



# Good clinical practice advice: Antenatal corticosteroids for fetal lung maturation<sup>☆</sup>

## FIGO Working Group on Good Clinical Practice in Maternal–Fetal Medicine<sup>\*,a</sup>

\*Correspondence: Gian Carlo Di Renzo, Department of Obstetrics and Gynecology, University of Perugia, Santa Maria della Misericordia University Hospital, Perugia, Italy. Email: giancarlo.direnzo@unipg.it

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<sup>a</sup>Working Group members and expert contributors are listed at the end of the paper.

### 1 | PREMISE

Respiratory distress syndrome (RDS) is a serious complication of preterm birth and the primary cause of early neonatal mortality and disability. RDS develops as a consequence of surfactant deficiency and immature lung development.

Data from 12 controlled trials, involving over 3000 participants, showed that corticosteroids reduce the occurrence of RDS, with an overall reduction of about 50% in the odds of this form of neonatal morbidity (odds ratio 0.49, 95% CI 0.41–0.60). This reduction in respiratory morbidity was associated with reductions in the risk of intraventricular hemorrhage (IVH), necrotizing enterocolitis (NEC), and neonatal death.<sup>1</sup>

In 1994 the National Institutes of Health (NIH) held a consensus conference to review the safety and efficacy of antenatal corticosteroids. Based on the recent meta-analysis and other available evidence, the panel recommended that antenatal corticosteroids be administered to all women at risk for preterm birth between 24 and 34 weeks' gestation.<sup>2</sup> Such steroid treatment has also been recommended by groups including WHO, the Royal College of Obstetricians and Gynaecologists, the Society of Obstetricians and Gynaecologists of Canada, the American Congress of Obstetrics and Gynaecology, and the American Academy of Paediatrics.

### 2 | WHO ARE CANDIDATES FOR ANTENATAL CORTICOSTEROID THERAPY?

Antenatal administration of corticosteroid therapy would be indicated to all women between 24 and 34 weeks of gestation who are at risk of preterm birth within 7 days.<sup>3</sup> Administration of corticosteroids for pregnant women during the periviable period who are at risk of preterm delivery within 7 days is linked to a family's decision regarding

resuscitation and should be considered in that context.<sup>4</sup> Due consideration should be given to local limits of fetal viability when determining the lowest limit of gestational age when antenatal steroids should be administered, including reference to local data on newborn survival and morbidity. The Guideline Development Group noted that the probability of survival without residual morbidity "intact" survival at less than 24 weeks is low, even in high-resource settings.<sup>5</sup>

Infants who are born at 34–36 weeks of gestation (late preterm) are at greater risk for adverse respiratory and other outcomes than those born at 37 weeks of gestation or later. Whether or not late preterm corticosteroids provide benefit in these populations is unknown.<sup>6</sup> The evidence shows that there are fewer infants with serious respiratory morbidity after maternal steroid treatment, but there are no long-term outcomes studies in this group of patients; therefore, long-term safety of corticosteroids is still not well known.<sup>5</sup>

Infants born before 39 weeks of gestation are at increased risk for neonatal adverse respiratory outcomes, and the risk increases progressively as gestational age at birth declines. Compared with infants born vaginally, those born by cesarean section are at increased risk for adverse respiratory outcomes, especially when delivery occurs before the onset of labor. Thus, prelabor elective delivery is proscribed before 39 weeks unless fetal lung maturity has been demonstrated.<sup>7</sup>

In planned cesarean for infants at term the risk of respiratory morbidity should be considered against the likely benefits of antenatal steroids compared with those of delaying delivery until 39 weeks. When it is necessary to deliver by prelabor cesarean section at 37–38.6 week's gestation, parents can be counseled about the benefits of a single course of antenatal corticosteroids, such as a reduction in RDS.<sup>8</sup>

The timing of cesarean delivery and its effect on infant outcomes have substantial public health importance. The American College of Obstetricians and Gynecologists advises against elective delivery before 39 weeks' gestation.<sup>9</sup>

### 3 | BEST DOSE AND ROUTE OF ADMINISTRATION

The common regimens of two doses of betamethasone 12 mg given intramuscularly 24 hours apart and the treatment of four doses of dexamethasone 6 mg given intramuscularly 12 hours apart was recommended by the National Institutes of Health.<sup>2</sup>

