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SPECIAL ARTICLE

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FIGO good practice recommendations on the use of prenatal corticosteroids to improve outcomes and minimize harm in babies born preterm

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Abstract

For women with a singleton or a multiple pregnancy in situations where active neonatal care is appropriate, and for whom preterm birth is anticipated between 24 and 34 weeks of gestation, one course of prenatal corticosteroids should ideally be offered 18 to 72 h before preterm birth is expected to improve outcomes for the baby. However, if preterm birth is expected within 18 h, prenatal corticosteroids should still be administered. One course of corticosteroids includes two doses of betamethasone acetate/phosphate 12 mg IM 24 h apart, or two doses of dexamethasone phosphate 12 mg IM 24 h apart. In women in whom preterm birth is expected within 72 h and who have had one course of corticosteroids more than a week previously, one single additional course of prenatal corticosteroids could be given at risk of imminent delivery. Prenatal corticosteroids should not be offered routinely to women in whom late preterm birth between 34 and 36 weeks is anticipated. In addition, prenatal corticosteroids should not be given routinely before cesarean delivery at term. Neither should prenatal corticosteroids be given "just in case". Instead, prenatal steroid administration should be reserved for women for whom preterm birth is expected within no more than 7 days, based on the woman's symptoms or an accurate predictive test.

KEYWORDS
"just in case treatment", antenatal, betamethasone, child outcome, corticosteroids, dexamethasone

1 | INTRODUCTION

The first randomized trial of prenatal corticosteroids to reduce respiratory distress syndrome in babies subsequently born preterm was published in 1972.[1] Evidence of their efficacy has been accumulating since then, and since the mid-1980s prenatal corticosteroids have been increasingly used for this indication. The robust evidence for their effectiveness in this regard has led many authorities worldwide to endorse their use to improve outcomes for the baby.[2]

While the lung maturational effects of a single course of corticosteroids are apparent, there are emerging concerns of potential harm; for example, when multiple courses are applied, when women given prenatal corticosteroids deliver at term rather than preterm, or

* The Members of the FIGO Working Group for Preterm Birth, 2018– 2021 are listed at the end of the article.

when corticosteroids are given in unproven scenarios such as elective cesarean section at term.

The purpose of this document is to review the evidence and provide good practice recommendations for the use of prenatal corticosteroids to improve outcomes in babies likely to be born preterm.

2 | CLINICAL SCENARIOS AND DRUG ADMINISTRATION

2.1 | *Singleton pregnancy where preterm birth is anticipated before 34+0 weeks of gestation*

Meta-analysis of 27 trials evaluating one or more courses of prenatal corticosteroids (betamethasone, dexamethasone, or hydrocortisone) in comparison with placebo or no treatment in babies anticipated to be born preterm has shown clear benefits for the baby, with a reduction in perinatal death (RR 0.85; 95% CI 0.77–0.93), respiratory distress syndrome (RR 0.71; 95% CI 0.65–0.78), intraventricular hemorrhage (RR 0.58; 95% CI 0.45–0.75), necrotizing enterocolitis (RR 0.50; 95% CI 0.32–0.78), and developmental delay in childhood (RR 0.51; 95% CI 0.27–0.97), but not cerebral palsy.[3] Potential harms included evidence of reduced glucose tolerance but not diagnoses of diabetes in offspring exposed to prenatal corticosteroids in utero.

For trials in this meta-analysis, the steroid most commonly used was a betamethasone acetate/phosphate mix, in a dose of 24 mg divided across 24 h. The majority of studies used a single course of steroids. The majority of trials included women with ruptured membranes. There was no evidence that ruptured membrane status led to any differences in fetal outcomes or rates of chorioamnionitis or endometritis. There is some evidence that different types of corticosteroid have different effects on chorioamnionitis, but no evidence of difference in outcome for the baby.[3]

Betamethasone, but probably not dexamethasone, appears to reduce chorioamnionitis (RR 0.69; 95% CI 0.51–0.93). However, the Cochrane review suggests fewer benefits of corticosteroids when administered at or after 35+0 weeks.[3] Additionally, the National Institute for Health and Care Excellence (NICE) in the UK notes that the evidence for benefit over harms of prenatal steroid use is strongest for babies born between 24+0 and 34+0 weeks of gestation.[4] Therefore, the lower limit for offering prenatal corticosteroids should be adjusted to the time when active care is appropriate in each specific location.

