WHO recommendation on use of a single repeat course of antenatal corticosteroid

17 November 2015

Recommendation

A single repeat course of antenatal corticosteroid is recommended if preterm birth does not occur within 7 days after the initial dose, and a subsequent clinical assessment demonstrates that there is a high risk of preterm birth in the next 7 days.

(Conditional recommendation based on moderate-quality evidence for newborn outcomes and low-quality evidence for maternal outcomes).

Publication history

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Updated: No update planned

Assessed as up-to-date: November 2015

Remarks

- The GDG acknowledged the lack of evidence on further reduction of neonatal mortality with the use of repeat corticosteroids. However, the group placed its emphasis on the associated further reduction in the respiratory morbidity and less surfactant use (which could save costs) and placed lower value on the small reduction in neonatal birth weight, and therefore recommended a single repeat course of steroid. Given that there are likely to be variations in these values across health system settings, the GDG lowered the strength of the recommendation and made it conditional.
- A single course in this context refers to a full dose of antenatal corticosteroid as recommended in this guideline.
- This recommendation should only be applied to women between 24 and 34 weeks of gestation.
- The GDG noted that only betamethasone was tested in this context, but concluded that there were no reasons not to extend the recommendation to dexamethasone. The group also noted the variations in the number of courses and doses of betamethasone used, but agreed that the recommendation should align with the previous recommendation on antenatal corticosteroid regimens.
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 question:

- 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**

Data on repeat course(s) compared with a single course of antenatal corticosteroids were extracted from a Cochrane systematic review of 10 trials with data for 4733 women and 5700 babies (13).

The review evaluated the use of repeat doses of betamethasone compared with no repeat corticosteroid treatment in women who had received one course of corticosteroid at trial entry and remained at risk of preterm birth for 7 or more days after initial treatment. Studies were mainly conducted in high-resource settings: Australia and New Zealand, Canada, Finland and India (1 study each) and the USA (5 studies). One multicentre trial took place in 20 countries (including a number of middle-income countries): Argentina, Brazil, Bolivia, Canada, Chile, China, Columbia, Denmark, Germany, Hungary, Israel, Jordan, the Netherlands, Peru, Poland, Russia, Spain, Switzerland, the United Kingdom and the USA. Additional comparisons included a subgroup of women with PPROM, and subgroup analysis compared different dosing regimens and intervals between initial treatment and repeat doses. Women included in the trials were between 23 and 34 weeks pregnant, though the specific criteria varied between studies.

**Repeat course(s) of antenatal corticosteroids versus placebo or no treatment**

**Maternal outcomes**

*Prolongation of pregnancy:* Repeat courses of corticosteroids were not associated with reduction in the rates of preterm birth before 28, 34 or 37 completed weeks of gestation (RR 1.07, 95% CI 0.83–1.38; 2 studies, 1632 women; RR 1.01, 95% CI 0.95–1.07; 4 studies, 2140 women; RR 0.97, 95% CI 0.92–1.02; 2 studies, 1181 women, respectively). Mean gestational age at delivery was not significantly different between comparison groups (MD -0.09 weeks, 95% CI -0.33 to 0.15; 8 studies, 3179 infants).

*Maternal infectious morbidity:* There were no significant differences between groups for rates of puerperal sepsis (RR 1.15, 95% CI 0.83–1.60; 5 studies, 3091 women) or maternal chorioamnionitis (RR 1.16, 95% CI 0.92–1.46; 6 studies, 4261 women).

*Maternal side-effects:* Maternal side-effects were not significantly different in the two groups (RR 0.97, 95% CI 0.24–3.90; 2 studies, 1474 women).

**Infant outcomes**

*Fetal and neonatal death:* There were no significant differences between groups in terms of fetal deaths (RR 0.82, 95% CI 0.24–2.84; 7 studies, 2755 fetuses), neonatal deaths (RR 0.91, 95% CI 0.62–1.34; 7 studies, 2713 infants) or fetal and neonatal deaths combined (RR 0.94, 95% CI 0.71–1.23; 9 studies, 5554 infants).

