J. Perinat. Med. 36 (2008) 191–196 • Copyright © by Walter de Gruyter • Berlin • New York. DOI 10.1515/JPM.2008.032

Recommendations and guidelines for perinatal practice

Guideline for the use of antenatal corticosteroids for fetal maturation*

Xavier Miracle[1,], Gian Carlo Di Renzo[2], Ann Stark[3], Avroy Fanaroff[4], Xavier Carbonell-Estrany[1] and Erich Saling[5] (Coordinators of WAPM Prematurity working group)**

[1] Neonatology Service, Hospital Clinic, Institut Clinic de Ginecologia, Obstetricia I Neonatologia, Universitat de Barcelona, Barcelona, Spain
[2] Department of Obstetrics and Gynecology and Center for Perinatal and Reproductive Medicine, University of Perurgia, Italy
[3] Baylor College of Medicine, Texas Children's Hospital, Houston, Texas, USA
[4] Rainbow Babies and Children's Hospital, Cleveland, Ohio and Case Western Reserve University School of Medicine, USA
[5] Institute of Perinatal Medicine, Berlin, Neukoelln

Abstract

The aim is to present a document, which is based on current evidence and serves as a guideline for use in clinical practice. The following questions are addressed:

- Is the use of antenatal corticosteroids (ACS) an effective therapy?
- Who are the candidates for antenatal corticosteroid therapy?
- Is there benefit after 34 weeks' gestation?
- When is the optimal time to treat?
- Which are the optimal steroids; what is the ideal dose and route of administration?
- Are there any contraindications to the administration of ACS?
- Are antenatal corticosteroids indicated in women with premature rupture of membranes (PROM)?
- Is the use of ACS recommended in pregnancies complicated by maternal diabetes mellitus?
- Should the treatment with corticosteroids be repeated?

*This paper was worked out under the auspices of the WAPM to achieve consensus on issues in perinatal practice. Coordinator of the working group: Xavier Miracle.

**Corresponding author:
Dr. Xavier Miracle
Neonatal Department
Hospital Clínic de Barcelona (Seu Maternitat)
Carrer Sabino Arana 1
08028 Barcelona
Tel: +3493 2275600 Ext: 7443-7503
Fax: +3493 2275605
E-mail: xmiracle@ya.com

Introduction

- Women at risk of preterm birth before 34 weeks' gestation are routinely given a course of antenatal corticosteroids (ACS) because there is good evidence that treatment reduces neonatal death, respiratory distress syndrome (RDS) and intraventricular hemorrhage (IVH).
- The origin of this practice comes from Liggins and Howie's first randomized trial in 1972 [26] which demonstrated a reduction in the incidence of RDS and mortality.
- Subsequent randomized controlled trials have compared single courses of corticosteroids with either placebo or no intervention, confirming the efficacy of this treatment [37].
- Three major institutions have been elaborating and updating recommendations and guidelines on the use of antenatal corticosteroids:

  1. The National Institutes of Health (NIH) published a Consensus Development Conference Statement in 1994 on the use of ACS [36] and in 2000 on the use of repeated courses of ACS [34].
  2. In May 2002, The American College of Obstetricians and Gynecologists' Committee on Obstetric Practice (ACOG) [5] supported the conclusions of the NIH consensus conference.
  3. The Royal College of Obstetricians and Gynecologists (RCOG) [35] published the third edition of their guideline in February 2004 (previously published in April 1996 and December 1999).

- In the last few years new relevant information has been published: The Cochrane Review on ACS (2006) [37] has been updated, aiming to assess the effects of ACS on fetal, neonatal and maternal morbidity and mortality and on child development.

  Regarding the controversial issue of single versus multiple courses of ACS therapy, two large randomized clinical trials have been recently published (Wapner et al. [43], and Crowther et al. [7]) and included in an updated Cochrane review on repeat doses of prenatal corticosteroids (2007) [9]. The larger study on multiple doses, the Canadian MACS trial [27] (Multiple Courses of Antenatal Corticosteroids for preterm birth Study) has finished recruitment and should probably be ready this year.