Recommendation: *For women with singleton pregnancies where active neonatal care is appropriate, for whom preterm birth is anticipated between 24+0 and 34+0 weeks of gestation, prenatal corticosteroids should be offered to improve outcomes for the baby.*

2.2 | *Multiple pregnancy where preterm birth is anticipated before 34+0 weeks of gestation*

There is much less evidence on the impact of prenatal corticosteroids in multiple pregnancies: the number of babies evaluated in trials restricted to multiple pregnancies is fewer than 250 for the outcomes of fetal, perinatal, or neonatal death, and 320 for the outcome of respiratory distress syndrome.[3,5] However, the effect size is similar for all mother and baby outcomes, regardless of whether the study recruited women with singleton, multiple pregnancy, or a mixed population.

Recommendation: *For women with multiple pregnancy where active neonatal care is appropriate, for whom preterm birth is anticipated between 24+0 and 34+0 weeks of gestation, prenatal corticosteroids should be offered to improve outcomes for the baby.*

2.3 | *Pregnancies where late preterm birth between 34+0 and 36+6 weeks of gestation is anticipated*

A high-quality US study assessed the effects of corticosteroids in 2831 women at risk of late preterm birth (34+0 until 36+5 weeks of gestation).[6] The administration of corticosteroids statistically significantly reduced the requirement for respiratory support in the first 72 h of life (11.6% vs 14.4%; RR 0.80; 95% CI 0.66–0.97; number needed to treat = 36). However, neonatal hypoglycemia was more common in the betamethasone group than in the placebo group (24.0% vs 15.0%; RR 1.6; 95% CI 1.37–1.87; number needed to harm = 11). While no long-term harms have been proven following corticosteroids at late preterm gestations, there has been no significant follow-up of trials. Observational studies using population data have shown prenatal corticosteroid exposure is associated with increased behavioral and psychiatric diagnoses in children.[7]

Recommendation: *Prenatal corticosteroids should not be offered routinely to women in whom late preterm birth is anticipated. Instead, the use of prenatal corticosteroids should be considered in light of the balance of risks and benefits for individual women.*

3 | TYPE AND DOSE OF PRENATAL CORTICOSTEROIDS

Most studies have used betamethasone acetate/phosphate or dexamethasone phosphate as the prenatal steroid.[3] Typical treatment regimens (one course) are two doses of betamethasone acetate/phosphate 12 mg intramuscularly 24 h apart, or four doses of 6 mg dexamethasone phosphate intramuscularly 6 h apart. However, other treatment regimens have been used. It is vital to use an effective steroid formulation and the correct dose regimen for the type of steroid used to ensure sustained fetal exposure to the agent.[8] Assuming this is achieved, there is no evidence that either is better for reducing fetal or neonatal adverse outcomes. The Asteroid study randomized 1356 women to two intramuscular injections of either 12 mg dexamethasone (dexamethasone sodium phosphate) or 11.4 mg betamethasone (Celestone Chronodose) 24 h apart, and found no differences in two-year outcomes between the two groups.[9] As mentioned above, the relative risk of maternal chorioamnionitis appears lower with betamethasone acetate/phosphate.[3]

Recommendation: *Where prenatal corticosteroids are given to improve fetal outcomes, appropriate regimens include two doses of betamethasone acetate/phosphate 12 mg (=one course) IM 24 h apart, or*

two doses of dexamethasone phosphate 12mg (=one course) IM 24 h apart.

4 | TIMING OF ADMINISTRATION

No large randomized trials compare different planned time intervals between prenatal corticosteroid administration and preterm birth. Retrospective studies have suggested that composite mortality and morbidity are lowest where the birth occurs 18–36 h after prenatal steroid administration, although some benefit was observable within 3 h.[10] Reduction in severe brain injury was most significant where the birth occurred 48–72 h after steroid administration. Almost all benefits of prenatal steroid administration had disappeared if the birth occurred 1 week or later after steroid administration.

Recommendations: *Prenatal corticosteroids should ideally be given 18–72 h—and certainly no more than 1 week—before preterm birth is anticipated. However, if preterm birth is expected within 18 h, prenatal corticosteroids should still be administered*.

5 | SINGLE OR MULTIPLE COURSES OF CORTICOSTEROIDS

Animal studies demonstrate the adverse effect of multiple courses of prenatal corticosteroids on the birthweight of the baby and subsequent hypothalamic-pituitary-adrenal axis function and neuronal myelination.

