VII, IX, X), even if present in sufficient concentration, are not activated due to the lack of their carboxylation, for which vitamin K is mandatory co-factor[7]. Coagulation and anticoagulation proteins appear at the 11th week of gestation, while their activity reaches adult levels mostly postnatally from 2 to 12 months[7]. Concomitant development of hemostasis and fibrinolysis prevent occurrence of intravascular coagulation, enabling free blood flow in the fetoplacental microcirculation[7]. Although the platelet function is immature, and the activity of vitamin K dependent coagulation factors is decreased, coagulation time in newborns is decreased or normal probably due to the decreased concentration of coagulation inhibitors as antithormbin III, protein C and heparin cofactor II[7]. Diagnostic tests for follow up of the newborn hemostasis and coagulation are related to adults, which should always be kept in mind when interpreting the results of coagulation tests which should always be correlated with clinical picture[7]. Hematocrit affects the results of coagulation tests, because it can influence the ratio between citrate and blood which in adults is 9:1, and in newborns it is different due to the higher hematocrit values[7].

ANEMIA IN THE NEWBORN PERIOD

Anemia is a deficiency in the concentration of erythrocytes and hemoglobin in the blood resulting in decreased ability of erythrocytes to transport oxygen to the tissues. Anemia is also defined as hemoglobin and hematocrit values below two standard deviations of the mean for postnatal and/or postconceptual age[1, 2, 3]. Anemia in the newborn results at least from one or more of the following basic mechanisms[1, 2, 3]:

- Acute or chronic blood loss.
- Decreased erythrocyte production.
- Shortened erythrocyte survival.

Etiologies of blood loss in the neonates are given in the table 2, while the etiologies of shortened erythrocyte life span are given in the table 3[1, 2, 3]. Drugs and chemicals shown to cause clinical significant hemolysis in infants with glucose 6 phosphate deficiency (G6PD) are presented in table 4[8]. G6PD can lead to an increased risk and earlier onset of hyperbilirubinemia, which may require phototherapy or exchange transfusion[8]. In some populations hyperbilirubinemia due to G6PD results in an increased rate of kernicterus and death[8]. Signs and symptoms of anemia in the newborn are shown in the table 5[1, 2, 3]. Laboratory tests and their meaning in anemic newborns are given in the table 6[1, 2, 3]. Figure 1 shows clinical decision tree in evaluation of anemia in newborns. As in any condition in neonatal period, the most important for the diagnosis are history and physical examination, while determination of total blood count (TBC) with differential and platelets is very helpful[9]. If reticulocyte count is low, than one should suspect underproduction of erythrocytes connected in most cases with infection and/or under nutrition, while other causes as congenital hypoplastic anemia and congenital leukemia are rare[1, 2, 3, 9]. If reticulocyte count is normal or high, than bilirubin, smear of the peripheral blood, and maternal and infant blood types should be performed.

Treatment of anemia is transfusion of packed erythrocytes when indicated. Indications for packed erythrocyte transfusion are given in the table 7[9, 10, 11].

Tests before transfusion include[1, 2, 3, 10, 11]:

- Patient's ABO and Rh group in order to provide ABO and Rh compatible blood.
- Having in place an independent Check Group System so that blood is not released for the patient before group is checked.
- Screening the maternal sample with cross matching.

Performing the transfusion[10] in stable preterm infants:

- Give packed red cells 20 ml/kg over 4 hours with furosemide 1 mg/kg IV at the beginning of transfusion.
- For acute blood loss: give whole blood or packed red cells 20 ml/kg or volume of estimated blood loss titrated to infants' response to transfusion (correction of tachycardia).
- Use CMV negative blood whenever possible.
- Use irradiated blood whenever possible especially for very low birth weight newborns.

Table 2. Etiologies of blood loss in the neonate[1, 2, 3].

I. Hemorrhage before birth	A. Fetomaternal. 1. Traumatic amniocentesis or perium-bilical blood sampling. 2. Spontaneous. 3. Chronic gastrointestinal. 4. Blunt trauma of maternal abdomen.	5. Postexternal positioning. B. Twin to twin transfusion syndrome. C. External. 1. Abruptio placentae. 2. Placenta praevia.
II. Hemorrhage during birth	A. Hematoma of the placenta or cord. B. Rupture of a normal or an abnormal umbilical cord. 1. Precipitous delivery. 2. Entaglement. 3. Varices. 4. Aneurysm.	C. Rupture of anomalous vessels. 1. Aberrant vessel. 2. Velamentous insertion of the cord. 3. Communicating vessel in the multi-lobular placenta. D. Incision of placenta during cesarean section. E. Placental malformation.
III. Internal fetal or neonatal hemorrhage	A. Intracranial. B. Cephalhematoma. C. Subcapsular liver or spleen.	D. Renal or adrenal. E. Pulmonary. F. Retroperitoneal.
IV. External neonatal hemorrhage	A. Deleyed clamping of the umbilical cord. B. Gastrointestinal. C. Iatrogenic from frequent blood sampling.	

Table 3. Etiologies of shortened red cell survival[1, 2, 3].

I. Isoimmune-mediated hemolysis	A. Rh incompatibility. B. ABO incompatibility.	C. Minor blood cell antigen incom-patibility.
II. Infection	A. Bactrial/viral sepsis. B. TORCH infections.	C. Parvo B 19. D. HIV.
III. Microangiopathic and macroangiopathic	A. Renal vein thrombosis. B. Disseminated intravascular coagulation. C. Severe coarctation of the aorta.	D. Renal artery stenosis. E. Cavernous hemangioma (Kasabach-Merritt syndrome).
IV. Vitamin E deficiency		
V. Congenital RBC membrane disorders	A. Hereditary spherocytosis. B. Hereditary elliptocytosis.	C. Infantile pyknocytosis.
VI. Congenital RBC enzyme disorders	A. Glucose 6-phosphate deficiency (G6PD).	B. Pyruvate kinase deficiency.
VII. Congenital hemoglobinopathies	Alpha and gamma thalassemia.	
VIII. Metabolic	A. Galactosemia. B. Organic acyduria, orotic acyduria.	C. Prolonged or recurrent acidosis.
IX. Liver disease		

Table 4. Drugs and chemicals clearly shown to cause clinically significant hemolytic anemia in G6PD[8].

Drug name	*Use*
Dapsone	Antimicrobial for treatment of leprosy.
Flutamide	Antiandrogen for treatment of prostate cancer.
Mafenide cream	Topical antimicrobial.
Methylene blue	Antidote for drug-induced methemoglobinemia.
Nalidixic acid	Antibiotic used primarily for urinary tract infections.
Nitrofurantoin	Antibiotic used primarily for urinary tract infections.
Phenazopyridine	Analgesic for treatment of dysuria.
Primaquine	Antimalaria agent.
Rasburicase	Adjunct to antineoplastic agents.
Sulfacetamide	Sulfonamide (ophthalmic and topical preparations).
Sulfamethoxazole	Sulfonamide used in combination preparations.
Sulfanilamide	Antifungal agent for treatment of vulvovaginitis.

Table 5. Signs and symptoms of anemia in the neonate[1, 2, 3].

Acute anemia *(with acute hemorrhage anemia may not be present initially; hemodilution will develop in 3 to 4 hours)*	***Chronic anemia*** *(may be well compensated)*
• Hypovolemia and hypotension. • Tachycardia. • Hypoxemia and tachypnea.	• Pallor, metabolic acidosis, poor growth. • High output congestive heart failure. • Persistent or increased oxygen requirement. • Iron deficiency with hypochromia, microcytosis.

Table 6. Laboratory tests and their meaning in anemic newborn[1, 2, 3].

Characterization	*Test*	
Blood loss	• Kleihauer-Betke on maternal sample.	
Bone marrow production	• Reticulocyte count. • Platelet and white blood cell count. • T3, T4, TSH.	• Erythropoietin level. • Bone marrow aspirate and biopsy. • Fetal hemoglobin, MCV.
Iron deficiency	• Ferritin, iron, and iron binding capacity.	
Antibody mediated	• Maternal and infant blood type. • Direct and indirect Coombs' test.	
Hemolysis	• Bilirubin. • Coagulation tests (if sepsis or liver disease is suspected).	• Osmotic fragility, specific determinations of red cell membrane proteins, enzymes, hemoglobin, and ceruloplasmin as indicated.
Infection	• Culture and serologies as appropriate.	
Microangiopathy, macroangiopathy	• Disseminating intravascular coagulation screen.	
Vitamin E deficiency	• Vitamin E level.	
Metabolic disorders	• pH, lactate, pyruvate, galactosemia screen.	

TSH Thyroid stimulating hormone, MCV mean corpuscular volume.

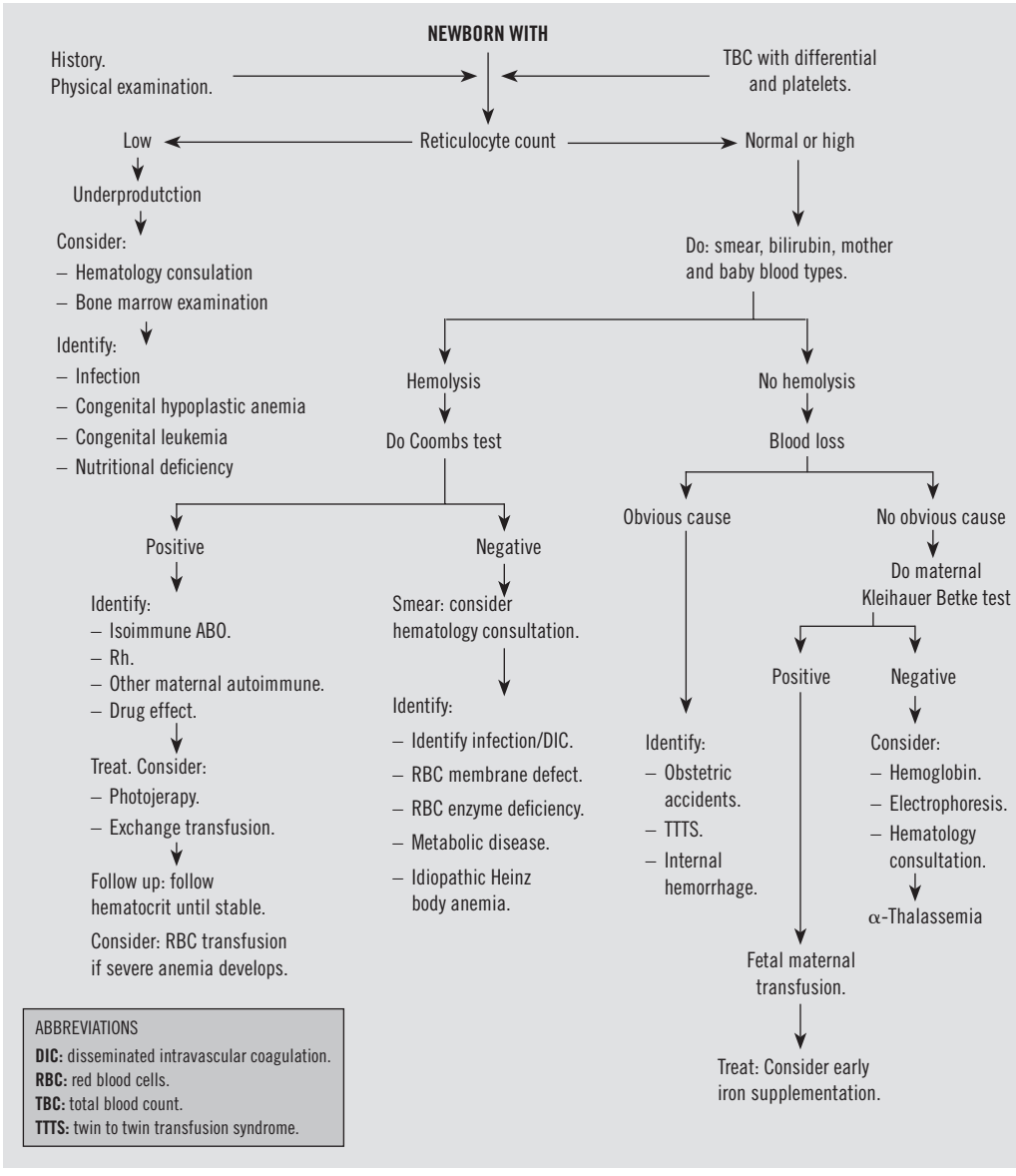

Figure 1. Approach to the anemic newborn[9].

Table 7. Transfusion criteria for the term neonate[13].

In the newborn with evidence of respiratory distress, transfusion is required for:	A hematocrit < 35 %-40 %. Clinical evidence of hypovolemia. Pallor.	Tachypnea. Hypotension. Inadequte perfusion.
In the newborn without evidence of respiratory distress transfusion is required for:	A hematocrit <30 % in the first week of life or in an infant requiring surgery. Tachycardia, tachypnea, significant apnea, or cardiomegaly on radiograph. Poor weight gain with hematocrit <30 %.	

Results of the liberal versus restricted guidelines for red blood cell transfusion are conflicting in low birth weight premature infants[10, 11]. Although it seams that it is more plausible to transfuse every symptomatic newborn with higher red blood cell volumes whenever possible, this problem needs to be further investigated[10, 11]. Hematocrit falls after birth in preterm infants due to physiological factors and frequent blood sampling. Low plasma levels of erythropoietin (EPO) in preterm infants provide a rationale for the use of EPO to prevent or treat anemia[12]. The effectiveness and safety of early (before 8 days after birth) versus late (between 8-28 days after birth) EPO treatment was assessed and it was concluded that the use of early EPO did not significantly reduce the primary outcome of «use of one or more red blood cell transfusions», or «number of transfusions per infant» compared to late EPO[12].