For the first time, data regarding long-term effects on the use of multiple steroid treatments have been released. Outcomes at 2–3 years from the studies of Wapner et al. and Crowther et al. have been published in The New England Journal of Medicine (September, 2007) [8, 44].

We would like to incorporate this new information in order to develop a practical clinical protocol for the use of antenatal corticosteroids.

- In the last Cochrane Review (2006) Roberts & Dalziel [37] included twenty-one randomized trials (3885 women and 4269 infants). Six new studies have been added since the previous review. Main results showed that "ACS does not increase risk to the mother of death, chorioamnionitis or puerperal sepsis. Treatment with ACS is associated with an overall reduction in neonatal death, RDS, IVH, necrotizing enterocolitis (NEC), respiratory support, intensive care admissions and systemic infections in the first 48 h of life". They also indicated that ACS is effective in women with premature rupture of membranes (PROM) and pregnancy related hypertension syndromes. "There is evidence to suggest benefit across a wide range of gestational ages from 26 to 34+6 weeks and in the current era of neonatal practice. "The authors concluded that the "evidence from this new review supports the continued use of a single course of antenatal corticosteroids to accelerate fetal lung maturation in women at risk of preterm birth. A single course of antenatal corticosteroids should be considered routine for preterm delivery with few exceptions. Further information is required concerning optimal dose to delivery interval, optimal corticosteroid to use, effects in multiple pregnancies, and to monitor the long-term effects into adulthood".

1. Who are candidates for antenatal corticosteroid therapy?

- Antenatal administration of corticosteroid therapy would be indicated to all women at high risk of preterm delivery between 24 and 34 weeks of gestation.
- Antenatal steroids could also be indicated over 34 weeks of gestation when there is evidence of pulmonary immaturity.

The 2006 Cochrane Review [37] stated in their conclusions that there is evidence to suggest benefit of ACS administration to a wide range of gestational ages from 26 to 34+6 weeks. Benefit under 28 weeks was the subject of debate in a previous analysis. This review shows that RDS is reduced in all age subgroups above 26 weeks, and there is also a significant reduction in IVH and neonatal death in the subgroup from 26 to 29+6 weeks.

Other studies show a decrease in the incidence of IVH and mortality between 24 and 28 weeks' gestation with a reduction in the severity of RDS but not the incidence at this interval [2].

After 34 weeks' gestation the use of ACS is still effective but the reduction in RDS, IVH and neonatal death is not significant. The number of women who will need to be treated to prevent one case of RDS would be much higher. In 2005, Stutchfield et al. [41] showed that ACS are still effective after 37 weeks' gestation in infants born by elective cesarean section. There was a significant reduction in RDS and transient tachypnea of the newborn (TTN).

Previous guidelines recommended considering the use of ACS after 34 weeks' gestation if there was evidence of pulmonary immaturity [5, 23, 35, 36]. We would concur with that recommendation.

2. When to treat?

- All women at high risk of preterm delivery should start a course of ACS unless delivery is imminent (less than one hour) even if only one dose is anticipated.
- Tocolytic drugs should be considered by the obstetricians in order to gain time to administer the preferred complete course of ACS.
- Accurate and standardized diagnosis of high-risk preterm labor is essential to avoid over-diagnosing and treating patients with unnecessary doses of corticosteroids and tocolytics.

The 2006 Cochrane Review [37] has shown that "ACS use reduces neonatal death even when infants are born $<$24 h after the first dose has been given". Another study has confirmed that incomplete courses of ACS are beneficial [13].

The exact time interval for ACS to become beneficial is unknown. There is a potential benefit commencing within hours of the first dose.

There is considerable variation in the way that spontaneous preterm labor is diagnosed, managed and treated internationally. Accurate and standardized diagnosis of high-risk preterm labor is essential to avoid overdiagnosing and overtreating patients with tocolytics and corticosteroids and unnecessary hospitalizations.

The European Association of Perinatal Medicine has published an international clinical guideline for the management of spontaneous preterm labor which states that contractions and cervical changes are not enough to define the risk of preterm labor. Oncofetal fibronectin (fFN) and ultrasonography to determine cervical length may be considered to complement the clinical assessment. With the use of biochemical markers and sonographic evaluation of the cervix, it is possible to identify the majority of women who are not in preterm labor [10, 11].