### 4 | SHOULD AN ANTENATAL COURSE OF CORTICOSTEROIDS BE REPEATED?

Because of concerns for maternal and fetal harm, and the balance of risk and benefits, planned multiple courses are not recommended. The National Institute of Child Health and Human Development 2000 Consensus Panel noted that, although there is a suggestion of possible benefit from repeated courses (especially in the reduction and severity of respiratory distress), some animal and human data suggest deleterious effects on the fetus regarding cerebral myelination, lung growth, and function of the hypothalamic–pituitary–adrenal axis.<sup>10</sup> Regularly scheduled repeat courses or serial courses (more than two) are not currently recommended.<sup>11</sup>

### 5 | SINGLE RESCUE COURSE

WHO recommends that a single repeat course of steroids may be considered if preterm birth does not occur within 7 days after the initial course and subsequent assessment demonstrates that there is a high risk of preterm birth in the next 7 days.<sup>5</sup> The American College of Obstetricians and Gynecologists recommends a single repeat course of antenatal corticosteroids in women who are at less than 34 weeks of gestation with a risk of preterm delivery within 7 days, and whose prior course of antenatal corticosteroids was administered more than 14 days previously.<sup>9</sup>

### 6 | IN MULTIFETAL PREGNANCY

Based on the improved outcomes reported in singleton gestations, unless a contraindication exists, one course of antenatal corticosteroids should be administered to all patients who are between 24 and 34 weeks of gestation with a risk of preterm delivery within 7 days, including multiple gestations.<sup>4</sup>

### 7 | IN WOMEN WITH DIABETES MELLITUS

Diabetes mellitus is not a contraindication to antenatal corticosteroid treatment for fetal lung maturation. Women with impaired glucose tolerance or diabetes who are receiving fetal steroids should have additional insulin according to an agreed protocol and be closely monitored.<sup>12</sup>

Antenatal corticosteroid therapy is recommended for women with pre-gestational and gestational diabetes who are at risk of imminent preterm birth, and this should be accompanied by interventions to optimize maternal blood glucose control.<sup>5</sup>

### 8 | IN PREGNANCIES WITH FETAL GROWTH RESTRICTION

The effect on corticosteroid administration on intrauterine growth restriction is conflicting, with large cohort studies revealing significantly lower rates of RDS/IVH and prenatal death than found in small randomized clinical trials, which showed no reduction in neonatal morbidity. Accordingly, steroid use for these patients should be individualized. If a single course of steroid treatment is used, the small decrement in birth weight noted after multiple courses of treatment in such patients appears to be negated. The benefit of maternal steroids in fetal growth-restricted fetus' outweighs the possible adverse effects.<sup>13</sup> A randomized controlled trial is merited to clarify whether treatment brings any added benefit in growth-restricted infants.

The use of antenatal corticosteroids for fetal maturation is a rare example of a technology that yields substantial cost savings in addition to improving health. They should not be administered if there is no a substantiated clinical suspicion of preterm delivery in the next 2–7 days. In women with symptoms of preterm labor, cervical length and fibronectin/PAMG1 measurements should be considered to prevent unnecessary hospitalization and use of tocolytic drugs and/or antenatal steroids.<sup>14</sup>

FIGO recommends the following:

1. Clinicians should offer a single course of prenatal corticosteroids to all women between 24 and 34 weeks of gestation who are at risk of preterm birth within 7 days.
2. Administration of corticosteroids for pregnant women at less than 24 weeks of gestation with a risk of preterm birth within 7 days is linked to a family's decision regarding resuscitation. Due consideration should be given to local limits of fetal viability when determining the lowest limit of gestational age at which steroids should be administered.
3. A single course of betamethasone is recommended for pregnant women between 34 and 36.6 weeks of gestation with a risk of preterm birth within 7 days, and who have not received a previous course of antenatal corticosteroids. Although there is a paucity of data on longer-term follow-up.
4. A single course of corticosteroids can be considered for women undergoing planned cesarean delivery at 37–38.6 week's gestation. However, there should be a clear medical reason; an elective delivery should not be performed before 39 week's gestation.
5. The most extensively studied regimens of corticosteroids treatment for the prevention of RDS are: two doses of betamethasone 12 mg given intramuscularly 24 hours apart, or four doses of dexamethasone 6 mg given intramuscularly 12 hours apart.