Iron deficiency in the neonatal period occurs as a result of chronic blood loss or rapid depletion of limited iron stores[1, 2, 3]. The severity of iron deficiency is increased in rapidly growing premature infants and in infants with lower stores of iron like low birth weight, and infants from multiple pregnancies[1, 2, 3]. They should be given 6 mg/kg/day of elemental iron daily, which will result in reticulocyte rise in 3 to 5 days and hematocrit rise in 2 weeks[1, 2, 3].

COAGULATION DISORDERS

Blood will clot when the blood vessel is injured if coagulation and anticoagulation mechanisms are in equilibrium, which means if concentration of coagulation and anticoagulation factors is appropriate[7]. After the injury platelets will form primary clot adhering to the injured endothelium, which is very complicated «organ» with so many functions in different physiological reactions[7]. The aim of the process is to maintain blood flow through injured vessels without any leakage, disabling at the same time anticoagulation reactions which may cause formation of thrombotic clots and thromboembolism[7]. In the coagulation phase of the process platelets release adenosine diphosphate and other substances which recruit more platelets to the primary clot formation. At the same time tromboxanes produced by the platelet prostaglandin pathway stimulate platelet aggregation, vasoconstriction and decreased local blood flow[7]. Beside platelets, clotting factors are also involved in the process of clot formation[7]. They are activated in the clotting cascade resulting in the formation of stable fibrin clot. Clotting proteins are divided in at lest two groups: dependent on vitamin K, and vitamin K independent factors. The first group consists of coagulation factors II, VII, IX and X, and anticoagulation factors protein C and S. Coagulation factors V, VIII, XIII and fibrinogen are not vitamin K dependent as well as anticoagulation factor antithrombin III[7].

The clotting system is evaluated using a hemostasis screening tests, which include partial thromboplastin time (PTT), prothrombin time (PT), thrombin time (TT), fibrinogen concentration and platelet count[7, 9]. The PTT may be within adult range at term, or may achieve adult levels by 2 months of age[7, 14, 15]. The PTT is near normal at birth, usually slightly prolonged during day 3, and may reach adult values by day 5[7, 24, 15]. Thrombin time is slightly prolonged because of fetal fibrinogen until 3 weeks of age[7, 14, 15]. Fibrinogen and platelet concentrations are within the adult range in stable term and preterm babies[7, 14, 15].

Approach to the bleeding neonate is given in the figure 2[9]. Assessment of any newborn with hemorrhagic complications includes a careful history of maternal illnesses, drug administration, outcome of previous pregnancy and thorough familial history concerning bleeding problems[7, 9]. The fact of neonatal vitamin K prophylaxis should be noted in medical records. Physical examination should include signs of localized versus diffuse blee-

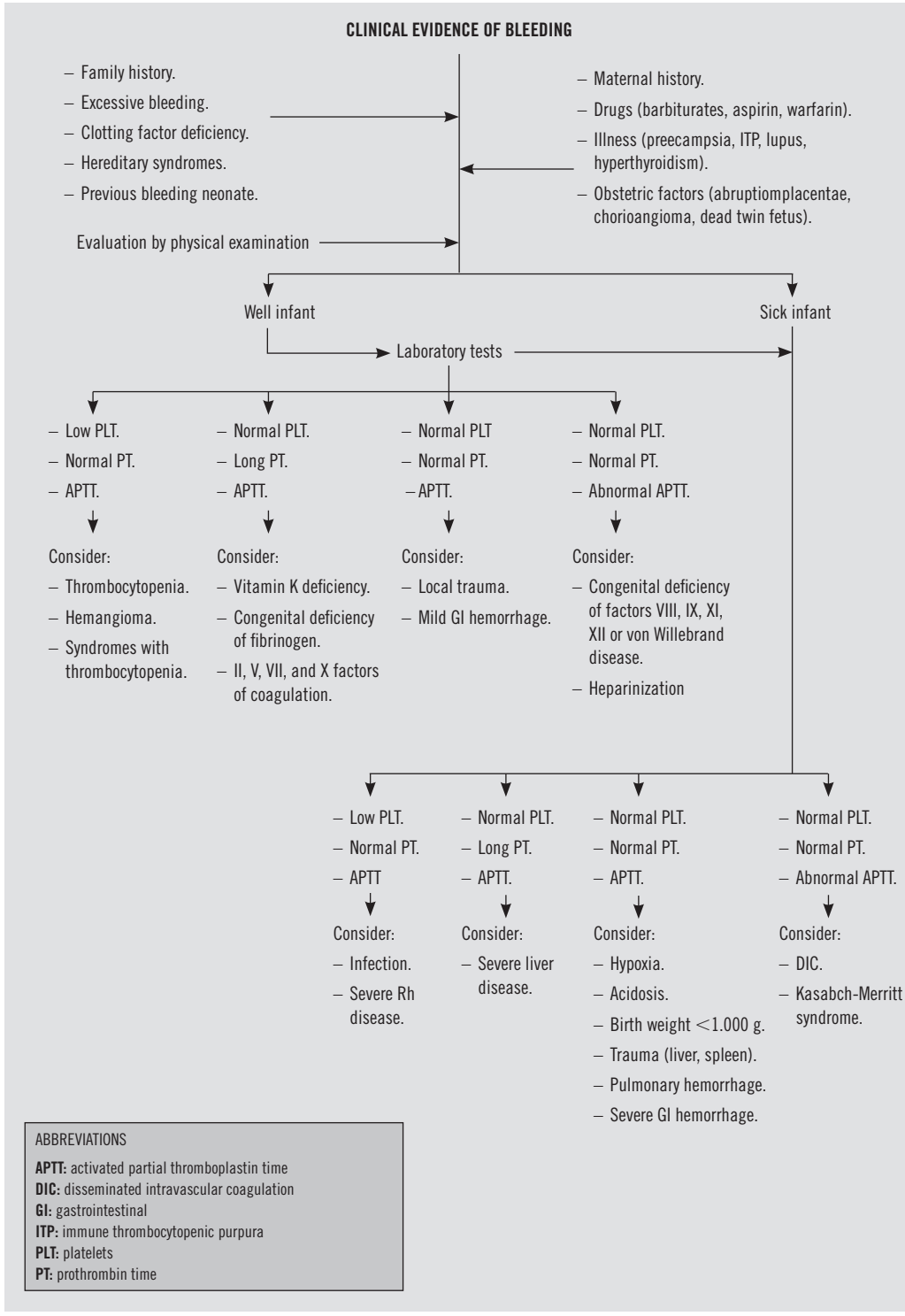

Figure 2. Diagnostic approach to the bleeding neonate[9].

ding, and sick or healthy appearance of the newborn[7, 9]. Vitamin K deficiency and inherited usually coagulation disorders manifest with localized ecchymoses or localized bleeding in apparently healthy newborn. Bleeding due to disseminated intravascular coagulation (DIC) or liver injury are manifest as diffuse bleeding from multiple sites in sick infants[7, 9]. Newborns with isolated decreased platelet count or isolated impaired platelet function have petechie, ecchymoses, or mucosal bleeding[7, 9]. Common bleeding sites in newborns include: umbilicus, the skin, the scalp, mucous membranes, and bleeding after the peripheral blood sampling sites, gastrointestinal, urinary and pulmonary bleeding[7, 9]. In some infants bleeding tendency could manifest as intracranial bleeding, especially as a result of early vitamin K deficiency bleeding (VKDB). Common cause of bleeding could be transplacental passage of a maternal antiplatelet antibody with thrombocytopenia, vitamin K deficiency, and less commonly hereditary coagulation disorders[7, 9].

In a majority of newborns with a hemorrhagic disorder after history and physical examination the working diagnosis should be made, while laboratory workup should include screening tests like PTT, APTT, TT, fibrinogen and platelet count[7, 9]. If all screening tests are normal than deficiency of factor XIII, should be suspected as well as α_2-antiplasmin and plasmin activator inhibitor-factors involved in the fibrinolysis[7, 9]. After screening tests, specific factor assays could be performed if available. The results of the tests should be interpreted with caution, considering possible patophysiological mechanisms of the underlying disease as well as the possibility of pre-laboratory and laboratory mistake. It is very difficult to make a distinction between the hereditary and acquired deficiencies of coagulation factors in the neonatal period[7, 14, 15].

Coagulation disorders in the newborns should be treated with replacement therapy[7]. The treatment of choice is fresh frozen plasma, platelet concentrates (if available), cryoprecipitate or specific factor concentrates (if available)[7]. Sometimes exchange transfusion should be taken under the consideration, especially if underlying cause is sepsis or severe hyperbilirubinemia[7]. If the vitamin K was not given to the newborn as a prophylactic dose, than it should be given as soon as possible in the bleeding neonate, because the frequency of classical vitamin K deficiency bleeding (VKDB) ranges from 0,25% do 1,7%[7, 16]. American Academy of Pediatrics still advocates intramuscular non selective prophylaxis of VKDB in newborns with 1 mg of phylokinone[16].

CONCLUSION

This short overview of anemia and coagulation disorders in neonatal period was not intended to give complete and systematic approach to the topic. This paper gives practical approach to the sick anemic or bleeding newborn, enabling to find possible quick answers to the most frequently appearing clinical situations. The readers are encouraged to read more detailed and systematic reviews in the classical textbooks and other relevant sources.

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CHAPTER 48

Perinatal infections

NEWBORN

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TOXOPLASMOSIS

Congenital toxoplasmosis refers to antenatal infection by the protozoan parasite *Toxoplasma gondii* transmitted to the fetus through the placental. The first acute infection presents with episodes of parasitemia. Thereafter, tissue cysts are formed within host cells being the cause of recrudescent disease in immunocompromised patients. In patients with normal immune response, no further episodes of parasitemia may be expected. Accordingly, transplacental transmission is only possible during the acute stage of infection. The most dangerous period for the fetus ranges between 10 and 24 weeks' gestation, and infections during the first trimester of pregnancy are the most severe.

EPIDEMIOLOGY

The infection is acquired by ingestion of oocysts that may be found in soils or foods contaminated by cat feces, or by ingestion of raw or fresh meat of contaminated animals. Toxoplasmosis is widely spread around the world and the burden of the disease is high.

DIAGNOSIS IN THE PREGNANT WOMAN

The following may be possible:

- IgG (−) and IgM (−): seronegative.
- IgG (+) and IgM (−): old infection.
- IgG (+) and IgM (+): possibility of acute infection. Studies should be completed with avidity of the IgG antibody.

DIAGNOSIS IN THE NEWBORN

Clinical features. According to the time of intrauterine infection, clinical manifestations of sepsis may be present or hepatosplenomegaly, intracranial calcifications and chorioretinitis as sequelae of infection

Laboratory data. Specific IgG and IgM to *T. gondii* (IgG may be maternal but IgM is only from the fetus). Biochemical analyses of cerebrospinal fluid (CSF) with cytological albumin dissociation. Detection of DNA in CSF samples by the polymerase chain reaction (PCR). Cranial radiography and cerebral ultrasound examination, although the brain CT scan is better to visualize calcifications. Fundoscopy is required for the assessment of chorioretinitis.

CONTROL AND TREATMENT OF THE PREGNANT WOMEN

Therapeutic approach is different depending on the results of serological studies:

- **Seronegative.** Prophylactic measures (avoid to each fresh meats or fresh pork sausage except if these have been previously frozen, thoroughly washing of fresh vegetable, avoid cats and especially cat feces, do not manipulate soils without wearing gloves). Serological control at the second and third trimester of pregnancy is recommended.
- **Old infection.** It is not necessary to repeat serological tests.
- **Possible acute infection.** It is necessary to confirm recent infection in the mother by means of avidity of the IgG antibody. Low avidity (<20%) suggests infection in the last few months; in contrast, high avidity (>30%) indicates infection of more than 3-5 months. In the acute stage of the disease, PCR in the amniotic fluid will show whether fetal is present or absent. Assay of *T. gondii* B1 and P30 genes in the amniotic fluid by PCR from 18-20 weeks' gestation has a negative predictive value of 87% and a positive predictive value of 100%.

TREATMENT OF THE NEWBORN

The following treatment schedule should be given alternatively at 4-week intervals:

- Pirimetamine, 1 mg/kg/day, orally; doses can be reduced to 0,5 mg/kg/day after 2 months of treatment.
- Folinic acid, 50 mg, once oral dose every week should be added.
- Sulfadiazine, 100-150 mg/kg/day, orally

  (In order to facilitate dosage, is advisable the use of magistral formulas rather than proprietary medicinal products)

and 4 weeks of:

- Spiramycin, 100 mg/kg/day, orally b.i.d.
- Prednisone, 1-2 mg/kg/day for 30 days may be added in patients with meningitis (abnormal CSF), chorioretinitis, jaundice or severe impairment of the general condition.
- Newborns with symptoms should be treated for 2 years, and asymptomatic infants for 1 year.

CONTROLS

Complete blood cell count with differential every 15 days during the first 2 months; at monthly intervals thereafter. Treatment should be stopped in the presence of neutropenia ($<1.000/mm^3$). Serological tests (IgG and IgM) should be performed at 1, 2, 4, 6, 9, and 12 months.

CONGENITAL SYPHILIS AND INFANT BORN TO A MOTHER WITH SYPHILIS

Syphilis is a chronic systemic infection caused by *Treponema pallidum,* a sexually-transmitted disease. In case of pregnancy, *T. pallidum* may be transmitted to the unborn child, via the placenta. Infants born to mothers with syphilis refer to a newborn whose mother has positive serological tests for syphilis independently of the clinical stage of the disease.