3. Which are the optimal steroids; what is the ideal dose and route of administration?

- We recommend betamethasone as the steroid of choice, when available, to be given in a course of two doses of 12 mg administered intramuscularly 24 h apart.

An alternative regimen would be four doses of 6 mg dexamethasone intramuscularly every 12 h.

These are the two most extensively studied steroid regimens, although there are no randomized trials directly comparing these two drugs. Both regimens were found to be equally effective for the prevention of RDS [6].

There is no absolute evidence to recommend betamethasone over dexamethasone and previous guidelines did not find enough evidence to recommend one above the other [5, 36]. However, in one recent study, Lee et al. [23] found that betamethasone was associated with a greater reduction in risk of death than dexamethasone, corroborating Jobe's results in 2004 [22].

Two other studies have indicated a decreased risk of cystic periventricular leukomalacia (PVL) in premature infants exposed to betamethasone, this association was not found with dexamethasone, particularly when using multiple doses [3, 40]. These results were not confirmed in Lee's study [23]. Because of this new evidence we recommend betamethasone as the steroid of choice. A course of betamethasone is still indicated in patients receiving treatment with hydrocortisone for other causes, because very little hydrocortisone crosses the placenta.

There is little data available on other routes of administration or dosage in humans, although extensive animal studies have been done: fetal intravascular hydrocortisone, given by cordocentesis, was shown to be ineffective in maturing the lungs [21]. Intra-amniotic betamethasone matures the lungs but the persisting presence of the drug is associated with increased fetal mortality and morbidity [32]. Some studies have been published on the possibility of giving steroids directly to the fetus intramuscularly rather than to the mother, showing that the lung maturing effects are similar to maternal injection, the negative effect on fetal growth is not seen and the effects on the brain are less than with maternal dosing [20, 33]. This effect seems to result from different pharmacokinetics of the drug [30].

4. Are there any contraindications to the administration of ACS?

- ACS therapy would be contraindicated in maternal systemic infections including tuberculosis. In women with chorioamnionitis caution is advised.

Administration of ACS is not related to an increase in either maternal or neonatal infection, even in the subgroup of patients with premature rupture of membranes (PROM) [37]. However, delaying delivery with established clinical chorioamnionitis could be detrimental for both mother and fetus.

5. Are antenatal corticosteroids indicated in women with premature rupture of membranes (PROM)?

- ACS therapy is indicated in women with PROM from 24 to 32 weeks' gestation not presenting clinical signs of chorioamnionitis.

This scenario includes considerable risk of infection for the mother and the fetus. The evidence justifying the use of ACS in PROM is based on two major meta-analyses: In the 2006 Cochrane Review [37] "ACS are shown to be beneficial in the subgroup of infants whose mothers have PROM. Neonatal death, RDS, IVH, NEC, and duration of respiratory support are all reduced, without an increase in either maternal or neonatal infection". Similar results were obtained from Harding et al.'s meta-analysis in 2001 [17]. Beyond 32 weeks of gestation, the risk of chorioamnionitis is higher than the risks derived from prematurity [15, 24].

6. Is the use of ACS recommended in pregnancies complicated by maternal diabetes mellitus?

- A course of ACS is indicated in pregnant women with pregestational or gestational diabetes at risk of preterm delivery.
- Close monitoring and treatment by an experienced obstetrical team is essential to guarantee diabetic control and avoid the possibility of severe transient hyperglycemia.

Infants of diabetic mothers delivered early might have pulmonary immaturity at a more advanced gestation than infants of nondiabetic mothers. Elective and spontaneous preterm delivery is more likely to occur in women with pregestational diabetes than in healthy controls, with preeclampsia, polyhydramnios and infections being common complications [38].

Close maternal glycemic control before and during pregnancy is essential, and has been demonstrated to reduce the incidence of hyaline membrane disease (RDS) in this group of infants [45].

