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MATERNAL-FETAL MEDICINE

Antenatal corticosteroids for fetal lung maturation in threatened preterm delivery: indications and administration

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Abstract
Introduction Antenatal maternal administration of corticosteroids has been shown to reduce morbidity and mortality rates in preterm delivery. Threatened spontaneous or medically indicated preterm delivery for maternal or fetal indications between 24 and 34 weeks of gestation with unknown fetal lung maturity status are indications for antenatal corticosteroid administration. Recent studies have challenged current practice of antenatal glucocorticoid use. The goal of this expert letter is to provide recommendations based for the clinical use of antenatal glucocorticoids based on the current evidence from published studies.
Methods The published literature (PubMed search), as well as the recommendations of other national societies, has been searched and taken into consideration for these recommendations.
Results/conclusions The standard regimen of antenatal corticosteroids involves a single course of 2 × 12 mg betamethasone administered intramuscularly within 24 h. The administration of corticosteroids usually is performed between 24 and 34 weeks gestation. However, under particular circumstances it may be beneficial even at 23 weeks and at 35–36 weeks of gestation. The evidence to date is clearly against the routine administration of multiple antenatal steroid courses. In special clinical situations, a second course of betamethasone ("rescue course") may be justifiable. Tocolysis during administration of steroids is not routinely indicated in the absence of contractions, cervical shortening or rupture of membranes.

Keywords Antenatal glucocorticoids · Preterm birth

Introduction

It has been known for years that antenatal maternal administration of corticosteroids reduces morbidity and mortality rates in cases of preterm delivery. Large randomized studies have shown a 50 % reduction in the incidence of respiratory distress syndrome (RDS) following administration of antenatal corticosteroids, as well as other complications such as severe intraventricular hemorrhage and necrotizing enterocolitis [1, 2]. This treatment can reduce the overall mortality of preterm delivery by approximately 50 %. Furthermore, the administration of antenatal steroids does not increase the risk of sepsis in premature infants.

Until recently, the dosing regimen of corticosteroids for fetal lung maturation was debated. Although several smaller studies suggested that repeated courses of corticosteroids could have certain benefits, others, including

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some animal studies, showed possible impairment of fetal neurodevelopment. Contradictory findings in the literature also exist regarding the timing of administration and the type of corticosteroid which should be given. Thus, the goal of this expert letter is to create a unified consensus with evidence-based recommendations regarding the administration of antenatal corticosteroids. The available literature, as well as the recommendations of other national societies, has been taken into consideration for these recommendations.

Indications for administration of antenatal corticosteroids

Threatened spontaneous delivery or medically indicated preterm delivery for maternal or fetal (e.g., severe intrauterine growth restriction due to placental insufficiency or preeclampsia) indications between 24 and 34 weeks of gestation with unknown fetal lung maturity status as well as documented pulmonary immaturity after 34 weeks of gestation (surfactant/albumin ratio <55).

Recently published, non-randomized studies have suggested that the administration of corticosteroids at 23 weeks of gestation may be beneficial and help reduce neonatal mortality, even at this extremely premature age [3]. Therefore, antenatal steroids may be administered several days prior to 24 weeks of gestation, depending on the individual case and indication.