EPIDEMIOLOGY

Nearly all cases of syphilis are acquired by sexual contact with infectious lesions. The incidence of the disease has decreased markedly in the past years due to the use of condoms and the wide use of antibiotics, but continues to be an endemic disease in some Eastern European countries and Central America.

DIAGNOSIS IN THE PREGNANT WOMAN

- **Clinical**. Detection of the typical chancre associated with regional lymphadenopathy in early primary syphilis. Serological tests may be negative (window period).
- **Serological.** Diagnosis is frequently established by serological tests during control of pregnancy.
- **Non-specific (reagin) antibody tests.** Rapid plasma regain (RPR) and Venereal Disease Reference Test (VDRL) with quantification.
- **Specific treponemal antibody tests.** FTA-Abs and MHA-TP (TPHA).

These are the most important tests for the diagnosis and control of treatment of syphilis in pregnancy. However, false negative and false positive results may occur.

Results	*Non-specific antibody tests*	*Specific treponemal antibody tests*
False positive	Viral exanthemas, vaccines, hepatitis, cirrhosis, mononucleosis, tuberculosis, endocarditis.	Presence of anti-DNA antibodies (systemic lupus, rheumatoid arthritis, polyarteritis), other spirochetoses.
False negative	Early primary syphilis (window period).	Very early primary infection or past infection treated before FTA-Abs became positive.

OTHER TESTS

Detection of specific IgG and IgM antibodies, and *T. pallidum* DNA detection by PCR in serum and CSF samples (suspicion of neurosyphilis).

TREATMENT OF THE PREGNANT WOMAN

Infection stage	*Treatment*
Primary, secondary, and early latent (<1 year).	Penicillin G benzathine 2.4 mU i.m. per week for 2 weeks.
Late latent (>1 years) and unknown duration.	Penicillin G benzathine 2.4 mU i.m. per week for 3 weeks.
Neurosyphilis and HIV-infected women.	Crystalline penicillin G 2-4 mU i.v. every 4 h (10-14 days) or penicillin G procaine 2,4 mU i.m. combined with probenecid 500 mg every 6 h (10-14 days).

In primary and secondary syphilis after appropriate antibiotic treatment, titers of non-specific antibody tests decrease to 1/4 at 3-6 months and 1/8 between 6 and 12 months, becoming negative thereafter. In patients with latent infections of after reinfection, decrease of antibody titers is gradual with persistence of low titers for more than 2 years. Specific treponemal antibody tests may remain positive for life.

DIAGNOSIS IN THE NEWBORN

Characteristics clinical features of congenital syphilis include rhinitis, palmoplantar pemphigous, hepatosplenomegaly, and bone anomalies (periostitis and osteochondritis). Bullae and vesicles of syphilitic pemphigous are very contagious. With regard to treatment, the following clinical forms should be differentiated: 1) multiorgan involvement (hydrops, hepatitis, pemphigous, etc.); 2) exclusive bone involvement; 3) asymptomatic with positive serology; and 4) neurosyphilis.

Serological tests. The same non-specific antibody tests (RPR or VDRL) as those carried out in the mother should be performed, with quantification of results to be able to compare serum titers. Infection is diagnosed in the presence of a fourfold increase of serum titers in comparison with maternal titers. Specific treponemal antibody tests include IgM-FTA-Abs, TPHA, and specific IgM antibodies. Diagnosis of neurosyphilis is established by VDRL reactivity in the CSF.

Radiographic studies long bones to assess the presence of periostitis and osteochondritis.

TREATMENT OF THE NEWBORN

1. Congenital syphilis with multiorgan involvement but without involvement of the central nervous system (CNS): penicillin G sodium 50.000 IU/kg every 12 h i.v. during the first week (every 8 h after the first week) during 10-14 days. The Herxheimer reaction may occur in patients with systemic involvement, and it may be advisable to increases the doses of penicillin progressively: 1.000 - 5.000 - 10.000 - 2.0000 and 50.000 IU/kg/day. Strict isolation measures should be implemented in infants with syphilitic pemphigous.
2. Syphilis with CNS infection (pleocytosis, increase of proteins or positive VDRL), the same regimen of penicillin G sodium but for 3 weeks.
3. Exclusive bone disease or asymptomatic with positive serology, penicillin G procaine 50.000 IU/kg/day i.m. during 10-14 days.
4. Asymptomatic infants born to mothers with syphilis should be treated in the following conditions:

   - Infants born to mothers treated before or during pregnancy whose serum titers do not decrease up to ¼ of the previous pre-treatment value in 3 months.
   - Infants born to mothers who had not received treatment during the last month, with negative assessment at birth.
   - Infants born to mothers treated during pregnancy with a non-penicillin antibiotic (e.g., erythromycin).
   - Infants born to untreated mothers, mothers insufficiently treated, or who had sexual contact with an infected person.
   - HIV-infected mothers whose treatment had been inferior to that for neurosyphilis.

   Treatment: penicillin G benzathine 50.000 IU/kg i.m. (single dose).

CYTOMEGALOVIRUS

It is a viral infection caused by cytomegalovirus (CMV), which belongs to the herpes virus group. The majority of patients with CMV infections are asymptomatic o present a febrile syndrome or more rarely a mononucleosis syndrome in patients with normal immune system.

EPIDEMIOLOGY

The infection is worldwide, and the rates of seropositive individuals range between 40 % and 100 % depending on the country. The fetus may become affected in women who experience a primary infection during pregnancy. During periods of reactivation of CMV disease, vertical transmission is very rare.

DIAGNOSIS IN THE PREGNANT WOMAN

Systematic study of all pregnant women is not recommended. CMV infection should be excluded in the presence of suggestive clinical features or any cause of immunodeficiency (HIV infection). It is particularly important to exclude CMV infection when early intrauterine growth retardation is diagnosed especially in association with enlarged organs, as well as in the presence of microcephaly, hydrops fetalis or polyhydramnios.

Very high serological titers of IgG- and IgM-specific CMV antibodies are found. The diagnosis of fetal CMV infection should be confirmed by CMV DNA identification by PCR in the amniotic fluid.

DIAGNOSIS IN THE NEWBORN

The diagnosis of CMV infection may be suspected in the presence of intrauterine growth retardation, microcephaly, and petequiae. The diagnosis if confirmed by DNA identification using PCR or by urine culture.

TREATMENT

There is no approved treatment for the management of congenital CMV infection. Infants with high viral load, infection of the nervous system, or severe thrombocytopenia, attempts have been made with i.v. gamma globulin and gamnciclovir (6 mg/kg/dose i.v. every 12 h during 6 weeks), with frequent hematological controls due to the risk of neutropenia.

Breastfeeding is not forbidden. Freezing breast milk and pasteurization reduces virus transmission, and should be considered in premature infants born to CMV carrier mothers.

INFANT BORN TO A MOTHER WITH HEPATITIS C VIRUS (HCV) INFECTION

Infection caused by a single-stranded, positive-sense RNA virus (a member of the Flaviviridae family).

EPIDEMIOLOGY

The infection is transmitted by the parenteral route, possible sexual transmission but there are a percentage of cases in which the mechanism of infection cannot be determined. Vertical transmission occurs in HCV positive mothers during pregnancy or at labor (2,4% of pregnant women are HCV positive). Blood transfusion is another route of infection (1,2% of blood donors in our environment are HCV positive). The rate of vertical transmission is 5,2-6,9% but increases to 13,7% in women co-infected with HIV.

DIAGNOSIS

Clinical features. HCV infection may present as an acute hepatitis with jaundice, or as an asymptomatic condition with moderate increase of serum aminotransferases. The course of the disease may be self-limited or may show progression to cirrhosis or hepatocarcinoma.

Laboratory tests. The diagnosis is established by positive HCV antibodies and HCV RNA PCR. Transient or persistent increases of serum aminotransferases are observed.

TRATAMENT OF THE NEWBORN

Invasive procedures during labor should be avoided. Postpartum secretions should be cleansed before punctures and blood sampling. Breastfeeding is allowed.

INFANT BORN TO A MOTHER WITH HEPATITIS B VIRUS (HBV) INFECTION

Infection caused by hepatitis B virus may show a clinical course towards resolution or, frequently, towards carrier states in which persistence of HBV. Chronic HBV carriers may transmit the infection to the fetus through the placenta or to the newborn at the time of delivery.

EPIDEMIOLOGY

HBV infection is an endemic disease in many countries, particularly In South-Eastern Asia and areas with deficient health care systems. A double mechanism of transmission, enteral and parenteral is possible.

DIAGNOSIS

HBV-infected pregnant women are asymptomatic. The diagnosis is established by serological controls, including systematic hepatitis B surface antigen (HBsAg) and hepatitis B virus core antigen (HBeAg).

TREATMENT OF THE NEWBORN

Invasive procedures during labor should be minimized. Postpartum secretions should be cleansed before punctures and blood sampling.

Anti-HB hyperimmune gamma globulin 0,5 mL (100 IU) i.m. together with specific hepatitis B vaccine 0,5 mL (5 μg) i.m. in the anterolateral aspect of both thighs should be administered, preferably during first 12 h of life, followed by the vaccination schedule with doses at 1 month and 6 months.

The administration of anti-HB hyperimmune gamma globulin and specific hepatitis B vaccine do not influence upon serological results (HBsAg).

In HBsAg-positive infants, vaccination is not indicated.

Infants born to HBeAg-postive mothers are at higher risk of infection.

Breastfeeding is not contraindicated.

Three months after the last vaccine dose and with a minimum age of the child of 9 months, protective antibody levels (anti-HBsAg) and HBsAg should be determined.

HUMAN IMMUNODEFICIENCY VIRUS (HIV)

The infection caused by the human immunodeficiency virus (HIV) produces a long-standing immunodeficiency syndrome.

EPIDEMIOLOGY

The disease is transmitted by sexual contact and by the parenteral route. Infants become infected by vertical transmission during gestation (last 6 weeks), at the time of delivery or by breastfeeding, which represents an added risk for acquiring HIV infection. At the present time, vertical transmission of HIV infection has been reduced almost to zero as a result of the use of antiviral treatment in the pregnant women and at the time of labor or caesarean section as well as the administration of zidovudine to the newborn.

DIAGNOSIS IN THE PREGNANT WOMAN

Identification of HIV-infected pregnant women by means of serological test and measurement of viral load (DNA).

TREATMENT OF THE PREGNANT WOMEN

A correct prophylaxis of vertical transmission and/or treatment of HIV infection are mandatory. Other potential infections affecting the fetus and the newborn should be identified and appropriate prophylactic measures applied: hepatitis B, hepatitis C, CMV, toxoplasmosis, syphilis. Invasive procedures during pregnancy should be avoided.

Detoxification programs for intravenous drug addicts should be offered.

Invasive procedures during labor should be avoided (fetal monitorization). Antiviral treatment during gestation should be maintained and treatment with zidovudine during labor (2 mg/kg i.v. bolus) followed by 1 mg/kg/h until ligation of umbilical cord. Elective caesarean section is indicated unless viral load is negative or very low.

DIAGNOSIS IN THE NEWBORN

Serological test and measurement of the viral load at the first hours of life and again after 2 weeks. If in both assessments the viral load is negative, vertical transmission can be excluded.

TREATMENT OF THE NEWBORN

Invasive procedures should be avoided (vitamin K i.m.) until the end of bath. Artificial feeding.

Zidovudine starting at 8-12 h of life, 2 mg/kg every 6 h, orally, until 6 weeks of life. Serial blood cells counts to assess the appearance of anemia and neutropenia are necessary.

In the presence of risk factors (no maternal treatment), nevirapine 120 mg/m^2 in 48 h should be administered.

MALARIA

INTRODUCTION

Malaria is caused by infection with one or more of four species of *Plasmodium (P. falciparum*, *P. vivax*, *P. ovale,* and *P. malariae)* and is a devastating health problem. Malaria has its greatest impact in sub-Saharian Africa, but the burden of the disease is increasing Asia and Oceania. It is transmitted by the bite of an infective female *Anopheles* sp. mosquito although it can be also transmitted through transfusion of infected blood and from the mother to the fetus. Near half of the world's population lives in endemic areas and it is estimated that more than 500 million episodes of clinical disease occur each year. The estimated death toll is 2,7 million, of which 75% occur in children younger than 5 years of age in Sub-Saharan Africa. In non-endemic areas, the majority of reported cases are imported from endemic regions concentrated largely among young children and pregnant women.

Placental infection is very variable and ranges from 3,5% to 75% depending on the malaria epidemiology in the area, seasonality of infection etc. The only species tat has proven to colonize the human placenta is *P. falciparum.*

There is no clear consensus on the definition congenital malaria. Congenital malaria is generally defined as malaria acquired by the fetus or newborn directly from the mother, either *in utero* or during delivery. In endemic areas, demonstration of parasites in the newborn within 24 h of birth, has been used as a diagnostic criteria. Outside endemic areas, where postnatal transmission can be reasonably excluded, it is evident that clinical onset of disease in congenital malaria is usually delayed several weeks.

SIGNS AND SYMPTOMS

Even asymptomatic pregnant women with parasitemia may infect its fetus. The majority of neonates with a congenital infection are asymptomatic. Onset may be as early as 14 h of age to as late as 8 weeks but on an average it is between 10 to 28 days of life. Fever, irritability, feeding problems, anemia, thrombocytopenia, reticulocytosis, loose motions, failure to thrive, jaundice, hepatosplenomegaly and respiratory distress may occur.

DIAGNOSIS

Malaria parasites. To assess the presence of parasites in adults or children, peripheral blood should be examined for parasites by a Giemsa-stained thick or thin film. This technique remains the «gold standard» for laboratory confirmation of malaria.