Administration of a course of betamethasone at the usual dose and interval is recommended in diabetic pregnant women although there is little evidence of efficacy and safety of this practice. Women with gestational or pregestational diabetes were excluded from the majority of early randomized trials [37].

Caution is advised during ACS administration with close glycemic control during three days after the first dose. The steroid effect begins approximately 12 h after the first dose and lasts for five days [28].

Obstetricians should consider the use of ACS in diabetic pregnant women above 34 weeks' gestation if there is evidence of pulmonary immaturity by amniotic fluid analysis. The fluorescence polarization test is the most common test used for assessing fetal lung maturation.

7. Should courses of corticoids be repeated?

- Despite the new evidence from the recently completed randomized trials comparing single versus multiple doses of steroids, we are not able at this time to modify the recommendations of The NIH Consensus Development Panel on the use of repeated courses of antenatal corticoids. On the basis of current evidence we are not able to provide a final answer on the number of doses or the interval between them that are safe for the fetus.

Early trials [26, 29, 37] on the use of ACS did not show any benefit in primary outcomes for infants born more than 7 days after steroid administration. Especially, no reduction in the incidence of RDS or neonatal mortality was demonstrated. This lack of benefit led to a common practice of repeating courses or doses of ACS in a non-standardized way [4].

Animal and non-randomized studies in humans suggested that multiple courses of steroids could lead to harmful effects on myelination of the brain [12, 18], reduction in birthweight [19] or effects on brain growth through to adulthood [31], neurodevelopmental problems in childhood behavior [1, 14], or effects on the hypothalamo-pituitary-adrenal axis with a spectrum from hyperactivity in young life to hypoactivity in adult life [39]. Approximately 50% of women given antenatal corticosteroids remained undelivered 7–14 days after an initial course. Large randomized trials on this field were needed.

The NIH Consensus Statement on the use of repeated courses of antenatal corticoids concluded in the year 2000 [34], that "because of insufficient scientific data from randomized clinical trials regarding efficacy and safety, repeat courses of corticosteroids should not be used routinely. In general it should be reserved for patients enrolled in randomized controlled trials."

Several large trials [7, 15, 27, 42, 43] have been developed in recent years comparing single versus multiple courses. The TEAMS [42] trial did not progress from the pilot phase due to lack of funding. The MACS [27] trial completed recruitment and results are expected this year. One more trial from the US is in progress (Obstetrix 2003). Three other major trials have already been completed and are included in a Cochrane review on repeat doses of prenatal corticosteroids, recently published in 2007 [9]. In this review, five trials met the inclusion criteria recruiting a total of 2028 women.

The first trial was published in 2001 by Guinn et al. [15]. No significant difference in composite neonatal morbidity was found between the single and the weekly course of ACS. However, a subgroup analyses showed a significant decrease in composite morbidity among infants born at <28 weeks' gestation, with a lower rate of severe RDS. Differences in head circumference and birth weight were not found in the multiple courses group.

Wapner et al.'s trial [43] was published in 2006. Like the previous study, no significant difference in the primary outcome was found between the two groups, a composite of severe RDS, CLD, grade III or IV IVH, or PVL. However, in the subgroup of infants delivered before 32 weeks of gestation, better neonatal lung function results were found in the repeat doses group. Some individual morbidities were significantly lower in the multiple course therapy group, including less need for mechanical ventilation, continuous positive airway pressure, use of surfactant and a reduction in the incidence of pneumothorax. Mean birth weight and head circumference were similar in both groups although a reduction in birth weight was found in infants exposed to repeat courses after adjustment for gestational age. The safety monitoring committee recommended stopping the trial early because of the lack of reduction in composite morbidity and concerns regarding the tendency toward decreased birth weight in the repeat courses group.

In the larger trial, published by Crowther et al. [7] in 2006, women received a single weekly dose of steroids rather than the standard weekly course given in the previous studies. Despite the lower global dose received, significant lower rates of RDS were found, with a reduction in severe lung disease, use of oxygen, surfactant administration and peak inspired oxygen concentration in the multiple dose group. There were no differences in the incidences of chorioamnionitis in the mother or IVH, PVL, NEC, ROP or infection in the newborn. However, z scores for weight and head circumference were lower at birth in the repeat doses group, although there were no significant differences by the time of hospital discharge.

