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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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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...
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. 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.

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. 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. 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. 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 Preganancies 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). 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.

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. 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. 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. As mentioned above, the relative risk of maternal chorioamnionitis appears lower with betamethasone acetate/phosphate.

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. 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. 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.

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). 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. 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.

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, perterm 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). 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.

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
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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**Conflicts of interest**

Jane Norman reports receipt of grants from government and charitable bodies for research into understanding the mechanism of term and preterm labour and understanding treatments; participation in a Data Safety and Monitoring Board for a study involving a preterm birth therapeutic agent for GlaxoSmithKline; and consultancy for Dilafor on drugs to alter labour progress. Andrew Shennan reports payment/honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events from Manipal India; support for attending meetings and/or travel from Hologic; leadership or fiduciary roles in the HTA Commissioning Board UK and Action on Pre-eclampsia charity. Lisa Story reports receipt of equipment, materials, drugs, medical writing, gifts or other services from Clinical Innovations. Bo Jacobsson reports research grants from Swedish Research Council, Norwegian Research Council, March of Dimes, Burroughs Wellcome Fund and the US National Institute of Health; clinical diagnostic trials on NIPT with Ariosa (completed), Natera (ongoing), Vanadis (completed) and Hologic (ongoing) with expendidures reimbused per patient; clinical probiotic studies with product provided by FukoPharma (ongoing, no funding) and BioGaia (ongoing; also provided a research grant for the specific study); collaboration in IMPACT study where Roche, Perkin Elmer and Thermo Fisher provided reagents to PLGF analyses; coordination of scientific conferences and meetings with commercial partners as such as NNFM 2015, ESPBC 2016 and a Nordic educational meeting about NIPT and preeclampsia screening. Bo Jacobsson is also Chair of the FIGO Working Group for Preterm Birth and the European Association of Perinatal Medicine’s special interest group of preterm delivery; steering group member of Genomic Medicine Sweden; chairs the Genomic Medicine Sweden complex diseases group; and is Swedish representative in the Nordic Society of Precision Medicine. Sarah J. Stock reports research funding from NIHR, Wellcome Trust, Chief Scientist Office Scotland, Tommy’s, and Medical Research Council; participation on a Data Safety Monitoring Board or Advisory Board for NIHR-funded WILL trial and NIHR-funded Giant Panda; leadership or fiduciary roles for SANDS and RCOG Stillbirth Clinical Studies Group; and receipt of equipment, materials or drugs from Hologic, Medix Biochemica, and Parsogen Diagnostics.

**Author contributions**

All authors and the FIGO Working Group for Preterm Birth drafted the concept and idea of the paper. SJ 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.

**Members of the FIGO working group for preterm birth, 2018-2021**

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