Antigen detection. Various rapid test kits are commercially available to detect antigens derived from malaria parasites and may offer a useful alternative to microscopy in situations where reliable microscopic diagnosis is not available. It is especially useful in the diagnosis of malaria infection in non-immune patients due to the frequently low parasite density and low reliability of microscopy.

In selected cases, if blood-film diagnosis or species determination is inadequate a PCR can be performed. It is also used for research purposes. This technique is more accurate than microscopy but expensive and requires a specialized laboratory.

Serology. Serology detects antibodies against malaria parasites, only detects a past and not a current infection. It is useful to assess the level of exposure and in seroepidemiological studies.

NON-PHARMACOLOGICAL INTERVENTIONS

Several strategies have been developed to reduce the risk of mosquito bite and patient susceptibility to infection. A reduction in human-vector contact by use of insecticide treated nets (ITN) has proven to be effective in Africa in reducing mortality due to malaria in children under 5 years of age.

Mosquito repellents such as N, N-diethyl-m-toluamide (DEET) are safe to use but clinical benefit remains to be demonstrated. Efficacy and safety of residual indoor spraying (RIS) has not yet been evaluated in the settings where it is used.

Treatment. Currently, information available regarding the clinical management of congenital malaria is scant.

All newborns with positive hematological examination or with risk factors (malarial parasite demonstrated in mother during pregnancy) and neonates with suggestive disturbances need treatment.

a) Mild infections or parasitemias by *P. vivax, P. ovale, P. malariae* and chloroquine sensitive *P. falciparu* should be treated with chloroquine orally 10 mg/kg initially, followed by 5 mg/kg after 6 h and then once a day for the next 2 days. Primaquine is not required for treatment as tissue phase is absent in congenital malaria.

b) Severe infection should be treated with quinine initially 20 mg/kg i.v. in 5% dextrose over 4 h followed by 10 mg/kg every 8 h i.v. until oral treatment is possible, for a total duration of 7 days.

c) Chloroquine-resistant cases (most frequent with *P. falciparum)* should be treated with quinine given parenterally until oral treatment is possible.

- *Duration of treatment:* 7 days.
- *Add clindamycin:* 20-40 mg/kg/day every 8 h for 5 days.

d) Quinine-resistant cases: Halofantrine-based therapies may be used.

e) Exchange transfusion may be required when parasitemia exceeds 10%. Supportive management for fever, fluids, calories and electrolytes need to be supervised.

f) Only very small concentration of antimalarial drugs is detected in breast milk, the amount is neither harmful nor protective against malaria.

CHAGAS' DISEASE

Chagas's disease is an infection caused by *Trypanosoma cruzi* transmitted to humans by reduviid bugs of the genera *Triatoma, Panstrongylus* and *Rhodnius.* The disease has a chronic clinical course and may be potentially life-threatening due lo late heart complications.

EPIDEMIOLOGY

About 6-18 million people are infected in Central America and South America, with 45.000 annual deaths. The infection is transmitted by reduviid bugs in endemic areas and blood transfusion or transplantations in non-endemic areas. The disease is occasionally transmitted via the placenta to the newborn infants (4-10 % of infants born to infected mothers).

50 % of infected infants are asymptomatic, whereas others present minimum clinical manifestations (hepatosplenomegaly) and 30 % have severe conditions (meningoencephalitis, myocarditis), with a 2-14 % mortality. There no evidence of passage of infection through the breast milk, so that breastfeeding in positive mothers is allowed.

DIAGNOSIS

Demonstration of *T. cruz*i in a concentrate leukocyte culture (parasitological diagnosis), antigen assay using biology molecular techniques (PCR, nested PCR) (immunological diagnosis), or positive serological serum antibody by ELISA, Western blot (serological diagnosis).

TREATMENT

In adults during the acute stage of the disease, treatment is very effective. In the chronic stage, the efficacy of treatment is about 50 %. Treatment is only indicated if parasitological and immunological tests are positive. Treatment should not be instituted in patients with positive serology.

Benznidazol orally 5-7 mg/kg/day during 60 days.

In infants weighing <3.000 g treatment should be initiated with 2-3 mg/kg/day, assessing hematological tolerance, and increasing the dose along one week until the standard dose.

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Recommendations to

- diminish the maternal mortality
- diminish the perinatal mortality
- diminish the morbimortality in children

Part of information and charts of these reports correspond
to official publications of WHO, FIGO and WAPM.

Recommendations to diminish the maternal mortality

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The World Association of Perinatal Medicine (WAPM) wishes with this Report to denounce the unacceptable situation of the maternal health in developing countries, particularly in Africa, and at the same time to collaborate with initiatives and interventions to reduce and prevent maternal deaths.

INTRODUCTION

«Maternal mortality is the death of a woman while pregnant or within 42 days of termination of pregnancy, regardless of the duration and site of the pregnancy, from any cause related to, or aggravated by the pregnancy or its management, but not from accidental or incidental causes[1].»

The situation of women in low-income countries is still difficult and, in some cases, particularly dramatic[2]. Besides the numerous socio-cultural shortcomings that women must endure (70 % of the poor and illiterate people in the world are women), they are also the victims of aggression and violence: 500 million are the victims of some kind of violence every year[3] and four million adolescents are forced into prostitution. Furthermore, they are prey to health-related problems: HIV/AIDS (18 million suffers); female genital mutilations that affect their sexual and reproductive lives (130 million); and particularly maternal morbi-mortality. In its 2000 report (based on data from 1990), The World Health Organisation (WHO) estimated that 527.000 women died annually in developing countries from complications of pregnancy, abortion attempts and childbirth[5, 6, 7]. Other reliable estimates state that, there are between 3 and 4 million women who are carriers of urinary or rectal fistulae caused by obstetrics problems.

In developed countries (high-income countries), the average maternal mortality ratio (MMR) is 20 per 100.000 live births (2.500 women), whereas in developing countries (low-income countries) this average rate increases to 400 per 100.000 live births (527.000 women) (table 1).

Table 1. Maternal mortality in the world.

WHO region	*Number of maternal deaths*	*MMR (maternal deaths for 100.000 live births)*	*Lifetime risk of maternal death 1 in:*
Developed countries	2.500	20	2.800
Developing countries	527.000	440	61
Eastern Asia	11.000	55	840
South-Central Asia	207.000	520	56
South-Easterb Asia	25.000	210	140
Western Africa	9.800	190	120
Northern Africa	4.600	130	210
Sub-Saharan Africa	247.000	920	16
Latin America and The Caribbean	22.000	190	160
Oceania	530	240	83

United Nations, 2000.

The situation is particularly dramatic in Africa's sub-Saharan countries, where the MMR is in the region of 1.000 per 100.000 live births. This is 200 times the rate in several European countries such as Sweden, Austria, Denmark and Spain[8]. Likewise, the proportion of skilled attendance at delivery in these countries is the lowest in the world (figure 1).

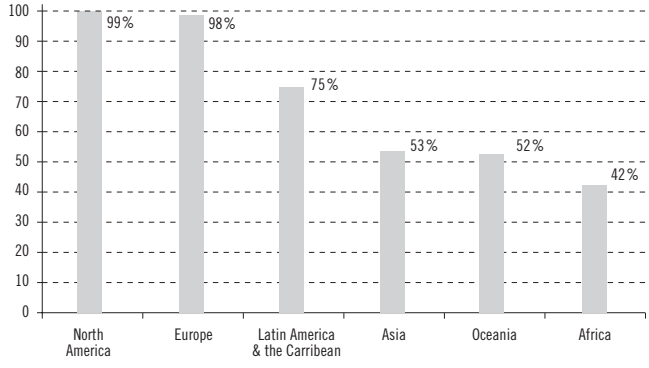

Figure 1. Skilled attendance at delivery by WHO Region.

Source: «Coverage of Maternal Care: A listing of Available information, fourth edition» WHO, Geneva 1997 (31).

It should be emphasised that these figures are probably underestimated due to the difficulty in obtaining reliable data from these countries, the fact that there is under-reporting of data, legal-medical problems, confusion about the indicators used and pure negligence. It is believed that in some countries MMR are underestimated by between 20 and 80 %[9, 10].

This high MMR in combination with the high fertility ratio and the low prevalence of contraceptive methods is increasing the «lifetime risk of maternal deaths». Maternal death is without a doubt one of the major challenges facing the development of Africa today[11, 12]. In the words of Dr Doyin Oluwole, the Director of the Division of Family and Reproductive Health at AFRO «The death of a woman is more than a personal tragedy. Her family is sadly deprived of her love, her care and her productivity within and outside the home»[12]. Every year, 2,5 million children are orphaned as a result of the death of their mother.

It is imperative that all stakeholders join hands to eradicate poverty, improve the health of the African population, and place African countries on the path to sustainable growth and development. Africa probably needs a multi-sectoral approach involving sectors such as education, social welfare, transportation, infrastructure, economic development as well as the culture and the traditions of the people[13, 14].

Governments, NGOs, charity agencies and various solidarity movements have become involved with this issue. Despite this and the scale of the economic resources at stake, results have been few and far between and in some places on our planet, especially in Africa, the MMR has reached completely unacceptable levels. Based on the lessons learnt from the implementation of the «Safe Motherhood Initiative» (1987), the WHO launched the «Making Pregnancy Safer» (MPS) initiative. There is no lack of institutional, international and regional statements that encourage the support and implementation of determined actions to deal with this issue.

CAUSES OF MATERNAL DEATHS IN DEVELOPING COUNTRIES

We are thrown into further confusion if we attempt to analyse the direct causes of these deaths, which in percentage terms are naturally far higher than in developed countries. According to the WHO, 80% of deaths in low-income countries may be directly traced back to obstetric causes (figure 2), whilst the remaining 20% are due to indirect causes (HIV/AIDS, malaria, anaemia, etc.).

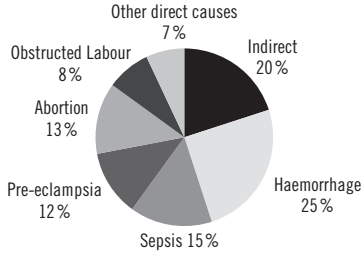

Figure 2.
Causes of maternal deaths in developing countries.

An analysis of these figures shows that, whereas in developed countries 55% of maternal deaths are due to indirect causes (cardiovascular pathologies, accidents, neoplasias, nephro-urological illness, etc.), in developing countries this group of causes accounts for less than 20% of deaths. Moreover, if we analyse deaths from direct obstetric causes (haemorrhages, pre-eclampsia, infections, obstructed labour, illegal abortions, etc.), the opposite happens: in developing countries this group increases to 80%, whilst in high-income countries these causes only account for 40% of deaths. These differences are particularly significant if we examine deaths from infections. Of all the women who die in childbirth, 90% do not apparently suffer from any high-risk factors[15-18] (table 2).

However, if we examine the problem as a whole, significant socio-economic factors underlie the great majority of these deaths, which include cultural prejudice, sparse or no health monitoring during pregnancy, restricted access by the people (90% of the population) to hospitals, etc. (table 3). The statistics available show that overall skilled attendants are present at only 40% of the deliveries in the African region, 52% in Oceania, 53% in Asia and 75 % in Latin-America and it would seem that this figure has varied little over the past 10 years (figure 1).

Table 2. Maternal Mortality: causes.

Causes	*Developed countries*	*Developing countries*
Obstetrical direct causes	**47 %**	**80 %**
Haemorrhage	20 %	25 %
Pre-eclampsia/hypertension	15 %	12 %
Infection	8 %	15 %
Unsafe abortion	—	13 %
Obstructed Labour and uterine rupture	—	8 %
Other (ectopic, etc.)	4 %	7 %
Indirect Causes	**53 %**	**20 %**
Cardiovascular Pat.	20 %	2 %
Cerebral haemorrhage	10 %	—
Nefro-Urologic Pat.	10 %	—
Neoplasies	10 %	2 %
Homicides/Suicides	3 %	—
HIV/AIDS, Malaria and Anemia	**—**	**16 %**

Source: Matres Mundi International (2007).

Table 3. Maternal mortality: Socioeconomic factors.

1. Maternal bad nutrition.
2. Labour overburden (physical effort).
3. Scare or null medical care during pregnancy
4. Violence, wards and armed conflicts.
5. Cultural prejudices, illiteracy.
6. Innaccesibility to hospitals.
7. Deficients sanitary infraestructures.
8. Short intervals inter-pregnancies.
9. Adolescent pregnancies (deficits in contraceptive service).
10. Administrative innefficiency and corruption.

At least 10 % of maternal deaths are due to induced abortions in unsafe conditions. Around 95 % of abortions of this nature take place in the third world, and are particularly prevalent in Africa. In some countries of Central Africa, the complications due to provoked abortions constitute 20 % of maternal death[19].

However, it must be remembered that 61 % of maternal deaths in the third world take place in the puerperium[20]. For each woman who dies as a result of maternal mortality, approximately 20 more will suffer disabilities: stress incontinence, fistulae, chronic pelvic pain, infertility, chronic anaemia, emotional depression, physical weakness, etc.

There is unanimous acceptance that in developing countries 60-80 % of maternal deaths could be avoided by improving the economic situation of these countries[5, 3, 21, 22, 23].

THE THREE DELAYS

Based on the model known as «the three delays» (figure 3), the above-mentioned socioeconomic factors are ultimately responsible for the high MMR. Indeed, experience has by far demonstrated that most of the maternal deaths, are due to one or more of the following causes[24].

1. Delay in decision-making in seeking skilled help.
2. Delay in patients going to healthcare centres.
3. Delay in receiving appropriate care after arrival at healthcare centres.