The authors of the Cochrane review on repeat doses of prenatal corticosteroids concluded that: "Repeat dose(s) of prenatal corticosteroids reduce the occurrence and severity of neonatal lung disease and the risk of serious health problems in the first few weeks of life. These short-term benefits for babies support the use of repeat dose(s) of prenatal corticosteroids for women at risk of preterm birth. However, these benefits are associated with a reduction in some measures of weight, and head circumference at birth, and there is still insufficient evidence on the longer-term benefits and risks".

For the first time, data regarding long-term effects on the use of repeat doses of antenatal corticosteroids have been published: Ronald Wapner [44] and Caroline Crowther [8] reported follow-up data on neurodevelopmental and growth outcomes at 24–36 months of age. Both studies show no significant differences in physical measures or growth, blood pressure, use of health services or child behavior and developmental scores, although attention problems were slightly more common in children exposed to repeat doses in Crowther's trial. No major neurodevelopmental complications have been documented, like cerebral palsy, blindness or deafness, although a higher rate of cerebral palsy among children who had been exposed to repeat doses of corticosteroids was observed in Wapner's trial, but without statistical significance.

The randomized clinical trials of single versus multiple courses of ACS therapy have provided new information regarding efficacy, showing improved short-term respiratory outcomes in the repeated courses group, mainly under 28 weeks' gestation. These results are consistent with previous animal studies [19] and observational human studies [38].

The two follow-up studies bring some reassurance that repeated courses or doses of antenatal steroids do not increase major neurosensory disability or affect childhood growth at 24–36 months of age. On the other hand, it is important to consider that long-term benefit is not demonstrated and possible harm is not ruled out.

We still need to remain very concerned about the long-term effects of repeated antenatal corticosteroids, mainly about alteration in child behavior. Caution is still needed since neurosensory abilities at 2 years are only moderately correlated with developmental outcomes in older children [16]. Many years will pass before follow-up studies of these children, and young adults, may provide appropriate reassurance.

For this reason, and despite the new evidence from the recently completed randomized trials comparing single versus multiple doses of steroids, we are not able at this time to modify the recommendations of The NIH Consensus Development Panel on the use of repeated courses of antenatal corticoids [34]. On the basis of current evidence' we are not able to provide a final answer on the number of doses or the interval between them that are safe for the fetus. Long-term follow-up of these studies and new evidence from the trials that are about to be concluded [27], could give us the answers.

In the meantime, if clinicians may wish to consider retreatment, senior staff should be always involved in the decision. Single doses rather than full repeated courses should be prescribed (as in the Crowther et al. study), preferably in gestations under 28 weeks, providing a very limited number of doses (no more than four in total). Parents should be informed on the limited data available on long-term outcomes. Administration of repeated ACS doses would be preferably contemplated in patients enrolled in randomized controlled trials and patients should be followed up for long-term neurodevelopmental outcomes.

References

[1] Aghajafari F, Murphy K, Matthews S, Ohlsson A, Amankwah K, Hannah M. Repeated doses of antenatal corticosteroids in animals: a systematic review. Am J Obstet Gynecol. 2002;186:843–9.

[2] Ballard PL, Ballard RA. Scientific basis and therapeutic regimens for use of antenatal glucocorticoids. Am J Obstet Gynecol. 1995;173:254.

[3] Baud O, Foix-L'Helias L, Kaminski M, Audibert F, Jarreau PH, Papiernik E, et al. Antenatal glucocorticoid treatment and cystic periventricular leukomalacia in very premature infants. N Engl J Med. 1999;341:1190–6.

[4] Brocklehurst P, Gates S, McKenzie-McHarg K, Alfirevic Z, Chamberlain G. Are we prescribing multiple courses of antenatal corticosteroids? A survey of practice in the UK. Br J Obstet Gynaecol. 1999;106:977–9.

[5] Committee on Obstetric Practice. ACOG committee opinion: antenatal corticosteroid therapy for fetal maturation. Obstet Gynecol. 2002;99:871.

