WHO recommendation on antenatal corticosteroid therapy for women with pre-gestational and gestational diabetes at risk of preterm birth

17 November 2015

Recommendation

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.

(Strong recommendation based on very low-quality evidence)

Publication history

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Updated: No update planned

Assessed as up-to-date: November 2015

Remarks

- The GDG acknowledged the paucity of evidence on the benefits of antenatal corticosteroid in this subgroup of women. However, the group placed its emphasis on the overall benefits of antenatal steroid in preterm, the potential benefits in terms of reducing the higher risk of newborn respiratory morbidity posed by maternal diabetes, and the potential impact on overall newborn survival, and therefore made a strong recommendation.
- The group considered the concern about the maternal hyperglycaemic effect of antenatal corticosteroids, but agreed that it was insufficient to counterbalance the potential benefits for the baby if appropriate measures are taken to ensure glycaemic control.
- Clinicians should ensure strict control of maternal blood glucose prior to and/or during pregnancy to reduce the risk of newborn respiratory distress syndrome.
- Delay in fetal lung maturity is generally more frequent in pregnant diabetic women compared with the general obstetric population. Therefore, in pregnant women with poorly controlled diabetes, the use of corticosteroids should also be considered at > 34 weeks of gestation if there is laboratory evidence of fetal lung immaturity.
**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 (pre-gestational and gestational diabetes)

A systematic review of randomized and nonrandomized studies evaluating the effectiveness of antenatal corticosteroid therapy compared with placebo or no treatment for reducing adverse outcomes in pre-gestational and gestational diabetic women at risk of preterm birth identified no eligible studies (13).

Importantly, previous trials on antenatal corticosteroids for reducing adverse outcomes in newborns have generally excluded women with gestational diabetes and diabetes mellitus. One randomized trial conducted in Brazil compared antenatal betamethasone with no treatment in nondiabetic pregnant women with severe pre-eclampsia between 26 and 34 weeks of gestation (14). This study showed increased risk of gestational diabetes mellitus among women receiving betamethasone compared with the controls (RR 2.71, 95% CI 1.14–6.46; 123 women). However, the reduction in RDS and other adverse outcomes in newborns among women receiving betamethasone in the same study was consistent with the findings of the Cochrane review that showed benefit of antenatal corticosteroids in preterm infants (15). Additionally, one observational study among 30 women in Mexico reported on glycaemic control following antenatal use of betamethasone in diabetic women at risk of premature rupture of the membranes (16). The study showed that following antenatal betamethasone therapy, 40% of women with diet-treated diabetes required de novo insulin administration, while insulin dose was increased 39–112% in women with diet-plus-insulin-treated diabetes and increased 26–64% among women with type 2 diabetes treated with diet or diet and insulin. The greatest changes occurred between days 2 and 4 following betamethasone treatment.

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


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