WHO recommendation on antenatal corticosteroid therapy in women with chorioamnionitis at risk of preterm birth

17 November 2015

Recommendation

Antenatal corticosteroid therapy is not recommended in women with chorioamnionitis who are likely to deliver preterm.

(Conditional 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

- Timely delivery of the baby to avoid further intrauterine insult should be the priority when the diagnosis of clinical chorioamnionitis is made. Antenatal corticosteroid therapy should not be initiated at the expense of timely delivery when indicated by maternal or fetal condition.
- Antenatal corticosteroids should be avoided in women with evidence of ongoing systemic infection, e.g. septicaemia or tuberculosis.
- In the light of evidence from the Antenatal Corticosteroids Trial (1), the GDG reviewed the concern about the risk of exacerbating maternal infection, particularly in low- and middle-income settings where baseline risk of maternal infectious morbidity is higher than that of the settings where the evidence on women with chorioamnionitis was generated. The group felt that this potential risk may outweigh the known benefits of antenatal corticosteroids in the majority of populations where steroid use is essential for improving newborn survival. They acknowledged that the balance of benefits and harms may be context-specific and chose to make a conditional recommendation against the intervention in this situation.
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. (2) Globally, it is the leading cause of perinatal and neonatal mortality and morbidity. (3) Preterm infants are particularly vulnerable to complications due to impaired respiration, difficulty in feeding, poor body temperature regulation and high risk of infection. (4-6) 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. (7-9)

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. (10) 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). (11) 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). (10) 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 (12). 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 (13). 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 (women with chorioamnionitis)**

Evidence on the effects of antenatal corticosteroid therapy for reducing adverse newborn outcomes in women with chorioamnionitis who are at risk of preterm birth was extracted from a systematic review that included eight cohort studies involving a total of 1424 mothers expected to deliver at or before 35 weeks of gestation (14). All studies were conducted in high-resource settings: two in the USA, two in France, and one each in Australia, Canada, Korea and the Netherlands. Infections among participants in these studies were diagnosed either clinically or histologically. Four studies reported the effects of corticosteroid therapy in infants of women with histological chorioamnionitis only, two on infants of women with clinical chorioamnionitis only, and two further studies on infants in both groups of women separately. All studies in the review evaluated the use of a corticosteroid compared with no treatment (or incomplete/suboptimal treatment). In four studies, betamethasone was used (996 mothers and infants), in two studies, dexamethasone was used (161 mothers and infants) and in the remaining two studies, either betamethasone or dexamethasone was used (267 mothers and infants).

This evidence was reviewed and interpreted in the context of the findings of a large cluster-randomized trial evaluating the effects on increasing antenatal corticosteroid coverage on neonatal mortality in low-income settings (1).

**Maternal outcomes**

None of the studies in the systematic review reported on maternal outcomes.

**Infant outcomes**

**Histological chorioamnionitis**

_Fetal and neonatal death:_ Antenatal corticosteroid use in women with histological chorioamnionitis was associated with a significant reduction in neonatal deaths (pooled OR 0.49, 95% CI 0.34–0.73; 6 studies, 1156 infants).

_Severe neonatal morbidity:_ Antenatal corticosteroid use in women with histological chorioamnionitis was associated with significant reductions in RDS (pooled OR 0.58, 95% CI 0.44–0.76; 5 studies, 1084 babies), intraventricular haemorrhage (IVH) (pooled OR 0.41, 95% CI 0.24–0.69; 5 studies, 621 babies) and severe IVH (grade 3–4) (pooled OR 0.40, 95% CI 0.20–0.79; 4 studies, 491 babies). One study found a significant
reduction in the incidence of babies with Apgar score < 7 associated with corticosteroid therapy (OR 0.45, 95% CI 0.28–0.70; 527 babies). In another study, no significant differences between exposed and control groups were observed in the need for mechanical ventilation (OR 0.30, 95% CI 0.08–1.07; 121 babies) nor in the duration of mechanical ventilation (MD -2.00, 95% CI -4.23–0.23; 88 babies). No significant differences were observed in periventricular leukomalacia (pooled OR 0.74, 95% CI 0.26–2.09; 3 studies, 419 babies), neonatal sepsis (pooled OR 1.03, 95% CI 0.72–1.48; 5 studies, 1084 babies), NEC (pooled OR 1.33, 95% CI 0.78–2.26; 5 studies, 1084 babies), surfactant use (pooled OR 0.93, 95% CI 0.67–1.30; 3 studies, 720 babies) or chronic lung disease/bronchopulmonary dysplasia (BPD) (pooled OR 0.66, 95% CI 0.38–1.14; 3 studies, 427 babies).