[6] Crowley PA. Antenatal corticosteroid therapy: a meta-analysis of the randomized trials, 1972 to 1994. Am J Obstet Gynecol. 1995;173:322–35.

[7] Crowther CA, Haslam RR, Hiller JE, et al. Neonatal respiratory distress syndrome after repeat exposure to antenatal corticosteroids: a randomised controlled trial. Lancet. 2006;367:1913.

[8] Crowther CA, Doyle LW, Haslam RR, Hiller JE, Harding JE, Robinson JS. Outcomes at 2 years of age after repeat doses of antenatal corticosteroids. N Engl J Med. 2007;357:1179–89.

[9] Crowther CA, Harding JE. Repeat doses of prenatal corticosteroids for women at risk of preterm birth for preventing neonatal respiratory disease. Cochrane Database of Systematic Reviews 2007, Issue 3. Art. No.: CD003935. DOI: 10.1002/14651858.CD003935.pub2.

[10] Di Renzo GC, Al Saleh E, Mattei A, Koutras I, Clerici G. Use of tocolytics: what is the benefit of gaining 48 h for the fetus? Br J Obstet Gynaecol: An Inter J Obstet Gynaecol. 2006;113:72–7.

[11] Di Renzo GC, Roura LC and the European Association of Perinatal Medicine–Study Group on "Preterm Birth". Guideline for the management of spontaneous preterm labour. J Perinat Med. 2006;34:359–66.

[12] Dunlop et al. J Mat Fetal Med. 1997;6:309–13.

[13] Elimian A, Figueroa R, Spitzer AR, et al. Antenatal corticosteroids: are incomplete courses beneficial? Obstet Gynecol. 2003;102:352.

[14] French et al. Am J Obstet Gynecol. 2004;190:588–95.

[15] Guinn DA, Atkinson MW, Sullivan L, et al. Single vs. weekly courses of antenatal corticosteroids for women at risk of preterm delivery: a randomized controlled trial. J Am Med Assoc. 2001;286:1581.

[16] Hack M, Taylor HG, Drotar D, et al. Poor predictive validity of the Bayley Scales of Infant Development for cognitive function of extremely low birth weight children at school age. Pediatrics. 2005;116:333–41.