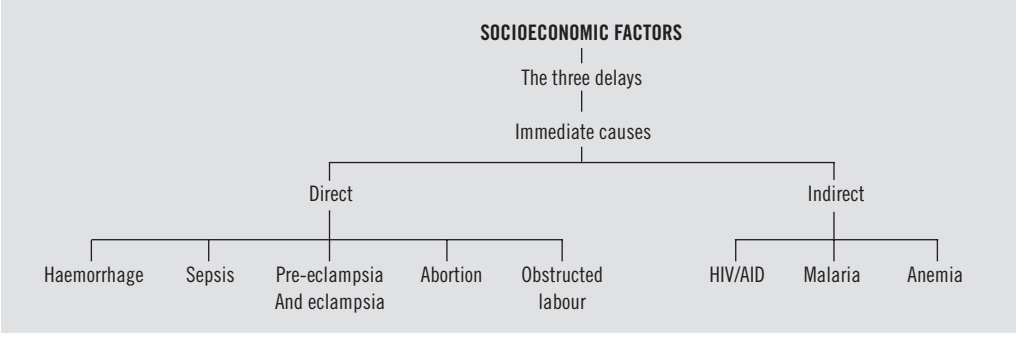

Figure 3. Relations among socioeconomic factors, delays in medical attendance and immediate causes.

DELAY IN DECISION-MAKING IN SEEKING SKILLED HELP

Around 80-90 % of the population in developing countries is concentrated in rural areas, where there is one doctor per 100.000 inhabitants[5]. The number of midwives with recognised qualifications is also paltry. This means that in the case of serious complications, it is not usually possible to obtain skilled help in the home. Therefore, patients must be taken to a healthcare centre. However, this move can give rise to complications as initial delays may arise for one or more of the following reasons:

a) The failure of the woman and her family to identify risks or possible complications[4].

b) Cultural prejudice, which leads them to mistrust institutional or hospital childbirths and to prefer traditional birth attendance (TBA) methods, which entails varied postures and lack of beds and equipment. Between 70 and 80 % of women in both rural areas and small towns share this preference[8]. Each year, 60 million women give birth without any medical assistance whatsoever[7].

c) The empirical or traditional midwife, bound by customs and ancient procedures, who is often illiterate, does not wish her work to be interfered with and is afraid of losing power and economic incomes[25, 26].

d) The lack of economic resources is a prime dissuasive factor. There is thus a general lack of preparation by both families and the community.

e) Women do not usually have decision-making powers. Any moves must be authorised by husbands, or failing that, by the men in the family who do not usually view the fact that traditional customs are not followed in good light. The men consider the subordi-

nation and powerlessness of women to be part of the natural order and are unaware of the women's health experience.

DELAY IN PATIENTS GOING TO HEALTHCARE CENTRES

Once it has been decided that a woman should be taken to hospital, her family come up against a double handicap: administrative and physical barriers.

a) Administrative barriers are mainly a consequence of the woman and her family's ignorance of the features of the Healthcare System in the area in which they live. A great deal of time is often wasted going from one primary healthcare centre to another until a suitable institution is finally reached. In many of these countries, the lack of cooperation between the various levels in the healthcare system is usually the rule rather than the exception.

b) Physical barriers are the cause of many delays. Around 80% of women in Africa, Asia and several countries of Latinamerica live more than 5 km away from the nearest primary healthcare centre. Between their homes and the centre they often have to cross physical barriers (mountains, jungles, rivers, etc.) and the roads are either inexistent, in a bad state of repair or simply impassable at certain times of the year. Furthermore, there is not usually any nearby means of public transport or any private vehicles in the villages in which they live. The only solution usually consists in using a stretcher, a bicycle with a cart on tow or simply the woman in labour is carried in the arms of family members.

DELAY IN RECEIVING APPROPRIATE CARE AFTER ARRIVAL AT HEALTHCARE CENTRES

Third-level hospitals that are well equipped and that have qualified healthcare workers at all levels are mainly found in large towns and cities. These hospitals use up most of a country's healthcare resources, but they only serve a small proportion of the overall population[5-7]. Rural or district hospitals however receive scant resources, there is a high turnover of the professionals working in them (as they emigrate to the city as soon as they can) and they are highly inefficient.

Thus, the causes of delayed, unskilled hospital treatment are usually the result of:

a) The lack of qualified staff (doctors, midwives, nurses, etc.).

b) The lack of good organisation and management practices.

c) The lack of a good referral system, with inadequate coordination with the primary healthcare level.

d) The lack of suitable technological equipment.

INTERVENTIONS FOR DECREASING THE MATERNAL MORTALITY RATIO

All UN agencies, scientific societies (FIGO, WAPM, etc.) and NGOs that are involved in this field highlight that the most efficient way of reducing the high MMRs is by ensuring that there is an acceptable level of antenatal control (which purpose is the early detection of

pregnancy complications) and that a qualified professional is present at each birth. The relationship between skilled attendance at delivery and maternal mortality is well established (figure 4). In addition, it is an excellent indicator of maternal and child health[27]. There exist a controversy about what must be understood by «skilled or qualified professional», in spite of attempts of WHO and several scientific societies to agree a consensuated definition[28, 29]. While in some countries it is included, under this term, only professional health properly titled, in some national surveys any person who has received a minimum training for attending births is considered qualified.

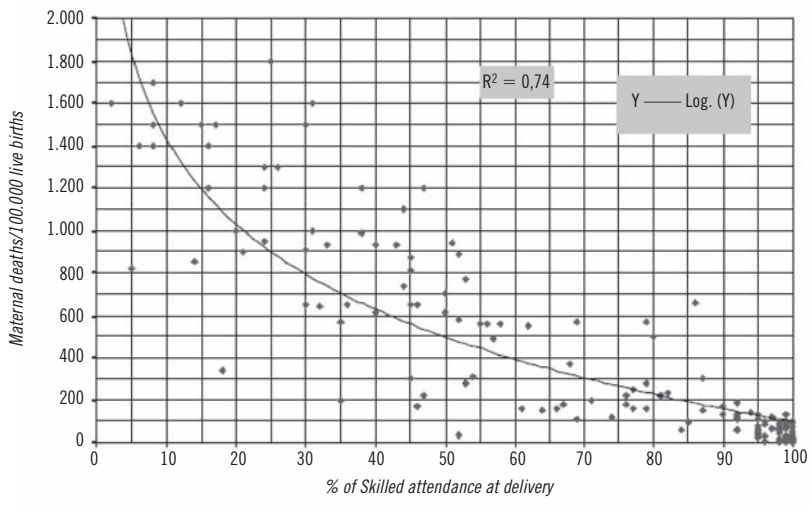

Figure 4. Relation between % of skilled attendance at delivery and MMR.

Source: A Review of the Evidence, 2001: Vincent the Brouwere & Kim van Lerberghe.

Therefore, the basic aim of the efforts in this field must be put into ensuring skilled assistance in all cases[30]. There is no point in concentrating on a single immediate cause of death, such as haemorrhages or infections, or of thinking that we are going to solve the problem just by sending clean delivery kits, or that the final aim consists in every birth taking place in a secondary or tertiary level hospital.

All plans and programmes that attempt to tackle the problem of maternal mortality efficiently and effectively must be based on an overall remedy to overcome the dysfunctions that give rise to the three delays.

DELAY IN DECISION-MAKING IN SEEKING SKILLED HELP

This delay should be tackled through:

a) Actions for gaining the trust of local leaders. The social complicity of these leaders is essential to the success of a cooperation programme. The aim is for them to accept and support the changes that we wish to bring about and that they take a more positive approach to health problems.

b) Awareness-raising campaigns about maternal and child health that mobilise the whole community. The promotion of the role of men as partners and fathers is essential to the success of these campaigns and for their involvement and support for maternal and newborn care programmes[31, 32].

c) Courses for women of reproductive age and their partners that teach them to overcome their prejudices, redress their misconceptions about reproductive health (pregnancy, childbirth, etc.), provide information about contraceptives, hygiene and diet, in addition to giving advice about vaccinations, the prevention of HIV/AIDS, etc.

d) Courses or talks specifically for pregnant women. The basic aim is that they learn how to recognise the signs of possible complications that may be life-threatening during pregnancy or labour by informing them of when and who they should address when they detect such complications. It must be stressed that although according to the WHO most obstetric complications cannot be avoided nor anticipated, they can be successfully treated if they are detected early[33-35].

e) The setting up and organisation of «rural health teams» that at a grassroots level have «auxiliary midwives or nurses» and «health agents». For a population of 4.000 people (with an average of 160 births per year), these teams should be trained by an auxiliary midwife and a health agent. The teams would be responsible for both giving care in normal births and also for basic prenatal care, family planning, general heath education and, above all, for detecting complications during pregnancy and childbirth. Naturally, these objectives can only be reached if:

— Training courses are run so that the empirical or traditional midwives are taught to become efficient «auxiliary midwives». This task requires patience, persuasion and adaptability to the environment. More importantly, there must be strict control over everything they do as, for example, the uncontrolled assess to oxytocin and ergometrine is probably responsible for the high incidence of ruptured uteruses[36]. However it is recommended to use ergotic, in a preventive way, in the immediate postpartum (specially Misoprostol)[37-39]. Unfortunately different reports have not been able to demonstrate that the introduction of asepsia in the birth attended by traditional midwives, reduce substantially the infections[40]. It goes without saying that these auxiliary midwives should be progressively replaced by qualified midwives.

— The «health agents» (or «health sentinels» as they are known in Bolivia) must be properly trained. Their basic tasks are to provide information about healthcare, about how to arrange moves to the appropriate healthcare centres and about healthcare logistics in the area: the dispensing of certain medicines and basic healthcare resources contraceptives, antibiotics, analgesics, anti-inflammatory drugs, etc.). They can also have decisive role in «Reproductive Age Mortality Survey» (RAMOS). This system, based in the «verbal autopsy» (interview with the relatives and people who attended the birth) permits to fix up the possible cause of death[41].

— They receive the supplies necessary for carrying out their task: clean delivery kits, sterile gloves, sterile syringes, basic medicines and information materials (posters, leaflets, books, etc.). In addition, a radio communications system may facilitate consultations between this primary healthcare level and the referral centre. With regard to receiving, providing information and dispensing contraceptives, it must be remembered that a drop in fertility rates is without a doubt one of the most effective ways of reducing maternal mortality in certain population groups[32, 36].

— Some health agencies insist specially in the need of having available the necessary material to make the «three cleans» (hands, delivery surface, cord cutting) by means of «clean delivery kits» (CDKs) that generally include soap, a plastic sheet, a new blade and clean cord ties. However the sending of CDKs, as an isolated way, doesn't improve substantially the results[42, 43].

f) The creation of friendly societies (mutual benefit societies) that for a minimum fee (3-5 dollars per year) allow families to receive healthcare services at their referral clinic. It has been suggested that a part of this money should go to the local auxiliary midwives or nurses, so that the transfer to referral center can be easily provided[47].

DELAY IN PATIENTS GOING TO HEALTHCARE CENTRES

The consequences of this delay could be tackled by adopting the following measures:

a) By creating small maternity centres that are equipped with a basic maternity ward where the women monitored by the above-mentioned «rural health team» can go for normal deliveries. These centres are named in different countries. Taylor and Berelson[44] called them «Rural Centres of MCH» (MCH: Maternal and Child Health). Perhaps the most appropriate name in order to properly distinguish them from hospitals would be «Delivery Houses» or «Childbirth Houses». This resource would avoid the need for women to give birth in completely inadequate places in which there is no water or hygiene and domestic animals are thrown into the bargain. According to preliminary estimations, there should be a delivery house for every 4.000 inhabitants. Thus, a scattered rural population of 100.000 people would need between 20 and 25 of these units[45].

However, the WHO proposes two levels of obstetric care: *a)* Basic Emergency Obstetrics Care (BEOC) at primary healthcare level, and *b)* Comprehensive Emergency Obstetric Care (CEOC) at referral level[6, 7, 45] (table 4).

Table 4. BEOC and CEOC functions.

BEOC	*COC*
Basic Emergency Obstetric Care signal functions at PHC level	Comprensive Emergency obstetric Care signal functions at referral level
• Parental administration of antibiotics. • Parental administration of oxytocic drugs. • Parenteral administration of anticonvulsants for pre-eclampsia and eclampsia. • Manual removal of placenta. • Removal of retained products. • Assisted vaginal delivery.	• All the functions for Basic Emergency Obstetric Care. • Perform surgery i.e. Cesaream Section. • Perform blood transfusions.
PHC: Primary Health Care	**Referral level**

The primary healthcare level would deal with normal deliveries, the manual removal of the placenta and retained products, and the parenteral administration of anti-convulsants, antibiotics and oxytocin. The CEOCs would undertake all basic obstetric care and surgical procedures (including caesarean sections under anaesthesia) and safe blood transfusions. Fore every 500.000 inhabitants, there should be at least four BEOCs (or 25 basic MCHs) and one CEOC. Establishing one model or the other will depend on the geographical characteristics of the area, the greater or lesser population densities in townships, the quality of communications networks and the state of already existing maternal and child healthcare facilities.

b) By drawing up a «protocol for moves» in order to anticipate the steps that must be taken should it be necessary to take a pregnant woman or a woman in labour to the

referral hospital. This protocol, which is especially important for outlying population pockets, should include a section of common recommendations for all communities and further sections for each particular one on itineraries, necessary resources (money, petrol, etc.) and the people involved.

c) By setting up groups of young volunteers to help transport patients, under the guidance of the health agent. Existing associations (religious, civic, music, etc.) may be engaged to carry out this task[46].

d) By providing the health agents, if possible and necessary, with vehicles that will adequately serve their specific needs (motorcycles, vans that can be converted into improvised ambulances, etc.) and with radio transmitters. The latter resource can be of prime importance if, as is often the case, there is no telephone or any other communications systems. The aim should be that any woman in labour should not take more than 45 minutes to reach the healthcare centre[46]. Unfortunately, this time limit is often exceeded in certain regions. Nevertheless, a study of the estimated times between the start of a major obstetric complication and death shows that there is an average 12-hour time lapse. Therefore, maternity hospital centres must be within reach in this time. Postpartum haemorrhages are of course a notable exception as they may cause death in less than one hour[20]. Ideally, referral centres should be informed by means of two-way radio communications systems of the arrival of referred patients, and thus be ready to receive them and manage their hospital stay. See essential drugs for transport and home delivery (pag. 449 and 450).

e) By building, equipping and organising «Maternal Houses» (or «Houses of Hope»). They are either built back-to-back with the referral hospital (generally, the District Hospital) or very close to it and are able to hold 10-15 women in the final period of their pregnancy. These houses are designed to take in pregnant women who are at risk of suffering complications (abnormal foetal presentation, bad pelvis, mild or moderate pre-eclampsia, bad obstetric history, etc.) or those who simply live far from the hospital. The basic aim of these facilities is to ensure immediate access to the hospital and to improve the mother's diet and provide her with information and training about hygiene, caring for newborn babies, etc.