*Severe neonatal morbidity:* A repeat course of antenatal corticosteroids was associated with a reduction in RDS in infants compared with placebo or no treatment (RR 0.83, 95% CI 0.75–0.91; 8 studies, 3206 infants). A repeat course was also associated with a reduction in surfactant use in preterm infants (RR 0.78, 95% CI 0.65–0.95; 9 studies 5525 infants). There was no significant difference in the duration of respiratory support between the groups (MD 0.30 days, 95% CI -0.90 to 1.50; 1 study, 37 infants). “Serious infant outcome”, a composite outcome that variably included infant mortality and serious morbidity outcomes, was significantly reduced in infants of women treated with repeat courses of corticosteroids compared to controls (RR 0.84, 95% CI 0.75–0.94; 7 studies, 5094 infants). However, no significant differences were seen between comparison groups for individual severe infant morbidity outcomes: any grade of IVH (RR 0.94, 95% CI 0.75–1.18; 6 studies, 3065 infants), severe IVH (RR 1.13, 95% CI 0.69–1.86; 6 studies, 4819 infants), NEC (RR 0.74, 95% CI 0.51–1.08; 8 studies, 5394 infants), retinopathy of prematurity (RR 1.02, 95% CI 0.81–1.28; 7 studies, 4883 infants), chronic lung disease (RR 1.06, 95% CI 0.87–1.30; 8 studies,
5393 infants), periventricular leukomalacia (RR 0.77, 95% CI 0.43–1.37; 7 studies, 4888 infants) or systemic neonatal infection (RR 0.93, 95% CI 0.79–1.11; 3 studies, 1544 infants). Rates of admission to NICU were very similar in the two groups (RR 1.01, 95% CI 0.95–1.07; 2 studies, 3448 infants). Infants whose mothers had received repeat courses of corticosteroids compared to those who had a single course had on average slightly lower birth weight (MD -75.79 g, 95% CI -117.63 to -33.96; 9 studies, 5626 infants). There was no significant difference between groups for frequency of SGA babies (RR 1.18, 95% CI 0.97–1.43; 7 studies, 3975 infants).

Long-term morbidity: Long-term outcomes were also similar in the two groups: survival free of any disability (RR 1.01, 95% CI 0.97–1.05; 2 studies, 3155 children); any neurosensory disability (RR 1.01, 95% CI 0.92–1.11; 2 studies, 1317 children); childhood disability at early childhood follow-up (RR 0.98, 95% CI 0.83–1.16; 1 study, 999 children); or development delay at early childhood follow-up (RR 0.97, 95% CI 0.84–1.13; 3 studies, 3202 children). Rates of blindness and deafness were very similar in the two groups, as was the frequency of cerebral palsy at early childhood follow-up (RR 1.03, 95% CI 0.71–1.49; 5 studies, 3883 children).

**Repeat course(s) of corticosteroids versus placebo or no treatment (PPROM, 7-day versus 14-day interval for repeat course, number of repeat courses)**

**Maternal and perinatal outcomes:**

One study with data for 160 women examined outcomes in women following PPROM. There were no significant differences between groups for most of the outcomes reported, including for puerperal sepsis, perinatal mortality, RDS and chronic lung disease. However, rate of chorioamnionitis was increased in women receiving the repeat course(s) of corticosteroids compared with those who received a single course (RR 1.56, 95% CI 1.05–2.31).

Subgroup analysis was conducted to examine whether the interval between one course and the repeat course made a difference (i.e. repeat course after 7 days versus repeat course after 14 days). There were no significant differences between subgroups for chorioamnionitis, fetal and neonatal mortality, or IVH. The results for RDS reflected the findings for the whole sample: both subgroups showed a reduction in RDS in the repeat course(s) group compared to the group receiving a single course of corticosteroids. Similarly, subgroup analysis reflected the findings for the whole sample for infant birth weight: the babies in the repeat course(s) group had slightly lower mean birth weights irrespective of the interval between the initial treatment and the repeat course(s).

Subgroup analysis was also conducted by the number of repeat courses of corticosteroids women in the repeat courses group received. Findings largely reflected the main analysis. For women receiving one repeat course of corticosteroids there were no significant differences between the repeat course and single course groups for most outcomes apart from RDS, which (as in the main analysis) was reduced in the repeat course group (RR 0.85, 95% CI 0.73–0.99; 2 studies, 399 infants). Data from one study indicated that babies exposed to four or more repeat courses of corticosteroids had an increase in the frequency of being small for gestational age compared with those who were exposed to a single course (RR 2.00, 95% CI 1.07–3.73; 368 infants). In the same study, repeat doses were also associated with reduced mean birth weight (MD -161.00 g, 95% CI -290 to -31.48).

Different dosing regimens were also compared. Subgroup interaction tests showed no significant differences between different dosing regimens for any of the outcomes reported, and findings largely reflected the overall findings for the whole sample.
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


Link to the supporting systematic review: Repeat doses of prenatal corticosteroids for women at risk of preterm birth for improving neonatal health outcomes

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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