[17] Harding JE, Pang JM, Knight DB, Liggins GC. Do antenatal corticosteroids help in the setting of preterm rupture of membranes? Am J Obstet Gynecol. 2001;184:131.
[18] Huang et al. Int J Devel Neuroscience. 2001;19:487–93.
[19] Ikegami et al. Am J Resp Crit Care Med. 1995;152:1256–61.
[20] Jobe A, Newnham J, Willet K, Sly P, Ikegami M. Fetal versus maternal and gestational age effects of repetitive antenatal glucocorticoids. Pediatrics. 1998;102:1116–25.
[21] Jobe AH, Polk D, Ikegami M, Newnham J. Lung responses to ultrasound-guided fetal treatments with corticosteroids in preterm lambs. J Applied Physiol. 1993;75:2099–105.
[22] Jobe AH, Soll RF. Choice and dose of corticosteroid for antenatal treatments. Am J Obstet Gynecol. 2004;190:878.
[23] Lee BH, Stoll BJ, McDonald SA, Higgins RD. Adverse neonatal outcomes associated with antenatal dexamethasone versus antenatal betamethasone. Pediatrics. 2006;117: 1503.
[24] Lee MJ, Davies J, Guinn D, et al. Single versus weekly courses of antenatal corticosteroids in preterm premature rupture of membranes. Obstet Gynecol. 2004;103:274.
[25] Lee MJ, Guinn D. Antenatal use of corticosteroids in women at risk for preterm delivery. UpToDate, version 15.1, 2006.
[26] Liggins G, Howie R. A controlled trial of antepartum glucocorticoid treatment for prevention of the respiratory distress syndrome in premature infants. Pediatrics. 1972; 50:515–25.
[27] MACS (Multiple Courses of Antenatal Corticosteroids for preterm birth Study) University of Toronto. www.utoronto.ca/macs.
[28] Mathiesen ER, Christensen AB, Hellmuth E, et al. Insulin dose during glucocorticoid treatment for fetal lung maturation in diabetic pregnancy: test of an algorithm [correction of analgoritm]. Acta Obstet Gynecol Scand. 2002;81: 835.
[29] McLaughlin KJ, Crowther CA, Walker N, Harding JE. Effects of a single course of corticosteroids given more than 7 days before birth: a systematic review. Aust N Z J Obstet Gynaecol. 2003;43:101.
[30] Moss TJ, Doherty DA, Nitsos I, Harding R, Newnham JP, Pharmacokinetics of betamethasone after maternal or fetal intramuscular administration. Am J Obstet Gynecol. 2003; 189:1751–7.
[31] Moss TJ, Doherty DA, Nitsos I, Sloboda DM, Harding R, Newnham JP. Effects into adulthood of single or repeated antenatal corticosteroids in sheep. Am J Obstet Gynecol. 2005;192:146–52.
[32] Moss TJM, Mulrooney NP, Nitsos I, Ikegami M, Jobe AH, Newnham JP. Intra-amniotic corticosteroids for preterm lung maturation in sheep. Am J Obstet Gynecol. 2003; 189:1389–95.
[33] Newnham JP, Evans SF, Godfrey M, Huang W, Ikegami M, Jobe A. Maternal, but not fetal, administration of corticosteroids restricts fetal growth. J Matern Fetal Med. 1999; 8:81–7.
[34] NIH Consensus Development Panel. Antenatal corticosteroids revisited: repeat courses—National Institutes of Health Consensus Development Conference statement, August 17–18, 2000. Obstet Gynecol. 2001;98:144–50.
[35] RCOG Guidelines. Number 7. ACS to prevent respiratory distress syndrome. London: RCOG; 1996.
[36] Report on the Consensus Development Conference on the Effect of Corticosteroids for Fetal Maturation on Perinatal Outcomes. U.S. Department of Health and Human Services, Public Health Service, NIH Pub No. 95–3784, November 1994.
[37] Roberts D, Dalziel S. Antenatal corticosteroids for accelerating fetal lung maturation for women at risk of preterm birth. Cochrane Database of Systematic Reviews 2006, Issue3.Art.No.:CD004454.DOI:10.1002/14651858.CD004454.pub2.
[38] Sibai BM, Caritis SN, Hauth JC, et al. Preterm delivery in women with pregestational diabetes mellitus or chronic hypertension relative to women with uncomplicated pregnancies. The national institute of child health and human development maternal fetal medicine units network. Am J Obstet Gynecol. 2000;183:1520.
[39] Sloboda DM, Moss TJ, Li S, Doherty D, Nitsos I, Challis JR, Newnham JP. Prenatal betamethasone exposure results in pituitary-adrenal hyporesponsiveness in adult sheep. Am J Physiol Endocrinol Metab. 2007;292:E61–70.
[40] Spinillo A, Viazzo F, Colleoni R, et al. Two-year infant neurodevelopmental outcome after single or multiple antenatal courses of corticosteroids to prevent complications of prematurity. Am J Obstet Gynecol. 2004;191:217.
[41] Stutchfield P, Whitaker R, Russell I. Antenatal betamethasone and incidence of neonatal respiratory distress after elective caesarean section: pragmatic randomised trial. B Med J. 2005;331:662.
[42] TEAMS Trial (Trial of the Effects of Antenatal Multiple courses of Steroids versus a single course) http://www.npeu.ox.ac.uk/teams/.
[43] Wapner RJ, Sorokin Y, Thom EA, et al. Single versus weekly courses of antenatal corticosteroids: evaluation of safety and efficacy. Am J Obstet Gynecol. 2006;195:633.
[44] Wapner RJ, Sorokin Y, Mele L, et al. Long-term outcomes after repeat doses of antenatal corticosteroids. N Engl J Med. 2007;357:1190–8.
[45] Weintrob N, Karp M, Hod M. Short- and long-range complications in offspring of diabetic mothers. J Diabetes Complications. 1996;10:294–301.