Ten trials have compared a repeat course of corticosteroids with no treatment in women who remain at risk of preterm birth 7 or more days after an initial course.[11] A repeat course of corticosteroids reduced the risk of respiratory distress syndrome (RR 0.83; 95% CI 0.75–0.91) and severe infant outcome (RR 0.84; 95% CI 0.75–0.94). There was a reduction in birthweight (mean difference of −75.79 g; 95% CI −117.63 to −33.96 g) but no difference in birthweight outcomes adjusted for gestational age. The follow-up to early childhood (18–24 months) showed no impact, including no effect on outcomes of total deaths, disability-free survival, serious outcome, or growth. No significant positive or negative effects were apparent for the mother. An individual patient data meta-analysis showed broadly similar results, with corticosteroids associated with a substantial reduction in birthweight z scores.[12]

Recommendations: *In women in whom preterm birth is expected within 72 h and who have had one course of corticosteroids more than a week ago, one additional course of prenatal corticosteroids could be given to improve outcomes for the baby*.

6 | USE OF PRENATAL CORTICOSTEROIDS IN LOW-RESOURCE SETTINGS

The initial randomized trials evaluating the benefits of prenatal corticosteroids have been conducted in high-income settings. It had been assumed that the results of these studies were generalizable to all settings. However, the ACT cluster-randomized trial conducted in Argentina, Guatemala, India, Kenya, Pakistan, and Zambia demonstrated that prenatal corticosteroids did not reduce the primary outcome of neonatal mortality in babies below the 5th centile for birthweight (RR 0.96; 95% CI 0.87–1.06).[13] Suspected maternal infection was increased in the intervention group (OR 1.67; 95% CI 1.33–2.09) and neonatal mortality across the entire intervention group (a secondary outcome) was increased (RR 1.12; 1.02–1.22). Reassuringly, a subsequent trial "ACTION", conducted in 29 hospitals across Bangladesh, India, Kenya, Nigeria, and Pakistan, has unequivocally shown that prenatal dexamethasone given from 24–34 weeks of gestation does improve outcome, reducing stillbirth and neonatal death (RR 0.88; 95% CI 0.78–0.99) without increasing maternal infection.[14] Rates of preterm birth were higher in ACTION than in ACT, and women were only included if gestational age had been confirmed by ultrasound. Data from ACTION are included in the latest Cochrane meta-analysis, which ensures the benefit of prenatal corticosteroids in low-resource settings.[3] The lower limit for offering prenatal corticosteroids should be adjusted to the time at which active care is appropriate at the specific location.

Recommendation: *In low-resource settings, prenatal steroids should be given to women with a singleton pregnancy where active neonatal care is appropriate and preterm birth is anticipated from 24–34 weeks of gestation, when ideally the following conditions are met: gestational age assessment can be accurately undertaken, preterm birth is considered imminent, there is no clinical evidence of maternal infection, adequate childbirth care is available (including the capacity to recognize and safely manage preterm labor and birth), the preterm newborn can receive adequate care if needed (including resuscitation, thermal care, feeding support, infection treatment, and safe oxygen use)*.

7 | BABIES BORN BY CESAREAN SECTION AT TERM

Three studies (1196 participants) have examined the impact of corticosteroids before cesarean section at term (≥39 weeks of gestation; data taken from a wider meta-analysis of corticosteroids prior to elective cesarean section).[15] There was no statistically significant effect on respiratory distress syndrome (RR 0.45; 95% CI 0.07–3.07), although only four of the 1196 babies had respiratory distress syndrome, nor were there any effects on transient tachypnoea of the newborn or other respiratory events. In addition, all three included studies had inadequate blinding of participants and/or personnel, leading to concern about potential bias. [Correction added on 14-February 2022 after first online and print publication: The preceding sentence has been amended in this version.]

Recommendation: *Prenatal corticosteroids should not be given routinely before cesarean section at term*.

