WHO recommendation on antenatal corticosteroid therapy for women at risk of preterm birth of a growth-restricted fetus

17 November 2015

Recommendation

Antenatal corticosteroid therapy is recommended for women at risk of imminent preterm birth of a growth-restricted fetus

(Strong recommendation based on very low-quality evidence)

Publication history

First published: November 2015

Updated: No update planned

Assessed as up-to-date: November 2015

Remarks

- The GDG noted the limited evidence on the benefits of antenatal corticosteroid in this subgroup of women. However, the group placed its emphasis on the overall benefits of antenatal corticosteroid, the potential benefits in terms of reduced handicap among surviving intrauterine growth-restricted (IUGR) infants, and evidence of reduced odds of adverse newborn mortality and morbidity outcomes, and therefore made a strong recommendation.
- The GDG acknowledged the concern about the effect of antenatal corticosteroids on fetal growth, but agreed that there is no evidence to suggest that steroids will perform differently in this subgroup compared to the overall preterm population.

Background

Preterm birth, defined as birth before 37 weeks of gestation, is the single most important determinant of adverse infant outcomes, in terms of survival and quality of life. (1) Globally, it is the leading cause of perinatal and neonatal mortality and morbidity. (2) Preterm infants are particularly vulnerable to complications due to impaired respiration, difficulty in feeding, poor body temperature regulation and high risk of infection. (3-5) With the increasing contribution of neonatal deaths to overall child mortality, it is
critical to address the determinants of poor outcomes related to preterm birth to achieve further reductions in child mortality. (6-8)

Infant mortality and morbidity from preterm birth can be reduced through interventions delivered to the mother before or during pregnancy, and to the preterm infant after birth. (9) Interventions can be directed at all women for primary prevention and reduction of the risk of preterm birth (e.g. smoking cessation programme) or aimed at minimizing the risk in women with known risk factors (e.g. progestational agents, cervical cerclage). (10) However, the most beneficial set of maternal interventions are those that are aimed at improving outcomes for preterm infants when preterm birth is inevitable (e.g. antenatal corticosteroids, magnesium sulfate and antibiotic prophylaxis). (9) Special care of the preterm newborn to prevent and treat complications of prematurity is also critical to newborn survival. In high-income countries, reductions in mortality rates in infants that were born preterm have been driven largely by improved care and, more importantly, by appropriate policy changes.

Methods

The recommendations were developed using standard operating procedures in accordance with the process described in the WHO handbook for guideline development (11). Briefly, these included (i) identification of priority questions and critical outcomes, (ii) retrieval of the evidence, (iii) assessment and synthesis of evidence, (iv) formulation of recommendations, and (v) planning for the dissemination, implementation, impact evaluation and updating of the guideline.

The scientific evidence underpinning the recommendations was synthesized using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach (12). Up-to-date systematic reviews were used to prepare evidence profiles for the priority questions. WHO then convened a Technical Consultation in May 2014 where an international group of experts – the Guideline Development Group (GDG) – formulated and approved the recommendations based on the evidence profiles.

In November 2014, an online consultation of the GDG was conducted to review and revise the recommendations in the light of the findings of a large implementation trial of antenatal corticosteroids in low-resource countries.

Further information on procedures for developing this recommendation are available here.

Recommendation question

For this recommendation, we aimed to answer the following questions:

- Among pregnant women at risk of imminent preterm birth (P), is antenatal corticosteroid therapy (I), compared with no antenatal corticosteroid therapy (C), effective in reducing adverse newborn outcomes (O)?

- Which population of pregnant women should be offered antenatal corticosteroids? (considering the gestational age at presentation or birth; interval between presentation and anticipated birth; single and multiple birth; status of amniotic membranes; and women undergoing elective caesarean section in late preterm)

- Which population of pregnant women should not be offered antenatal corticosteroids? (considering
conditions where there are concerns that associated risks may outweigh benefits: women with diabetes mellitus, hypertensive disorders, chorioamnionitis and growth-restricted babies

- Which corticosteroids (and regimens) should be used for eligible women?
- Should repeat course(s) of corticosteroids be offered to a woman who has completed a course of corticosteroid but remains at risk of preterm birth 7 days or more after the initial treatment?

Evidence summary

**Antenatal corticosteroids versus placebo or no treatment (growth-restricted fetus and small-for-gestational-age infant)**

Evidence relating to the effectiveness and safety of antenatal corticosteroid therapy for reducing adverse newborn outcomes in women with small-for-gestational-age (SGA) infants, including intrauterine growth-restricted (IUGR) infants, was extracted from one systematic review of nine observational studies (13).

The studies included women who were pregnant with babies diagnosed with IUGR through confirmation of placental insufficiency and those identified as SGA (a total of 2846 mothers and infants). Three of the studies were specifically on IUGR only, five were on SGA infants only, and one study included both IUGR and SGA infants. The studies evaluated betamethasone or dexamethasone compared with no treatment (or incomplete treatment) in women expected to deliver at or before 35 weeks of gestation. All studies were conducted in high-resource countries: Canada (1 study), France (1 study), Italy (2 studies), the Netherlands (3 studies), Sweden (1 study) and the USA (1 study).