After 34 weeks of gestation, severe long-term neonatal morbidity is not significantly higher as in those delivered at term. Nevertheless, the risks of pulmonary complications (RDS, possibly pneumothorax) and neonatal infection are the main concerns in neonates delivered at this gestational age, although the risk of RDS continuously decreases from this point until term. No larger studies regarding antenatal corticosteroid administration in preterm delivery after 34 weeks of gestation exist, which demonstrate its efficacy in this time period [4]. Nevertheless, one randomized study of nearly 1,000 pregnant women prior to elective cesarean section in the 37th to 39th week of pregnancy demonstrated a significant (50 %) reduction of pulmonary complications up to the 38th week of gestation when corticosteroids had been administered [5]. This study also showed that delaying the timing of elective cesarean section until 39 weeks of gestation had the equivalent or an even better effect than antenatal steroids. Thus, a carefully timed cesarean section (after 39 0/7 weeks gestation) is preferable to steroids, which may have possible fetal side effects. On the other hand, it can be assumed from these data that antenatal corticosteroids have an effect on pulmonary maturity even after 34 weeks of gestation, which would be biologically plausible. Therefore, in the case of preterm delivery at 35–36 weeks of gestation and in the absence of extreme time pressure to deliver the fetus, the administration of antenatal steroids could be considered prior to cesarean section as well as prior to induction of labor. This coincides with the guidelines of the Royal College of Obstetricians and Gynaecologists (RCOG) [6]. Nevertheless, the risks and benefits of antenatal corticosteroid administration and the individual clinical situation must be carefully considered. In general, it appears that the potential risks of antenatal steroids as well as those of prolonging pregnancy, for example, in the case of premature rupture of membranes, outweigh the likely limited benefits of steroid administration after this time point.

Contraindications against antenatal glucocorticoid administration

Antenatal glucocorticoid administration is contraindicated when urgent delivery of the fetus is needed (e.g., pathological fetal heart rate tracing, placental abruption) [7].

Severe, fulminant chorioamnionitis is another contraindication; immediate delivery is indicated in these cases. In contrast, mild, generalized signs of maternal infection, in particular in very early gestational ages (less than 26 weeks) do not comprise an absolute contraindication to administration of antenatal glucocorticoids [8, 9]. In this situation, therapy with a broad-spectrum antibiotic is essential, and the risks and benefits of antenatal steroids versus immediate delivery must be carefully weighed.

Non-gynecological infections as well as well-controlled maternal diabetes mellitus (gestational diabetes or preexisting type 1 or 2 diabetes) are not contraindications against antenatal corticosteroid administration. In the case of diabetes mellitus, blood glucose values must be closely monitored during therapy and insulin dosages adjusted accordingly [2].

In cases of preeclampsia between 24 and 34 weeks of gestation, antenatal steroids can be administered as long as delivery can be safely delayed for at least 12–24 h [10]. Additionally, steroids may help stabilize platelet and liver enzyme levels in the case of thrombocytopenia and elevated liver enzymes in HELLP syndrome, thus justifying the administration of betamethasone even shortly before or after delivery. Whether the effects are simply “cosmetic” or have a truly beneficial effect on the progress of HELLP syndrome, however, remains unclear.

Administration of antenatal corticosteroids

The standard regimen of antenatal corticosteroids involves 12 mg betamethasone administered intramuscularly,

repeated once after 24 h (2 × 2 ampules of Celestone Chronodose®; 1 ampule = 3 mg betamethasone natrium phosphate plus 3 mg betamethasone acetate).

In the very rare instance when intramuscular administration is contraindicated (e.g., extremely elevated risk of bleeding), Celestan® i.v. (2 × 3 ampules of 1 ml, each containing 4 mg betamethasone, dosage repeated once after 24 h) may be given. However, the intravenous regimen has not been evaluated in studies; in particular, there is no evidence for a more rapid effect with the i.v. administration, even when the interval between doses is shortened to 12 or 6 h. Therefore, the intramuscular administration of corticosteroids as described above comprises the international, evidence-based standard. Oral administration is obsolete [11]. Recent evidence suggests that a 12-h interval might be equivalent to the standard 24-h interval. However, the incidence of necrotizing enterocolitis is increased and therefore the 12-h interval cannot be recommended [12].

The full effect of antenatal corticosteroids is reached 48 h after first administration of the medication [13].

Repeated courses of antenatal corticosteroids?

In many European clinics in the 1990s, repeated courses of antenatal corticosteroids were often administered in 1- to 2-week intervals, since their effectiveness on pulmonary maturity was well known. At that time, there was no evidence from randomized studies demonstrating any additional benefit to repeating steroid courses. It was, however, becoming increasingly apparent that glucocorticoids could have potential negative effects in the fetus, particularly on the central nervous system. They affect primarily the proliferation and differentiation of oligodendrocytes, which are responsible for generation of the myelin sheath around the pyramidal tract. This is especially important in the third trimester of pregnancy, when cellular division of oligodendrocytes reaches its peak. Animal studies have shown neurological developmental deficits in newborns following multiple courses of antenatal steroids in comparison with a single course [14, 15].