DELAY IN RECEIVING APPROPRIATE CARE AFTER ARRIVAL AT HEALTHCARE CENTRES

This delay could be managed by adopting the following measures:

a) By eliminating bureaucratic procedures and hospitals' administrative barriers in urgent cases. Admissions procedures should be made more flexible. There is unanimity in considering that the existence of accessible, fully prepared and with qualified personal hospitals, are the three critical ingredients to assure the success of a maternal-infantil health programme[26, 47].

b) By coordinating the information between BEOCs (or local «health agents») and the hospital by means of radio communications equipment, which would make it possible to warn the hospital of the imminent arrival of a woman in labour with complications[46].

c) By improving the information *in situ* of healthcare workers through specific training courses at various levels: general practitioners, surgeons, obstetricians—courses in obstetric-gynaecological surgery, fistula surgery, general ultrasound scans, obstetric-gynaecological ultrasound scans, etc.; midwives—courses on partographs, the kangaroo method, new techniques in obstetrics, etc.; nurses—courses in obstetric and neonatal

nursing, etc. This is without a doubt the most important action in terms of cooperation. Well trained medical staff and other professional hospital workers is of far greater significance than the technology available. Strategies must be designed for encouraging health staff continuity and loyalty in hospitals, particularly in the case of doctors.

d) By improving the technological equipment in hospitals, through the supply of new or second-hand (but not obsolete) equipment form high-income countries. It should be highlighted that these hospitals are sometimes in need of basic infrastructures, such as wells, solar panels, etc. The center must rely on the support of clinical laboratory and a system in order to have blood available (blood collection, conservation and transfusion equipment).

e) By setting up protocols for providing help that are properly adapted to the needs of low-income countries.

f) By ensuring the proper organisation and management of hospital resources.

Naturally, irrespective of these measures, it is necessary to promote acceptable healthcare systems in every country, improve their track records and ensure that the results of all interventions are assessed impartially[48] and rely on with better indicators of maternal health. Unfortunately the present indicators are insufficient[49].

THE MILLENNIUM DEVELOPMENT GOALS

Over the past 20 years, there have been a number of institutional statements and initiatives that have fostered the need for universal healthcare treatment for women and their children (International Conference on Primary Health Care (1978), Alma-Ata (1979), Safe Motherhood Initiative [1987], Making Pregnancy Safer [2000])[50].

From the Conference on Safe Motherhood (Nairobi, 1987) a Group of Work was created (Agency Group) formed by WHO, UNFPA, UNICEF, IPPF, FCI and afterwards FIGO. Doubtless this group has invigoreated the projects to improve the maternal and infant health in the developing countries[51, 52].

On the other hand, the International Conference on Population and Development (Cairo, 1994),, the Fourth World Conference on Women (Beijing, 1995) and the Safe Motherhood Technical Consultation (Colombo, 1997) have helped to focus the attention of the international community on the need to reduce the unacceptable MMR of developing countries.

At the 2000 summit meeting in New York, 189 countries signed a declaration known as the «Millennium Development Goals» (MDGs), which contained 8 goals and 18 targets[53-56]. Its fifth goal was related to maternal health, and its sixth target explicitly stated that it would «Reduce by three quarters, between 1990 and 2015, the maternal mortality rate» (table 5).

There is no doubt that this is a highly praiseworthy objective, but almost seven years have passed since the declaration was made and there have been no substantial improvements in maternal health in developing countries. In some places (Zambia, Tanzania, Afganistan, Senegal, etc.), the situation has worsened. As has happened in the case of other solemn declarations, it is most likely that these objectives will not be reached. The «Health for All in 2000» campaign (1997) well illustrates this.

That is why MATRES MUNDI, which acts with the support of «The International Perinatal Medicine Group» formed by the World Association of Perinatal Medicine (WAPM), the In-

Table 5. Health in the Millenium Development Goals.

Goal 4	**Reduce child mortality**
Target 5	Reduce by two-thirds, between 1990 and 2015, the under-five mortality rate.
Goal 5	**Improve maternal health**
Target 6	Reduce by three-quarters, between 1990 and 2015, the maternal mortality ratio.
Goal 6	**Combat HIV/AIDS, malaria and other diseases**
Target 7	Have halted by 2015 and begin to reverse the spread of HIV/AIDS.
Target 8	Have halted by 2015 and begin to reverse the incidence of malaria an other major deseases.

Source: «Implementation of the United Nations Milennium Declaration», Report of the Secretary-General, A/57/270 (31 July 2002), First annal report based on the «Road map towards the implementation of the United Nations Milennium Declaration», Report of the Secretary-General, A/56/326 (6 September 2001), United Nations Division, Milennium indicators Database, verified in July 2004; World Health Organization, Department of MDG, Health and Development Policy (HDP).

ternational Academy of Perinatal Medicine (IAPM), the «International Society The Foetus as a Patient» and the «Ian Donald Inter-University School of Ultrasounds in Obstetrics and Gynaecology», has designed an «Integral Plan for the Reduction of Maternal Mortality» in conjunction with the aforementioned associations.

ETHICAL PRINCIPLES OF AID

Health aid to developing countries, must be undertaken based in ethical principles, which have not always been heeded in the past. This is especially true of NGOs. The underlying principles of cooperation projects as follows:

1. They will be undertaken free of political and religious criteria.
2. They will be set up depending on the needs of the beneficiary population.
3. They must be set up with reliable partners. It is essential to ensure that projects are viable and sustainable in the long-term.
4. They must not have any commercial ties that compromise the freedom and independence of projects.
5. They must respect the cultural identity, the dignity and the values of the local population.
6. They will promote improved medical care and also attempt to improve the societies they serve as a whole.
7. They must avoid social imbalance at all costs.
8. They must not set out to automatically transfer the healthcare systems in developed countries to developing countries. They should adapt to the local culture and customs.
9. They must not be solely based on technology, but also place emphasis on training, education, awareness-raising and friendship.
10. They must be set up in cooperation with the local authorities and leaders in the communities in which aid is to be given.

INTEGRAL PLAN FOR THE REDUCTION OF MATERNAL MORTALITY (WAPM/MATRES MUNDI)

The aim of this Plan is to effectively deal with the three delays mentioned above. It does so by setting all of the interventions and actions described into motion.

This Plan takes account not only of health aspects, but also of the sanitary education, alimentation and basic social resources. Because, as says the Joint WHO/UN/UNICEF, World Bank statement: «An important lesson learned over the past decade has been that interventions to reduce maternal deaths cannot be implemented as vertical, stand-alone programmes. Maternal mortality is not merely a «health disadvantage», it is a «social disadvantage». Health, social and economic interventions are most effective when they are implemented simultaneously. Safe motherhood interventions should be implemented in the context of broader health programmes, including nutritional advice and micro-nutrient supplementation, child survival and development, immunization, safe water and sanitation, family planning, the avoidance of unwanted pregnancies, and the prevention and control of malaria and of HIV/AIDS and other sexually transmitted diseases» (1999).

The NGO, MATRES MUNDI, will be responsible for the design, organisation, setting up, monitoring and assessment of the Plan. Additional collaboration will be given by all of the academic institutions that make up «The International Perinatal Medicine Group».

A «Pilot Experience» wil be started up in Ruanda. Includes an Integral Programme for healthcare cooperation (the construction and endowment of «Delivery Houses» and «Maternal Houses», suitable equipment for the referral hospitals, etc.), a specific Training and Information Programme (19 courses for healthcare professionals at various levels), and a specific awareness-raising programme comprising 14 actions (public campaigns, information open days for specific groups, etc.). A great deal of care has been taken to ensure the viability and sustainability of the project, whether from a socio-cultural, technical, financial, environmental or political point of view.

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Recommendations to diminish the perinatal mortality

B. Serra

INTRODUCTION

Maternal and perinatal mortality are the most important adverse perinatal outcomes with a special impact on developing countries, where near almost 600.000 maternal deaths and near 7 million perinatal deaths occur every year. As these countries generally have less developed health systems and therefore incomplete epidemiologic registers, these numbers have been calculated based on estimates, and therefore reality could be even worse. The estimates of perinatal and neonatal deaths made by WHO on 2001 are shown on table 1.

Table 1. Estimated perinatal and neonatal mortality, by WHO region, 1999.

WHO Region	*N.º of live births (,000)*	***Perinatal mortality***		***Neonatal mortality***	
		Mortality rate	*N.º of deaths (,000)*	*Mortality rate*	*N.º of deaths (,000)*
Africa	24,415	79	2,035	42	1,035
Americas	15,542	22	352	14	213
Eastern Mediterranean	15,413	61	966	43	667
Europe	10,502	15	157	9	100
South-East Asia	36,212	67	2,509	42	1,508
Western Pacific	27,183	32	878	19	509
World	129,595	52	6,905	31	4,035

Source: WHO Geneva, *Department of Reproductive Health and Research, Perinatal and Neonatal Mortality: Global, Regional and Country Estimates, Second Edition, Draft 5, November 2001.*

As figures of maternal and perinatal mortality rates are closely related, measures directed to reduce any of both will also have effects on the other. Perinatal deaths are not only the result of inadequate care during pregnancy, delivery and immediate postpartum, but also of poor maternal health and inadequate live conditions. Medical strategies to lower perinatal mortality have therefore not only to focus on strict obstetrical issues, but also on live conditions and nutrition.

Mortality has decreased where women have increasingly given birth with a professionally skilled attendant whether at home, in a primary health care facility or in a hospital[1]. As shown in figure 1, considerable improvements have been achieved in the last decade especially in Northern African and in South-eastern and Eastern Asian countries, but little progress has been made in Sub-Saharan African countries, which nowadays have the worst perinatal figures.

Information on how to stay healthy during pregnancy and the need to obtain the services of a skilled birth attendant, on recognizing signs of the onset of labour, and on recognizing danger signs for pregnancy-related complications and what to do if they arise would significantly increase the capacities of women or their families to take appropriate steps to ensure a safe birth and to seek timely skilled care in emergencies. Educational programs directed to general population, especially women before they reach childbearing age, or even pregnant women, are therefore of paramount importance.

While around one third of the perinatal deaths are stillborns, two thirds are newborn deaths, mainly due to infections, prematurity and asphyxia. 30 % of stillborns occur during labour and 30-50 % of newborn deaths occur during the first day of live. This makes the day of delivery and the first day after the period of time where most efforts should be directed to reduce perinatal mortality. The causes of newborn deaths in Africa are shown in figure 2[2]. This data prove that not only the birth attendance but also the postnatal care of the newborn and the mother are of capital importance not only to reduce perinatal mortality, but also maternal mortality, as around 50 % of maternal deaths occur during the first day after giving birth. Between the postnatal causes, infections are the biggest cause of newborn death and the more feasible to prevent and treat.

The interventions listed in table 2 have been proposed by The Partnership For Maternal, Newborn & Child Health[3] to improve maternal and perinatal morbidity and mortality rates in African countries, but for sure they could also be recommended for all low resource settings around the world.

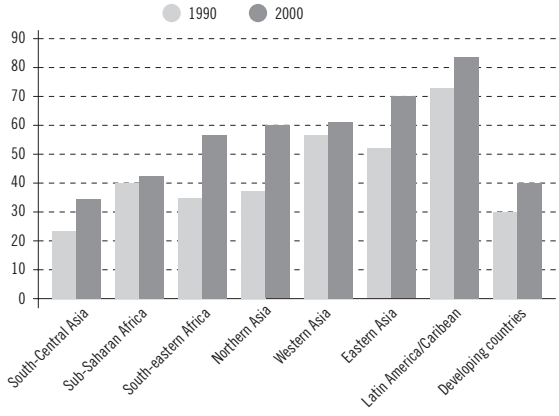

Figure 1. Skilled attendance at delivery (1990-2000).

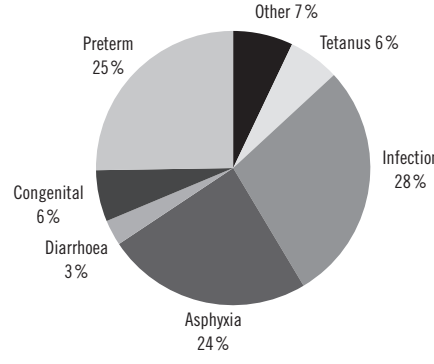

Figure 2. Causes of newborn deaths in Africa.

Table 2. Evidence based interventions to save newborn lives.

