Recommendation

Either intramuscular (IM) dexamethasone or IM betamethasone (total 24 mg in divided doses) is recommended as the antenatal corticosteroid of choice when preterm birth is imminent.

(Strong recommendation based on low-quality evidence)

Publication history

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Assessed as up-to-date: November 2015

Remarks

- The GDG noted that there is no conclusive evidence on the comparative efficacy of dexamethasone and betamethasone that would support a recommendation of one over the other. The group acknowledged that dexamethasone has an advantage over betamethasone in terms of lower cost and wider availability, and it is currently listed for use in pregnant women on the WHO Essential Medicine List and in WHO’s Managing complications in pregnancy and childbirth: a guide for midwives and doctors.
- The GDG acknowledged that the doses and regimens for both dexamethasone and betamethasone varied slightly across trials comparing the two, but noted that in the majority a total steroid dose of 24 mg was administered in divided doses 12 hours or 24 25 hours apart. Four doses of dexamethasone 6 mg IM 12 hours apart or two doses of betamethasone 12 mg IM 24 hours apart were the preferred choice in most of the studies. When deciding on the dosing frequency, consideration should be given to the likely timing of preterm birth to ensure that the woman completes the total dose of steroid or receives a substantial amount of the total dose before birth. Although there were no data on women’s satisfaction, women are likely to prefer fewer injections.
- The GDG reviewed the important differences in the type and preparation of steroids across settings.
and emphasized that local protocols on the type and dosing regimen of antenatal steroid should be informed by the preparations that are readily available in the setting. This will not only encourage uptake and ease their use by health-care providers but also avoid incorrect dosing and wastage of resources.

- The panel felt there might be important differences in pharmacological properties of dexamethasone and betamethasone dosage regimens and therefore considered this as a research priority.

**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

Evidence on the effectiveness and safety of different corticosteroids and different drug regimens was extracted from a Cochrane systematic review that included 12 trials (1557 women and 1661 infants) evaluating antenatal corticosteroid therapy for preterm birth (13).

Ten trials compared dexamethasone with betamethasone and two trials compared different regimens of the same drug in women at high risk of giving birth between 23 and 35 weeks of gestation. In the comparison between dexamethasone and betamethasone, both drugs were administered intramuscularly (IM); betamethasone was given as 24 mg in two to four divided doses 12–24 hours apart and dexamethasone was given as 24 mg (except in one trial which used 16 mg) in two to four divided doses 12 hours apart. However, 6 of the 10 studies in this comparison used two doses of 12 mg betamethasone 24 hours apart and four doses of 6 mg dexamethasone 12 hours apart. In four of the trials, women may have received repeat doses of corticosteroid. Three of the trials were conducted in the USA, two in France and one trial each in Iran, Israel, the Netherlands, Poland, Taiwan and the United Kingdom, as well as a two-centre study in Italy and Israel.

Dexamethasone versus betamethasone (any dose or regimen)

Maternal outcomes

Pregnancy prolongation: Pregnancy prolongation was reported in only one trial with results reported separately for women with intact and ruptured membranes. For women with intact membranes, the mean interval between hospital admission and birth was identical (7.1 days) in the two groups (MD 0.00 days, 95% CI -0.99 to 0.99; 120 women). However, for women with intact membranes, pregnancy was prolonged for a mean difference of 7 days in the dexamethasone group compared with the betamethasone group (MD 7.0 days, 95% CI 5.56 to 8.44; 120 women).

Infant outcomes
There were no significant differences in most critical infant outcomes between groups receiving dexamethasone and those receiving betamethasone.

**Neonatal death:** Neonatal death was similar in the two groups (RR 1.41, 95% CI 0.54–3.67; 4 studies, 596 infants).

**Severe neonatal morbidity:** There were no significant differences in RDS (RR 1.06, 95% CI 0.88–1.27; 5 studies, 753 infants), neonatal sepsis (RR 1.30, 95% CI 0.78–2.19; 2 studies, 516 infants), NEC (RR 1.29, 95% CI 0.38–4.40; 3 studies, 598 infants), retinopathy of prematurity (RR 0.93, 95% CI 0.59–1.47; 2 studies, 516 infants), periventricular leukomalacia (RR 0.83, 95% CI 0.23–3.03; 4 studies, 703 infants) or BPD (RR 2.50, 95% CI 0.10–61.34; 2 studies, 464 infants). The use of dexamethasone was associated with a reduction in the frequency of any IVH (all grades) (RR 0.44, 95% CI 0.21–0.92; 4 studies, 549 infants), but no difference was observed between the drugs for severe IVH (RR 0.40, 95% CI 0.13–1.24; 4 studies, 549 infants). There was no significant difference in the rate of low infant Apgar score (<7 at 5 minutes after birth) (RR 0.97, 95% CI 0.43–2.18; 2 studies, 207 infants) or admission to NICU (RR 1.72, 95% CI 0.44–6.72; 2 studies, 345 infants) between the groups. In one trial (70 infants), the mean duration of NICU stay was reduced by approximately 1 day in the dexamethasone group as compared to the betamethasone group (MD -0.91, 95% CI -1.77 to -0.05). One trial reported the difference in low infant birth weight (<2500 g) and identified no significant difference between groups (RR 0.89, 95% CI 0.65–1.24; 105 infants). In addition, in five trials, the mean birth weights in the dexamethasone and betamethasone groups were almost identical (MD 0.01 kg, 95% CI -0.11 to 0.12; 3 studies, 734 infants).

**Long-term morbidity:** Only one trial (with 12 children) reported assessment of neurosensory disability at 18 months. The trial did not have sufficient statistical power to detect meaningful differences between the comparison groups. Subgroup analyses were conducted comparing different dosing regimens of dexamethasone and betamethasone. There were no differences between the different dosing regimens with regard to neonatal death or severe infant morbidity. For most outcomes, estimable data were only available for one subgroup, or low event rates meant that studies lacked statistical power to identify possible subgroup differences.

**Oral versus intramuscular dexamethasone**

One study with data for 183 women compared oral (32 mg 12-hourly) with intramuscular (24 mg 12-hourly) dexamethasone.

**Maternal outcomes**

No maternal outcomes were reported in this trial.

**Infant outcomes**

**Neonatal death and severe neonatal morbidity:** There were no significant differences between groups receiving oral or IM dexamethasone in terms of neonatal death, NEC, IVH or infant birth weight. Neonatal sepsis was increased in the oral compared with the IM dexamethasone group, and for this outcome the difference between groups was significant (RR 8.48, 95% CI 1.11–64.93).

**Betamethasone 12 mg 12-hourly versus betamethasone 12 mg 24-hourly**

One trial with data for 255 women compared 12 mg doses of betamethasone every 12 hours versus 24 hours.

**Maternal outcomes**

**Maternal morbidity:** Maternal postpartum hospital stay was reduced in the group receiving betamethasone 12-hourly as compared to the group receiving 24-hourly treatment, although the magnitude of this difference
between groups may not be clinically significant (mean of 2.82 versus 3.55 days; MD -0.73 days, 95% CI -1.28 to -0.18). There was no significant difference observed in the rates of maternal fever >100.4°F (RR 0.71, 95% CI 0.25– 2.02).

**Infant outcomes**

*Neonatal mortality and early morbidity:* There were no significant differences between the two regimens for all newborn critical outcomes reported, although the study lacked statistical power to identify differences between groups for most outcomes.

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: Different corticosteroids and regimens for accelerating fetal lung maturation for women at risk of preterm birth

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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