In addition, repeated administration of steroids resulted in lower birth weights, decreased brain size at birth and reduced neuronal myelinization [16–20].

Since then, the results from several large randomized clinical studies have been published [17, 21–24]. With the exception of one group [21], none of the studies showed any significant benefit for the newborn. Furthermore, the largest study, which included nearly 2,000 patients [17], confirmed the negative effects of repeated courses of antenatal steroids, including diminished birth weight, body length and head circumference at birth in comparison with administration of a single course. One study [24] was even terminated early due to the increased (although not statistically significant) incidence of cerebral palsy in the group receiving repeated courses of corticosteroids.

The conclusion that can be made from these studies is that the findings to date are against the routine administration of multiple antenatal steroid courses. Long-term outcomes of the children in these studies are not yet available.

It was assumed in certain clinical situations, namely, in acute deterioration with renewed threatened preterm delivery, that repeating antenatal steroids once ("rescue course") could be advantageous. Although there has been limited evidence to date to support this, a recently published, randomized study with nearly 500 patients showed that a second course of antenatal steroids administered up to 32 weeks of gestation—with a minimal interval of 2 weeks from the first course—can improve neonatal outcome without increasing short-term risks [25]. In specific clinical situations (e.g., first course of steroids administered very early in the pregnancy, e.g., 24 weeks of gestation, followed by deterioration of the situation 4–6 weeks later), the authors believe that a single repeated course of steroids ("rescue course") can be justified.

Short- and long-term effects of antenatal glucocorticoids on fetus and newborn

Antenatal administration of glucocorticoids has several well-known short-term effects on the fetus [26]. Fetal heart rate as determined by cardiotocography shows marked reduction of variability, 2–3 days after betamethasone administration. These changes are thought to due to a shift in the sympatho-vagal balance [27]. Similarly, fetal body movements and breathing activity are reduced. Fetal magnetoencephalographic studies suggest that administration of betamethasone to expectant mothers was associated with acute change in higher cortical functions in the exposed fetuses [28]. Doppler flow measurements in the umbilical artery are unchanged in fetuses with normal pulsatility before administration. However, in fetuses with absent or reversed end-diastolic flow in the umbilical artery show decreasing vascular resistance in the placental circulation, leading to return of end-diastolic flow and decreased pulsatility in the umbilical artery. These changes can be observed in two-third of all cases 24 h after betamethasone injection and last for a median of 72 h (in single cases up to 10 days). If this phenomenon is beneficial or harmful for the fetus, is a matter of debate.

Less is known about long-term effects of antenatal glucocorticoids on neonatal and child development. In newborns exposed to a single course of antenatal betamethasone, cardiac autonomic balance seems to be

preserved in neonates [29]. In children, some effects on behavior were described in some studies [30], while studies in adults showed no alterations of cognitive functioning, working memory and attention, psychiatric morbidity, handedness, or health related quality of life after a single course of antenatal betamethasone [31]. Fetal programming effects on cardiovascular functions (e.g., hypertension) have been described in humans and are currently further studied in animal models [32].

Practical issues

Antenatal corticosteroids are best administered in an inpatient setting. Tocolysis during administration of steroids is not routinely indicated in the absence of contractions, cervical shortening or rupture of membranes. A note of caution: concurrent administration of antenatal corticosteroids and tocolysis using beta-mimetics in the presence of maternal infection increases the risk of development of pulmonary edema [33, 34].