Packages along the continuum of care	*Care for girls and women before pregnancy*	• Education with equal opportunities for girls. • Nutrition promotion, especially for girls and adolescents. • Prevention of female genital mutilation. • Prevention of management of HIV and sexually transmitted infections (STI) • Family planning.
	Care during pregnancy	• Focused antenatal care (ANC) including: – At least 2 doses of tetanus toxoid vaccination (TT2+). – Management of syphilis/STIs. – Management of pre-eclampsia. – Intermittent preventive treatment for malaria in pregnancy (IPTp) and insecticide treated bednets (ITN). – Prevention of mother-to-child transmission of HIC (PMTCT). • Birth and emergency preparedness at home, increasing demand for care.
	Childbirth care	• Skilled attendance at birth. • Emergency obstetric care (EmOC). • Improved linkages between home and health facility. • Companion of the woman's choice at birth. • Where there is no skilled attendant, support for clean childbirth practices and essential newborn care (drying the baby, warmth, higiene and early and exclusive breastfeeding) at home.
	Postnatal care	• Routine postnatal care (PNC) for early identication and referral of illness as well as preventive care: – For the mother: promotion of hearlthy behaviours, danger sign recongnition, and family planning. – For the baby: promotion of healthy behaviours —hygiene, warmth, breastfeeding, danger sign recongnition and provision of eye prophylaxis and immunisations according to local policy. • Extra care for small babies or babies with otres problems (e.g. mothers with HIV/AIDS).
	Integrated Management of Childhood Illness (IMCI)	• Management and care of low birhweight (LBW) babies including Kangaroo Mother Care (KMC). • Emergency newborn care for illness, especially sepsis.
Cross-cutting programmes	*Nutrition and breastfeeding promotion*	• Nutrition promotion, especially in girls and adolescents. • Maternal nutrition during pregnancy and lactation. • Early and exclusive breastfeeding for babies.
	Prevention of mother-to-child transmission of HIV	• Prevention of HIV and STIs and avoiding unintended pregnancy. • PMTCT through antiretroviral therapy and safer infant feeding practices.
	Malaria control	• Intermittent preventive treatment for malaria in pregnancy (IPTp) and insecticide treated bednets (ITN).
	Immunisation	• Tetanus toxoid vaccination (at least 2 doses) for pregnant women.

The same authors[2] emphasize following opportunities to reduce perinatal mortality:

1. Promote the delay of first pregnancy until after 18 years and spacing birhs at least 24 months apart.
2. prevent and manage HIV and sexually transmitted infections, specially among adolescent girls.
3. Increase the quality of antenatal care, ensuring that women receive four visits and the evidence based interventions that comprise focused antenatal care.
4. Promote improved care for women in the home and look for opportunities to actively involve women and communities in analyzing and meeting maternal, neonatal and child health needs.
5. Increase availability of skilled care during childbirth and ensure skilled attendants are competent and equipped for essential newborn care and resuscitation.
6. Include emergency neonatal care when scaling up emergency obstetric care.
7. Promote better linkages between home and facility (e.g. emergency transportation schemes).
8. Develop a global consensus regarding a postnatal care package.
9. Undertake operations research in Africa to test models of postnatal care, including care at the community level in order to accelerate scaling up.
10. Increase availability and quality of postnatal care.
11. Adapt integrated management of childhood illness case management algorithms to address newborn illness and implement these at scale.
12. Ensure hospitals can provide care for low birth-weight babies including kangaroo mother care and support for feeding.
13. Strengthen community practices for newborn health.
14. Address anemia in pregnancy through iron and folate supplementation, hookworm treatment and malaria prevention.
15. Review and strengthen policy and programmes to support early and exclusive breastfeeding, adapting the global strategy for infant and young child feeding.
16. Increase coverage and improve integration of prevention of mother-to-child transmission of infectious diseases, especially with antenatal and postnatal care.
17. Use opportunities presented by expanding HIV and malaria programmes to strengthen maternal, neonatal and child health services (e.g. better laboratory and supply management as well as tracking of women and babies, especially in the postnatal period).
18. Increase coverage of insecticide treated bed nets and intermittent preventive treatment for malaria in pregnancy.
19. Accelerate the elimination of maternal and neonatal tetanus.
20. Use the solid management and wide reach of immunization programmes to strengthen maternal, neonatal and child health services (e.g. social mobilization, linked interventions, and monitoring).

As the specific treatments of the different pathologies related to perinatal deaths are exposed elsewhere in this book, we will focus in this chapter on organizational aspects of antenatal care, birth attendance and maternal and newborn postnatal care.

During pregnancy women have to be encouraged to make at least 4 routine antenatal visits, the first before 16 weeks (4 months), the second at 24-28 weeks (6 months), the third at 30-32 weeks (8 months) and the last at 36-38 weeks (9 months). The first visit should be as soon as possible, and during the last visit, the woman should be advised to come back if she does not deliver within the 2 weeks after the expected delivery date. More visits should be scheduled according to national malaria or HIV policies.

During these antenatal visits health providers should answer the questions and concerns women may have, provide treatment for the different pathologies that the patient may suffer and give advice and counsel about nutrition, activity, etc. It is also during these prenatal visits when the patient and the health staff should develop a birth and emergency plan. If the women doesn't meet risk criteria and she is planning to deliver at home with a skilled attendant, she should be advised how to prepare the delivery and to arrange a plan for emergency transportation to the nearest facility if needed. Either if she is planning to deliver at home or at a facility, the women has to be instructed about the signs or symptoms of labour or danger, and informed about the expected expenses that she or her family will have to face. If the woman is going to deliver at home without a skilled attendant, a disposable delivery kit should be given to her and she should be informed about how to use it and:

1. To ensure a clean delivery surface for the birth and that the attendant washes his/her hands before delivery.

2. To use the ties and razor of the delivery kit or a new razor blade and three 20 cm large strings to tie and cut the cord once it stops pulsating.

3. To dry the baby after cutting the cord and place him on the mothers chest, covering both to keep them warm and starting breast feeding when the baby shows signs of readiness, within the first hour after birth.

4. To go to the health center without delay if:

   a) Waters break and not in labour after 6 hours.

   b) Painful contractions continue for more than 12 hours.

   c) Fever appears.

   d) The baby is very small, has difficulty in breathing or is not able to feed.

Essential emergency drugs and supplies recommended[4] for transport and home delivery are listed in table 3. On the other hand referral centers should have the appropriate equipments, supplies, drugs and tests for routin and emergency pregnancy and postpartum (table 4) and childbirth (table 5) care, and specific protocols to face the complications that could appear during pregnancy, delivery and postpartum. If no local or national guidelines should be available, WHO has published an extensive guide that provides a full range of updated, evidence-based norms and standards that will enable health providers to give high quality care during pregnancy, delivery and the postpartum period[4].

As reduction of perinatal, maternal and infant mortality in the developing world will only be achieved in a national or even regional level with the involvement of local, national and international agencies, societies, politicians and NGOs, one of the major challenges of these agents is to develop efficient collaboration protocols to obtain the greatest possible improvements in perinatal, maternal and child health in these specially disadvantaged countries. Figure 3 shows an example of interaction proposed by WHO.

Table 3. Essential emergency drugs and supplies for transport and home delivery.

	Strength and Form	*Quantity for carry*
Emergency drugs		
Oxytocin	10 IU vial	6
Ergometrine	0,2 mg vial	2
Magnesium sulphate	5 g vials (20 g)	4
Diazepam (parenteral)	10 mg vial	3
Calcium gluconate	1 g vial	1
Ampicillin	500 mg vial	4
Gentamicin	80 mg vial	3
Metronidazole	500 mg vial	2
Ringer's lactate	1 litre bottle	4 (if distant referral)
Emergency supplies		
IV catheters and tubing		2 sets
Gloves		2 pairs, at least, one pair sterile
Sterile syringes and needles		5 sets
Urinary catheter		1
Antiseptic solution		1 small bottle
Container for sharps		1
Bag for trash		1
Torch and extra battery		1
If delivery is anticipated on the way		
Soap, towels		2 sets
Disposable delivery kit (blade, 3 ties)		2 sets
Clean cloths (3) for receiving, drying and wrapping the baby		1 set
Clean clothes for the baby		1 set
Plastic bag for placenta		1 set
Resucitation bag and mask for the baby		1 set

Source: WHO

Table 4. Equipment, supplies, drugs and tests for routine and emergency pregnancy and postpartum care.

Warm and clean room
- Examination table or bed with clean linen.
- Light source.
- Heat source.

Hand washing
- Clean water supply.
- Soap.
- Nall brush or stick.
- Clean towels.

Waste
- Bucket for solled pads ans swabs.
- Receptable for solled linens.
- Container for sharps disposal.

Sterilization
- Instrument sterilizer.
- Jar for forceps.

Miscellaneous
- Wall clock.
- Torch with extra batteries and bulb.
- Log book.

- Records.
- Refrigerator.

Equipment
- Blood pressure machine and stethoscope.
- Body thermometer.
- Fetal stethoscope.
- Baby scale.

Supplies
- Gloves:
  - Utility.
  - Sterille or highly desinfected.
  - Long sterile for manuyal removal of placenta.
- Urinary catheter.
- Syringes and needles.
- IV tubing.
- Suture material for tear or epislotomy repair.
- Antiseptic solution (lodophors or chiorhexidine).
- Spirit (70% alchohol).
- Swabs.
- Bleach (chiorine base compound).
- Impregnated bednet.
- Condoms.

Tests
- RPR testing kit.
- Proteinuria sticks.
- Container for catching urine
- HIV testing kit (2 types).
- Haermoglobin testing kit.

Disposable delivery kit
- Plastic sheet to place under mother.
- Cord ties (sterile).
- Sterils blade.

Drugs
- Oxytocin.
- Ergometrine.
- Magnesium sulphate.
- Clacium gluconate.
- Diazepam.
- Hydralazine.
- Ampicillin.
- Gentamicin.
- Metronidazole.
- Benzathine penicillin.
- Cloxacillin.
- Amoxycillin.
- Ceftriaxone.
- Trimethoprim + sulfamethoxazole.
- Clotrimazole vaginal pessary.
- Erythromycin.
- Ciprofloxacin.
- Tetracycline or doxicycline.
- Arthemether or quinine.
- Chloroquine tablet.
- Ugnocaine.
- Adrenaline.
- Ringer lactate.
- Normal saline 0,9 %.
- Glucose 50 % solution.
- Water for injection.
- Paracetamol.
- Gentian violet.
- Iron/folic acid tablet.
- Mebendazole.
- Sulphadoxine-pyrimethamine.
- Navirapine (adult, infant).
- Zidovudine (AZT) (adult, infant).
- Lamivudine (3TC).

Vaccine
- Tetanus toxoid.

Table 5. Equipment, supplies and drugs for childbirth care.

Warm and clean room
- Delivery bed: a bed that supports the woman in a semi-sitting or lying in a lateral position, with removable stirrups (only for repairing the pirineum or instrumental delivery).
- Clean bed linen.
- Curtains if more than one bed.
- Clean surface (for alternative delivery position).
- Work surface for resuscitation of newborn near delivery beds.
- Light source.
- Heat source.
- Room thermometer.

Hand washing
- Clean water supply.
- Soap.
- Nail brusch or stick.
- Clean towels.

Waste
- Container for sharps disposal.
- Receptable for solled linens.
- Bucket for soiled pads and swabs.
- Bowl and plastic bag for placenta.

Sterilization
- Instrument sterillzer.
- Jar for forceps.

Miscellaneous
- Wall clock.
- Torch with extra batteries and bulb.
- Log book.

Equipment
- Blood pressure machine and stethoscope.
- Body thermometer.
- Fetal stethoscope.
- Baby scale.
- Self inflating bag and mask-neonatal size.
- Mucus extractor wit suction tube.

Delivery instruments (sterile)
- Scissors.
- Needle holder.
- Artery forceps or clamp.
- Dissecting forceps.
- Vaginal speculum.

Supplies
- Gloves:
  - Utility.
  - Sterille or highly disinfected.
  - Long sterille for manual removal of placenta.
  - Long plastic apron.
- Urinary catheter.
- Syringes and needles.
- IV tubing.
- Suture material for tear or episiotomy repair.
- Antiseptic solution (lodophors or chiorhexidine).
- Spirit (70 % alcohol).
- Swabs.
- Bleach (chiorine-base compound).
- Clean (plastic) sheet to place under mother.
- Sanitary pads.
- Clean towels for drying and wrapping the baby.
- Cord ties (sterille).

- Blanket for the baby.
- Baby feeding cup.
- Impregnated bednet.

Drugs
- Oxytocin.
- Ergometrine.
- Magnesium sulphate.
- Clacium gluconate.
- Diazepam.
- Hydralazine.
- Ampicillin.
- Gentamicin.
- Metronidazole.
- Benzathine penicillin.
- Ugnocaine.
- Adrenaline.
- Ringer lactate.
- Normal saline 0,9 %.
- Water for injection.
- Eye antimicrobial (1 % silver nitrate or 2,5 % povidone Iodine).
- Tetracycline 1 % eye ointment.
- Vitamin A.
- Izoniazid.
- Nevirapine (adult, infant).
- Zidoudine (AZT) (Adult infant).
- Lamivudine (3TC).

Vaccine
- BCG.
- OPV.
- Hepatitis B.

Contraceptives
(see Decision-making tool for family planning providers and clients).

Test
- RPR testing kit.
- HIV testing kits (2 types).
- Haemoglobin testing kit.