8 | PRENATAL CORTICOSTEROIDS AS A "JUST IN CASE" THERAPY

Given the undoubted short-term benefits of corticosteroids for babies delivering preterm ≤34+0 weeks of gestation within 7 days

(ideally 48 h) of steroid administration, clinicians may be tempted to give them "just in case" to women at high risk. However, there is no evidence that such a strategy is beneficial for babies in the short term. This lack of benefit has to be balanced against the evidence that corticosteroids can cause long-term harm to babies, particularly to those babies who are subsequently born at term. For example, a population cohort from Finland of over 4000 pairs of term-born siblings discordant for steroid exposure demonstrated a hazard ratio of 1.33 (95% CI 1.26–1.41) for mental and behavioral disorders.[7]

Recommendation: Prenatal corticosteroids should not be given "just in case." Prenatal steroid administration should be reserved for women for whom preterm birth is expected within no more than 7 days, based on the woman's symptoms (including contractions or preterm prelabor membrane rupture) or an accurate predictive test.

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AUTHOR CONTRIBUTIONS

All authors and the FIGO Working Group for Preterm Birth drafted the concept and idea of the paper. SJS and JN wrote the first version of the manuscript. AS and BJ revised various versions of the manuscript. All authors and working group members commented on the manuscript and approved the final version.

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REFERENCES

1. Liggins GC, Howie RN. A controlled trial of antepartum glucocorticoid treatment for prevention of the respiratory distress syndrome in premature infants. *Pediatrics*. 1972;50(4):515-525.
2. Effect of corticosteroids for fetal maturation on perinatal outcomes. NIH Consensus Development Panel on the effect of corticosteroids for fetal maturation on perinatal outcomes. *JAMA*. 1995;273(5):413-418.
3. McGoldrick E, Stewart F, Parker R, Dalziel SR. Antenatal corticosteroids for accelerating fetal lung maturation for women at risk of preterm birth. *Cochrane Database of Systematic Reviews*. 2020;(12):CD004454.
4. Excellence NIfHaC. Preterm labor and birth. 2015.
5. Roberts D, Brown J, Medley N, Dalziel SR. Antenatal corticosteroids for accelerating fetal lung maturation for women at risk of preterm birth. *Cochrane Database Syst Rev*. 2017;(3):CD004454.
6. Gyamfi-Bannerman C, Thom EA, Blackwell SC, et al. Antenatal betamethasone for women at risk for late preterm delivery. *N Engl J Med*. 2016;374(14):1311-1320.
7. Raikkonen K, Gissler M, Kajantie E. Associations between maternal antenatal corticosteroid treatment and mental and behavioral disorders in children. *JAMA*. 2020;323(19):1924-1933.
8. Ballard PL, Ballard RA. Scientific basis and therapeutic regimens for use of antenatal glucocorticoids. *Am J Obstet Gynecol*. 1995;173(1):254-262.
9. Crowther CA, Ashwood P, Andersen CC, et al. Maternal intramuscular dexamethasone versus betamethasone before preterm birth (ASTEROID): a multicentre, double-blind, randomised controlled trial. *Lancet Child Adolesc Health*. 2019;3(11):769-780.
10. Norman M, Piedvache A, Børch K, et al. Association of short antenatal corticosteroid administration-to-birth intervals with survival and morbidity among very preterm infants: results from the EPICE cohort. *JAMA Pediatr*. 2017;171(7):678-686.
11. Crowther CA, McKinlay CJ, Middleton P, Harding JE. Repeat doses of prenatal corticosteroids for women at risk of preterm birth for improving neonatal health outcomes. Cochrane

database of systematic reviews (Online). *Cochrane Database Syst Rev*. 2015;(7):CD003935.
12. Crowther CA, Middleton PF, Voysey M, et al. Effects of repeat prenatal corticosteroids given to women at risk of preterm birth: an individual participant data meta-analysis. *PLoS Medicine*. 2019;16(4):e1002771.
13. Althabe F, Belizán JM, McClure EM, et al. A population-based, multifaceted strategy to implement antenatal corticosteroid treatment versus standard care for the reduction of neonatal mortality due to preterm birth in low-income and middle-income countries: the ACT cluster-randomised trial. *Lancet*. 2015;385(9968):629-639.
14. Collaborators WAT, Oladapo OT, Vogel JP, et al. Antenatal dexamethasone for early preterm birth in low-resource countries. *N Engl J Med*. 2020;383(26):2514-2525.
15. Sotiriadis A, Makrydimas G, Papatheodorou S, Ioannidis JP, McGoldrick E. Corticosteroids for preventing neonatal respiratory morbidity after elective caesarean section at term. *Cochrane Database Syst Rev*. 2018;(8):CD006614.

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