6. Antenatal corticosteroids are most effective in reducing RDS in pregnancies that deliver 24 hours after and up to 7 days after administration of the second dose of antenatal corticosteroids.
7. Weekly repeat courses of antenatal corticosteroids are not recommended.
8. A single repeat course of antenatal corticosteroids should be considered in women at less than 34 weeks of gestation who have an imminent risk of preterm delivery within the next 7 days, and whose prior course of antenatal corticosteroids was administered more than 7–14 days previously.
9. One course of antenatal corticosteroids should be administered to all patients who are between 24 and 34 weeks of gestation and at risk of delivery within 7 days, irrespective of whether a single or multiple birth is anticipated.
10. Antenatal corticosteroid therapy is recommended for women with pre-gestational and gestational diabetes who are at risk of imminent preterm birth. Women who are receiving fetal steroids should have additional insulin according to an agreed protocol and be closely monitored.
11. There is insufficient evidence to conclude on the benefits or harms of antenatal corticosteroids therapy in women whose infants are growth restriction.
12. Antenatal corticosteroids should not be administered if there is no substantiated clinical suspicion of preterm delivery in the next 2–7 days.
13. In women with symptoms of preterm labor, cervical length and fibronectin/PAMG1 measurements should be considered to prevent unnecessary hospitalization and use of tocolytic drugs and/or antenatal steroid.

## FIGO WORKING GROUP ON GOOD CLINICAL PRACTICE IN MATERNAL-FETAL MEDICINE (2015-2018)

Gian Carlo Di Renzo, Italy (Chair); Eduardo Fonseca, Brazil; Eduardo Gratacos, Spain; Sonia Hassan, USA; Mark Kurtser, Russia; Fergal Malone, Ireland; Shilpa Nambiar, Malaysia; Kypros Nicolaides, UK; Nancy Sierra, Mexico; Huixia Yang, China (members). Carlos Fuchtnr, Bolivia (FIGO President Elect, Ex Officio); Vincenzo Berghella, USA (Society for Maternal-Fetal Medicine); Ernesto Castelazo Morales, Mexico (FIGO Committee for Capacity Building in Education and Training); Mark Hanson, UK (FIGO Working Group on Adolescent, Preconception and Maternal Nutrition); Moshe Hod, Israel (Committee on Pregnancy and NCD; Working Group on Hyperglycemia in Pregnancy); Yves Ville, France (International Society of Ultrasound in Obstetrics and Gynecology); Gerard Visser, Netherlands (FIGO Committee for Safe Motherhood and Newborn Health); Joe Leigh Simpson, USA (March of Dimes).

### EXPERT CONTRIBUTORS

Abdallah Adra (Department of Obstetrics and Gynecology, American University of Beirut Medical Center, Lebanon); Roza Bataeva (Fetal

Medicine Centre, Russian Medical Academy of Advanced Studies, Moscow, Russia); Luis Cabero Roura (Autonomous University of Barcelona, Hospital Materno-infantil Valle Hebrón, Barcelona, Spain); Ramen H. Chmait (Department of Obstetrics and Gynecology, Division of Maternal-Fetal Medicine, Keck School of Medicine, University of Southern California, USA); Yvonne Cheng (Department of Obstetrics and Gynaecology, Chinese University of Hong Kong); Irene Giardina (Centre of Perinatal and Reproductive Medicine, University of Perugia, Italy); Jon Hyett (Department of Women and Babies, Royal Prince Alfred Hospital, Australia); Asma Khalil (Fetal Medicine Unit, Department of Obstetrics and Gynaecology, St. George's University Hospitals NHS Foundation Trust, London, UK); Narendra Malhotra (Global Rainbow Healthcare, India); Pierpaolo Mastroiacovo (Alessandra Lisis International Centre on Birth Defects and Prematurity, International Clearinghouse for Birth Defects Surveillance and Research, Rome, Italy); John Morrison (Department of Obstetrics & Gynaecology, National University of Ireland); Amala Nazareth (Emirates Medical Association Ob Gyn, United Arab Emirates); Liona Chiu Yee Poon (Department of Obstetrics and Gynaecology, Chinese University of Hong Kong); Chittaranjan N. Purandare (International Federation of Gynecology and Obstetrics [FIGO], St. Elizabeth Hospital, Walkeshwar and BSES Hospital Mumbai, India); Ruben Quintero (Plantation General Hospital and Wellington Regional Medical Center, Coral Gables, Florida, USA); Waldo Sepulveda (Maternal-Fetal Diagnostic Center, Santiago, Chile); Valentina Tosto (Centre of Perinatal and Reproductive Medicine, University of Perugia, Italy).

### CONFLICTS OF INTEREST

The authors have no conflicts of interest.

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