Careful counseling of the couple prior to administration of antenatal corticosteroids, particularly between 23 and 25 weeks of gestation and preferentially in the presence of a neonatologist, is essential. Furthermore, the course of action regarding fetal monitoring and potential intervention (cesarean section) for fetal indications during this time period should be clearly established with the couple and carefully documented. Likewise, the care of the neonate in case of delivery (maximal intervention with full resuscitation efforts vs. comfort care) must be discussed with the neonatologist in advance. Ideally, the plan should be established in an interdisciplinary setting whenever possible. Regarding this topic, one can refer to the interdisciplinary guidelines from the Swiss Society of Neonatology from 2011 on the care of the premature infant at the edge of viability [35].

Another important measure involves expedient transfer of the pregnant woman from 22 weeks onwards to a perinatal center with a neonatal intensive care unit capable of treating neonates delivered prior to 34 weeks of gestation. Many studies have shown that neonatal morbidity and mortality can be reduced through this action. The first dose of corticosteroids should be administered prior to transfer of the patient.

Although administering antenatal betamethasone for fetal lung maturity must be regarded as off-label use, the authors and the quality assurance commission of the Swiss Society of Gynecology and Obstetrics believes that official informed consent is not necessary in this case, since its use is undisputed and no other alternative, licenced drugs exist to date.

Conflict of interest Authors do not have any conflict of interest.

References

1. Crowley P (2000) Prophylactic corticosteroids for preterm birth. Cochrane Database Syst Rev (2):CD000065
2. Roberts D, Dalziel S (2006) Antenatal corticosteroids for accelerating fetal lung maturation for women at risk of preterm birth. Cochr Database Syst Rev 3:CD004454
3. Hayes EJ et al (2008) Effect of antenatal corticosteroids on survival for neonates born at 23 weeks of gestation. Obstet Gynecol 111(4):921–926
4. Porto AM et al (2011) Effectiveness of antenatal corticosteroids in reducing respiratory disorders in late preterm infants: randomised clinical trial. BMJ 342:d1696
5. Stutchfield P, Whitaker R, Russell I (2005) Antenatal betamethasone and incidence of neonatal respiratory distress after elective caesarean section: pragmatic randomised trial. BMJ 331(7518): 662
6. RCOG (2010) Antenatal corticosteroids to reduce neonatal morbidity (Green-top 7). http://www.rcog.org.uk/womens-health/clinical-guidance/antenatal-corticosteroids-prevent-respiratory-distress-syndrome-gree
7. NIH (1994) Effect of corticosteroids for fetal maturation on perinatal outcomes. NIH consensus statement 12(2):1–24
8. Been JV et al (2011) Antenatal steroids and neonatal outcome after chorioamnionitis: a meta-analysis. BJOG 118(2):113–122
9. Locatelli A et al (2008) Which factors affect the occurrence of severe cerebral lesions in preterm neonates who are born with intrauterine infection? Am J Obstet Gynecol 199(4):404 e1–404 e5
10. Amorim MM, Santos LC, Faundes A (1999) Corticosteroid therapy for prevention of respiratory distress syndrome in severe preeclampsia. Am J Obstet Gynecol 180(5):1283–1288
11. Jobe AH, Soll RF (2004) Choice and dose of corticosteroid for antenatal treatments. Am J Obstet Gynecol 190(4):878–881
12. Khandelwal M, Chang E, Hansen C, Hunter K, Milcarek B (2012) Betamethasone dosing interval: 12 or 24 hours apart? A randomized, noninferiority open trial. Am J Obstet Gynecol 206(3):201.e1–201.e11
13. Elimian A et al (2003) Antenatal corticosteroids: are incomplete courses beneficial? Obstet Gynecol 102(2):352–355
14. Whitelaw A, Thoresen M (2000) Antenatal steroids and the developing brain. Arch Dis Child Fetal Neonatal Ed 83(2):F154–F157
15. Huang WL et al (1999) Effect of corticosteroids on brain growth in fetal sheep. Obstet Gynecol 94(2):213–218
16. Crowther CA, Harding JE (2007) Repeat doses of prenatal corticosteroids for women at risk of preterm birth for preventing neonatal respiratory disease. Cochr Database Syst Rev 3:CD003935
17. Murphy KE et al (2008) Multiple courses of antenatal corticosteroids for preterm birth (MACS): a randomised controlled trial. Lancet 372(9656):2143–2151
18. Wapner RJ et al (2006) Single versus weekly courses of antenatal corticosteroids: evaluation of safety and efficacy. Am J Obstet Gynecol 195(3):633–642
19. Aghajafari F et al (2001) Multiple courses of antenatal corticosteroids: a systematic review and meta-analysis. Am J Obstet Gynecol 185(5):1073–1080
20. Jobe AH et al (1998) Single and repetitive maternal glucocorticoid exposures reduce fetal growth in sheep. Am J Obstet Gynecol 178(5):880–885