Long-term morbidity: One small study that followed participants through childhood was unable to show any difference in incidence of cerebral palsy (OR 0.35, 95% CI 0.07–1.67; 72 children) or neurodevelopmental outcome (general development quotient) at the ages of 1 year (MD 6.00, 95% -9.94 to 20.94; 72 children) and 3 years (MD 13.00, 95% CI -3.75 to 29.75; 72 children).

Clinical chorioamnionitis

Fetal and neonatal death: Antenatal corticosteroid therapy in women with clinical chorioamnionitis was not associated with a significant difference in neonatal mortality (pooled OR 0.77, 95% 0.36–1.65; 3 studies, 247 babies).

Severe neonatal morbidity: Corticosteroid therapy in women with clinical chorioamnionitis was not associated with significant differences in RDS (pooled OR 0.73, 95% CI 0.73–1.12; 4 studies, 417 babies), neonatal sepsis (pooled OR 0.94, 95% CI 0.40–2.18; 2 studies, 150 babies) or NEC (pooled OR 2.63, 95% CI 0.72–9.68; 2 studies, 150 babies). Significant reductions in IVH (pooled OR 0.36, 95% CI 0.16–0.82; 3 studies, 318 babies), severe IVH (pooled OR 0.29, 95% CI 0.10–0.89; 3 studies, 318 babies) and periventricular leukomalacia (pooled OR 0.35, 95% CI 0.14–0.85; 3 studies, 318 babies) were observed among babies of mothers who were treated with antenatal corticosteroids. In one study, corticosteroid therapy significantly decreased the need for mechanical ventilation (OR 0.05; 95% CI 0.00–0.94; 93 babies), but had no significant effect on the duration of mechanical ventilation (MD -2.00, 95% CI -4.23 to 0.23; 88 babies). No significant differences were observed in the frequencies of chronic lung disease/BPD (pooled OR 0.91, 95% CI 0.44–1.86; 3 studies, 232 babies).

Clinical and/or histological chorioamnionitis

Fetal and neonatal death: Corticosteroid treatment in mothers with clinical and/or histological chorioamnionitis was associated with significant reductions in neonatal mortality (pooled OR 0.54, 95% CI 0.38–0.76; 7 studies, 1403 babies).

Severe neonatal morbidity: Corticosteroid therapy was associated with significant reductions in RDS (pooled OR 0.62, 95% CI 0.49–0.78; 7 studies, 1501 babies), IVH (pooled OR 0.39, 95% CI 0.25–0.61; 6 studies, 939 babies), severe IVH (grade 3–4) (pooled OR 0.36, 95% CI 0.20–0.65; 5 studies, 854 babies) and periventricular leukomalacia (pooled OR 0.47, 95% CI 0.24–0.90; 4 studies, 737 babies). One study found a significantly decreased need for mechanical ventilation (OR 0.18, 95% CI 0.06–0.57; 214 babies) in babies of treated women, but corticosteroid therapy had no significant effect on the duration of mechanical ventilation (MD -2.00, 95% CI -4.23 to 0.23; 88 babies). No significant difference was observed in neonatal sepsis (pooled OR 1.02, 95% CI 0.73–1.42; 5 studies, 1234 babies), NEC (pooled OR 1.49, 95% CI 0.91–2.53; 5 studies, 1234 babies) or chronic lung disease/BPD (pooled OR 0.74, 95% CI 0.48–1.15; 4 studies, 659 babies).
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 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?
References

14. Amiya RM ML, Ota E, Suwa T, Mori R, Oladapo OT. Antenatal corticosteroids for reducing adverse maternal and child outcomes in special populations of women at risk of imminent preterm birth: a