**Maternal outcomes**

**Maternal morbidity:** There were no significant differences in the rates of chorioamnionitis (OR 0.77, 95% CI 0.36–1.63; 1 study, 220 women) or caesarean section (OR 0.48, 95% CI 0.03–8.68; 1 study, 165 women) between women with SGA or IUGR infants exposed to antenatal corticosteroids versus no antenatal corticosteroids (or incomplete corticosteroid treatment).

**Infant outcomes**

**Fetal and neonatal death:** There was no observed difference in perinatal mortality (fetal or neonatal death) between groups in any of the IUGR studies (pooled OR 0.81, 95% CI 0.58–1.04; 4 studies, 504 babies), nor in the majority of reports on SGA infants (pooled OR 0.78, 95% CI 0.58–1.04; 6 studies, 958 babies).

**Child death:** No significant difference in childhood deaths was observed in the study that reported longterm follow-up (OR 0.79, 95% CI 0.20–3.08; 124 babies).

**Severe neonatal morbidity:** No significant difference was observed for RDS between treated and untreated groups in any of the IUGR studies (pooled OR 0.81, 95% CI 0.59–1.11; 4 studies, 504 babies), nor in the majority of reports on SGA infants, though pooled analyses showed a trend in favour of antenatal corticosteroid-exposed infants (pooled OR 0.83, 95% CI 0.66–1.05; 8 studies, 1126 babies). No difference was observed in the risk of major cerebral morbidity between corticosteroid-exposed compared with unexposed IUGR infants in two studies (pooled OR 0.86, 95% CI 0.35–2.10; 211 babies), but a reduction in brain lesions was observed for SGA infants who were exposed to antenatal corticosteroids (OR 0.57, 95% CI 0.41–0.78; 5 studies, 761 babies). There was no significant difference noted in exposed versus control groups for other neonatal outcomes (neonatal sepsis, BPD, NEC, Apgar < 7 at 5 minutes, use of mechanical ventilation, chronic lung disease, or low birth weight defined as < 3rd percentile for gestational age).

**Long-term morbidity:** Only one study reported on long-term outcomes after antenatal corticosteroid
treatment. Survival without handicap at two years was more likely in IUGR infants exposed to antenatal steroids (82% in the exposed versus 65% in the unexposed group: OR 2.55, 95% CI 1.11–5.87; 124 babies). However, physical growth beneath the 10th percentile appears more likely after antenatal steroid exposure (OR 5.20, 95% CI 1.38–19.62).

Further information and considerations related to this recommendation can be found in the WHO guidelines, available at:

http://apps.who.int/iris/bitstream/handle/10665/183037/9789241508988_eng.pdf?sequence=1

http://apps.who.int/iris/bitstream/handle/10665/183038/WHO_RHR_15.17_eng.pdf?sequence=1

Implementation considerations

- The successful introduction of this recommendation into national programmes and health-care services depends on well-planned and participatory consensus-driven processes of adaptation and implementation. The adaptation and implementation processes may include the development or revision of existing national guidelines or protocols based on this recommendation.
- The recommendation should be adapted into a locally appropriate document that can meet the specific needs of each country and health service. Any changes should be made in an explicit and transparent manner.
- A set of interventions should be established to ensure that an enabling environment is created for the use of the recommendations, and that the behaviour of the healthcare practitioner changes towards the use of this evidence-based practice.
- In this process, the role of local professional societies is important and an all-inclusive and participatory process should be encouraged.

Research implications

The GDG identified these priority questions related to antenatal corticosteroids for imminent preterm birth recommendations:

- What are the long-term outcomes of all infants exposed to antenatal corticosteroids (including term infants)?
- What strategies can effectively and safely increase the use of corticosteroids in low- and middle-income country (LMIC) settings to improve outcomes?
- What are the effects of antenatal corticosteroid at different gestational ages at birth (using independent patient data analysis)?
- Assessment of coverage of antenatal corticosteroids before and after guideline implementation (and associated reduction in neonatal mortality).
- Assessment of implementation strategies and monitoring of adverse events (in LMIC settings).
- What are the effects of antenatal corticosteroid administration in women undergoing prelabour caesarean section in late preterm?
- What are the effects of task shifting in the context of antenatal corticosteroid administration (e.g. using the first dose in the community followed by referral to a health-care facility)?
- Are there differences in the pharmacokinetic properties of betamethasone acetate versus betamethasone phosphate (consider using available data in settings where they are routinely used)?
- What is the impact of antenatal corticosteroid administration among mothers with evidence of infection who also receive appropriate antibiotic therapy on both maternal and neonatal outcomes?
- What is the minimum effective dose of corticosteroids to achieve fetal lung maturation and other improved outcomes?
- What is the minimum effective dose required for repeat courses of antenatal corticosteroids?
- What is the most effective regimen and dose for antenatal corticosteroids?
- In what contexts can antenatal corticosteroids be used safely and effectively in low-income countries?

**Related links**

WHO recommendations on interventions to improve preterm birth outcomes (2015) – [full document](http://www.who.int/kms/handbook_2nd_ed.pdf) and evidence tables

Managing Complications in Pregnancy and Childbirth: A guide for midwives and doctors

Pregnancy, Childbirth, Postpartum and Newborn Care: A guide for essential practice

WHO Programmes: Sexual and Reproductive health

Maternal Health

Infant, Newborn Health

**References**


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