21. Crowther CA et al (2007) Outcomes at 2 years of age after repeat doses of antenatal corticosteroids. N Engl J Med 357(12):1179–1189
22. Crowther CA et al (2006) Neonatal respiratory distress syndrome after repeat exposure to antenatal corticosteroids: a randomised controlled trial. Lancet 367(9526):1913–1919
23. Guinn DA et al (2001) Single vs weekly courses of antenatal corticosteroids for women at risk of preterm delivery: a randomized controlled trial. JAMA, J Am Med Assoc 286(13): 1581–1587
24. Wapner RJ et al (2007) Long-term outcomes after repeat doses of antenatal corticosteroids. N Engl J Med 357(12):1190–1198
25. Garite TJ et al (2009) Impact of a 'rescue course' of antenatal corticosteroids: a multicenter randomized placebo-controlled trial. Am J Obstet Gynecol 200(3):248 e1–248 e9
26. Mulder EJ, de Heus R, Visser GH (2010) Antenatal corticosteroid therapy: short-term effects on fetal behaviour and haemodynamics. Semin Fetal Neonatal Med 14(3):151–156
27. Schneider U, Fiedler A, Schröder B, Jaekel S, Stacke A, Hoyer D, Schleussner E (2010) The effect of antenatal steroid treatment on fetal autonomic heart rate regulation revealed by fetal magnetocardiography (fMCG). Early Hum Dev 86(5):319–325
28. Schneider U, Arnscheidt C, Schwab M, Haueisen J, Seewald HJ, Schleussner E (2011) Steroids that induce lung maturation acutely affect higher cortical function: a fetal magnetoencephalography study. Reprod Sci 18(1):99–106
29. Schäffer L, Burkhardt T, Tomaske M, Schmidt S, Luzi F, Rauh M, Leone A, Beinder E (2010) Effect of antenatal betamethasone administration on neonatal cardiac autonomic balance. Pediatr Res 68(4):286–291
30. French NP, Hagan R, Evans SF, Mullan A, Newnham JP (2004) Repeated antenatal corticosteroids: effects on cerebral palsy and childhood behavior. Am J Obstet Gynecol 190(3):588–595
31. Dalziel SR, Lim VK, Lambert A, McCarthy D, Parag V, Rodgers A, Harding JE (2005) Antenatal exposure to betamethasone: psychological functioning and health related quality of life 31 years after inclusion in randomised controlled trial. BMJ 331(7518):665–671
32. Shaltout HA, Rose JC, Chappell MC, Diz DI (2012) Angiotensin-(1–7) deficiency and baroreflex impairment precede the antenatal Betamethasone exposure-induced elevation in blood pressure. Hypertension 59(2):453–458
33. Beer P, Passweg D (1992) Maternal pulmonary edema as an anesthesia complication after intravenous tocolysis and stimulating of lung maturation. Gynakol Geburtshilfliche Rundsch 32(2):100–103
34. Ogunyemi D (2007) Risk factors for acute pulmonary edema in preterm delivery. Eur J Obstet Gynecol Reprod Biol 133(2):143–147
35. Berger TM et al (2011) Perinatal care at the limit of viability between 22 and 26 completed weeks of gestation: New Swiss recommendations: Revision of the 2002 recommendations. Swiss Med Wkly 141:1–13