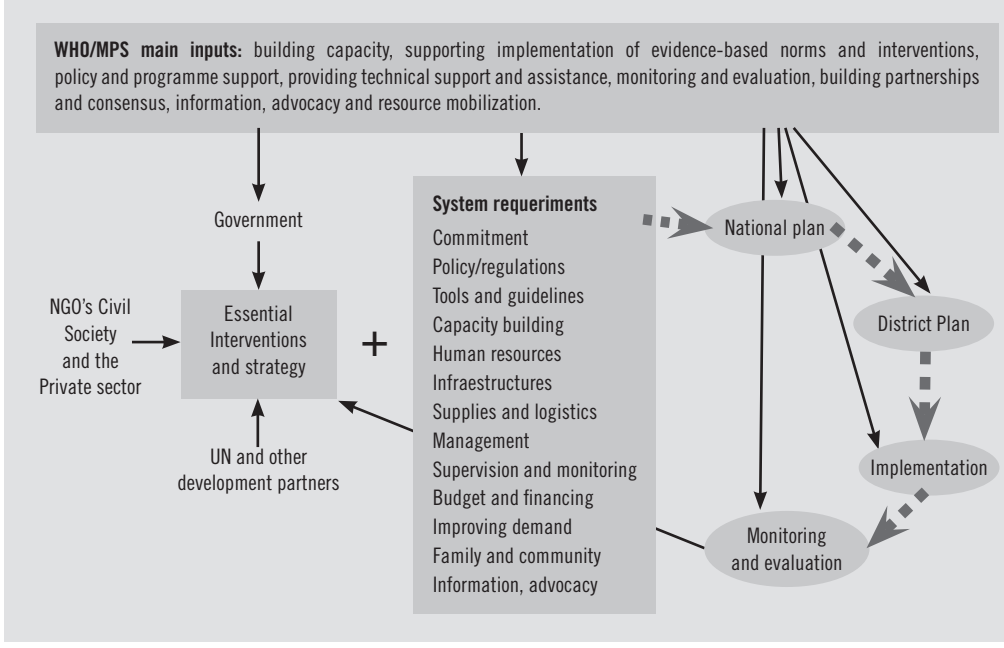

Figure 3.

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Recommendations to diminish the morbimortality in children

X. Carbonell-Estrany

INTRODUCTION

Our mission as health workers to ensure proper child health and survival along with the defence of their rights unfortunately can not be accomplished equally in all the countries. The 2000-2003 year World Health Organization report tell us that 10,7 million children under 5 years of life day every year, being undernutrition the underlying cause in 53% of the case (figure 1). The distribution of deaths is clearly located especially in Sub-Saharan Africa and South of Asia (figure 2).

Every year 4 million babies die in the first month of life —most in developing countries of causes that are rare in rich countries figure 3— and of them probably more than 3 million could be saved with very low interventions that could be provided to 90% of the cases spending only 1$ extra per inhabitant and year. The influence of the country development in neonatal morbimortality is quite clear as can be seen in tables 1 and 2.

The declaration by 191 countries ratifying the Convention on Rights of the Child (CRC) and the Millennium Declaration helped to become aware of the problem and improved slightly the situation. Strategies as Integrated Management of Children illness (IMCI) (figure 4) have been useful to decrease slightly the morbimortality rates but still we are too far away in the progress to achieve the year 2015 goals (figure 5).

AN UNSOLVED PROBLEM

This book is focused basically to those countries with middle and low development. Probable most of the protocols can be real useful tools to develop or to renew in all those places that take care of mother and babies with short resources. Some guidelines may be a little more sophisticated than others but we must realize than some very simple intervention can be very rewarding with very short investment or without the need of expensive material. As is summarized by WHO we must remember that following birth a newborn needs:

— **Air**. Stimulate and resuscitate infants who are not breathing at birth.

— **Warmth**. Dry the baby at birth. Maintain warmth through skin-to-skin contact, warm ambient temperature, and head and body covering. Promote kangaroo care for low-birth weight infants.

— **Breastfeeding.** Breastfeed within the first hour after birth. Continue exclusive breastfeeding on demand day and night for six months.

— **Care.** keep the newborn close to the mother, father, or other caregiver. Keep the mother healthy.

— **Infection control.** Maintain cleanliness when handling the infant. Keep the cord clean. Provide prophylactic eye care. Promote early and exclusive breastfeeding. Immunize according to schedule. Treat infections promptly.

— **Management of complications.** Recognize and respond urgently to serious and life-threatening conditions

As neonatologist we have to try to guarantee that those simple measures are applied everywhere and fallowed children rights as school teaching —great impact of girls education—, hygienic measures control, accidents prevention, proper country adapted feeding and consistent immunizations program.

Technical assistance is capital and the lack of health workers in those countries has to be solved teaching the families what to do in case of possible illness and bringing closer health resources.

Walking all together in this direction for sure will give soon the benefits that all this children deserve and we are obliged to demand.

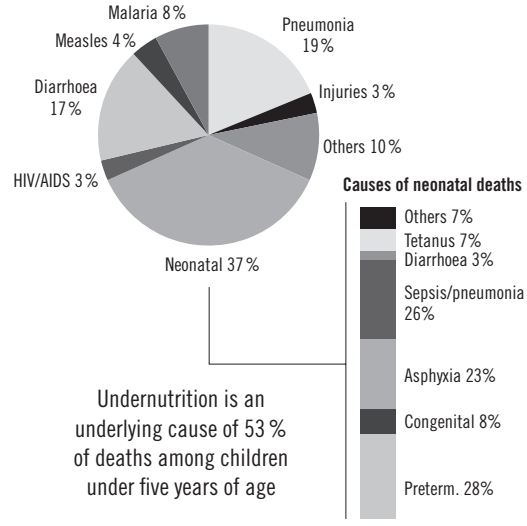

Figure 1. Major causes of death among children under 5 years of age and neonates in the world, 2000-2003.

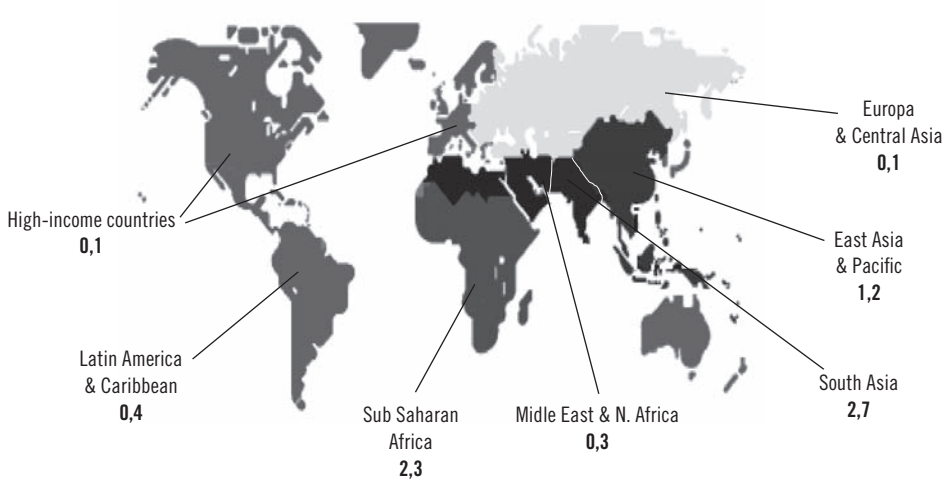

Figure 2. Deaths at a young age. Infants deaths (milions). 1998.

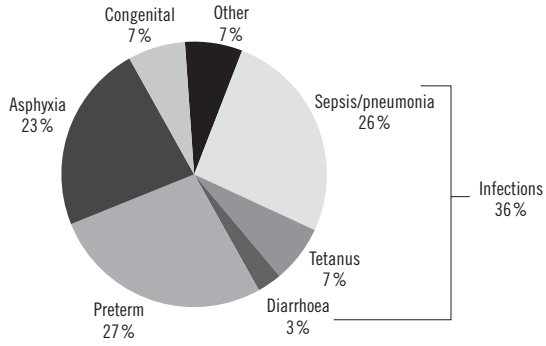

Figure 3. Estimated distribution of direct causes of 4 million neonatal deaths for the year 2000. Based on the vital registration data for 45 countries and modelled estimates for 147 countries.

Table 1. Underfive mortality rates (per 1.000 live births).

	1960	*1994*
Industrialized countries	37	9
Developing countries	216	101
Least developed countries	282	170

Table 2. Regional or country variations in NMRs and numbers of neonatal deaths, showing the proportion of deaths in children younger than age 5 years.

	NMR per 1.000 livebirths (range across countries)	*Number (%) of neonatal deaths (1.000s)*	*Percentage of deaths in children aged younger than 5 years in the neonatal peeriod*	*Percentage change in NMR between 1996 and 2005 estimates**
Income groups				
High income countries	4 (1-11)	42 (1 %)	63%	−29%
Low income and middle-income countries	33 (2-70)	3.956 (99 %)	38%	−8%
WHO regions				
Africa	44 (9-70)	1.128 (28 %)	24 %	5 %
Americas	12 (4-34)	195 (5 %)	48 %	−40 %
Easter Mediterranean	40 (4-63)	603 (15 %)	40 %	−9 %
Europe	11 (2-38)	116 (3 %)	49 %	−18 %
Southeast Asia	38 (11-43)	1.443 (36 %)	50 %	−21 %
Western Pacific	19 (1-40)	512 (13 %)	56 %	−39 %
Overall	**30 (1-70)**	**3.998 (100 %)**	**38 %**	**−16 %**

* The data imnputs cover at least a 5 year period before each set of estimates. Period of changes may be assumed to be up to 15 years. 139 countries with NMR data of 54 countries with gross national income per person of >US$ 9.386.

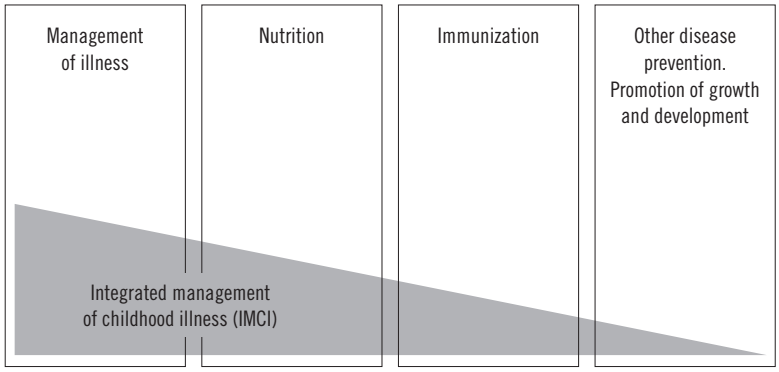

Figure 4. Integrated management of childhood illness (IMCI) as a key strategy for improving child health.

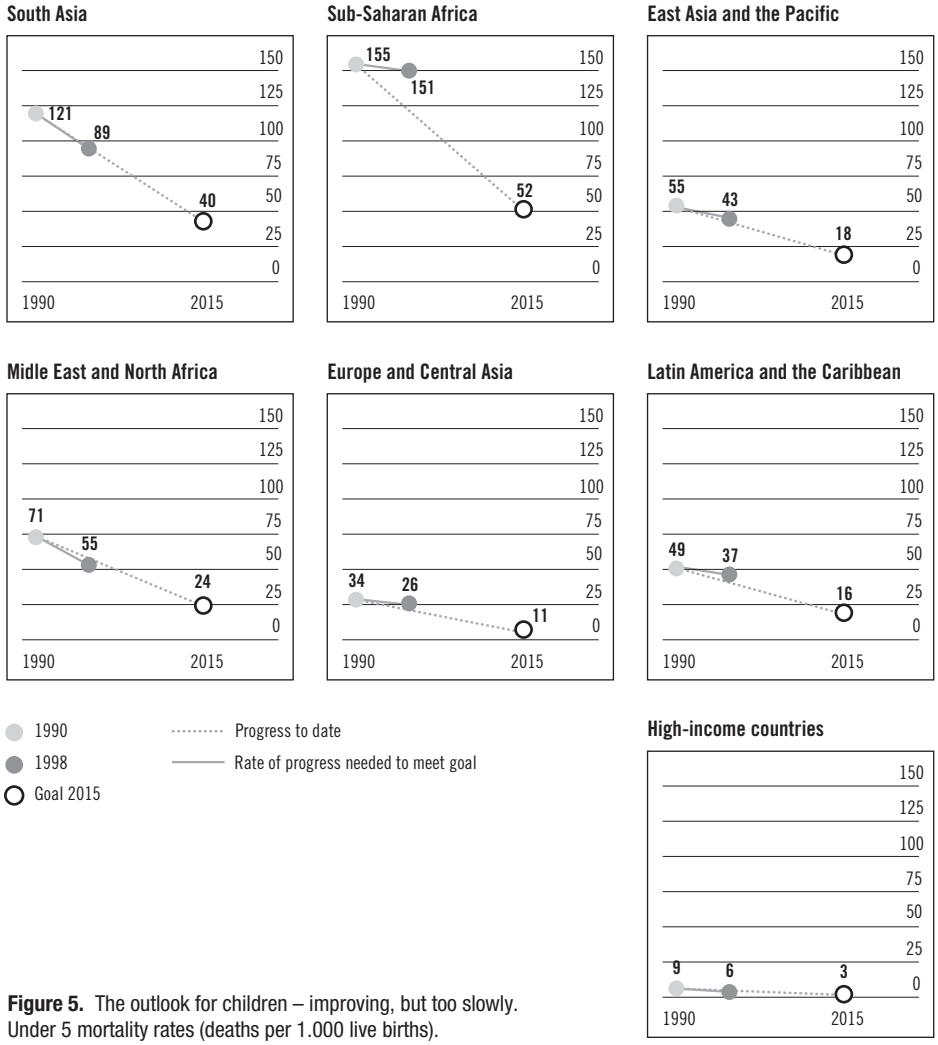

Figure 5. The outlook for children – improving, but too slowly.
Under 5 mortality rates (deaths per 1.000 live births).

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