WHO recommendation on routine antibiotic administration for women in preterm labour with intact amniotic membranes

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**Recommendation**

Routine antibiotic administration is not recommended for women in preterm labour with intact amniotic membranes and no clinical signs of infection.

*(Strong recommendation based on moderate-quality evidence).*

**Publication history**

*First published:* November 2015

*Updated:* No update planned

*Assessed as up-to-date:* November 2015

**Remarks**

- It is important that women with any diagnostic or clinical signs of infection are treated accordingly with antibiotics.
- Management of group B streptococcal colonization is not within the scope of this recommendation.
- The GDG placed its emphasis on the potential risk of harm to the baby and placed less value on the minimal benefit to mothers, and therefore recommended against the intervention.

**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:

- Among pregnant women at risk of imminent preterm birth (P), is routine antibiotic prophylaxis (I), compared with no antibiotic prophylaxis (C), effective in improving maternal and newborn outcomes (O)? If so:
  - Which population of pregnant women should not be offered antenatal prophylactic antibiotics? (considering women with intact amniotic membranes)
  - Which antibiotics (and regimens) should be used in eligible women?

Evidence summary
Evidence on the use of antibiotics for women in preterm labour with intact amniotic membranes was extracted from a Cochrane systematic review of 14 RCTs involving more than 7800 women (13).

Studies were mainly conducted in high-resource settings: six trials in the USA, and one trial each in Canada, Chile, Denmark, Germany, Iran, South Africa and Uruguay, as well as a large multicentre trial with data predominantly from women in the United Kingdom. Most of the results of meta-analysis were dominated by the findings of this latter placebo-controlled trial with data for more than 6000 women (the ORACLE II trial) (14). All studies recruited women with uterine contractions and cervical dilatation, with intact membranes and no clinical signs of infection. The mean gestational age at recruitment was between 30 and 32 weeks. Women received only oral antibiotics in three trials, only IV antibiotics in another three trials, and IV followed by oral antibiotics in eight trials. Antibiotics examined included ampicillin (with or without sulbactam or clavulanic acid), amoxicillin (with or without sulbactam or clavulanic acid), erythromycin, clindamycin, mezlocillin, ceftizoxime or metronidazole, mostly as combinations. The duration of treatment varied from 3 to 10 days. In 13 of the 14 trials, antibiotics were administered alongside tocolytic therapy to women in both intervention and control groups, according to local protocol at the study sites. Women participating in most of the trials conducted in the mid-1990s also received corticosteroids.

Any prophylactic antibiotic versus placebo or no antibiotics

Maternal outcomes

Pregnancy prolongation: Overall, there was no clear evidence that prophylactic antibiotics prolong pregnancy. No statistically significant differences were observed in birth prior to 36 or 37 weeks (RR 0.98, 95% CI 0.92–1.05; 10 studies, 7387 women), birth within 48 hours of randomization (RR 1.04, 95% CI 0.89–1.23; 4 studies, 6800 women), birth within 7 days of randomization (RR 0.98, 95% CI 0.87–1.10; 8 studies, 7053 women) or gestational age at birth (MD 0.53 weeks, 95% CI 0.00–1.06; 10 studies, 986 women). However, the interval between randomization and birth was on average 5 days longer among women receiving prophylactic antibiotics (MD 5.59 days, 95% CI 0.31–10.87; 6 studies, 2499 women).

Maternal morbidity: There was a significant reduction in the frequency of maternal infection in the group receiving antibiotics (RR 0.74, 95% CI 0.63–0.86; 10 studies, 7371 women). Adverse effects: There was no significant difference between groups for maternal adverse drug reaction requiring cessation of treatment (RR 1.32, 95% CI 0.92–1.89; 5 studies, 626 women).

Infant outcomes

Perinatal death: There were no significant differences between groups for perinatal death (RR 1.22, 95% CI 0.88–1.69; 10 studies, 7304 infants), stillbirth (RR 0.73, 95% CI 0.43–1.26; 8 studies, 7080 infants) or infant death after 28 days (RR 1.06, 95% CI 0.68–1.67; 1 study, 4654 infants). Neonatal death, however, was increased in infants of women receiving antibiotics (RR 1.57, 95% CI 1.03–2.40; 9 studies, 7248 infants).
Severe neonatal morbidity: Overall, there was no evidence that prophylactic antibiotics significantly reduced serious infant morbidity. No significant differences were observed between comparison groups with regard to RDS (RR 0.99, 95% CI 0.84–1.16; 9 studies, 7200 infants), NEC (RR 1.06, 95% CI 0.64–1.73; 6 studies, 6880 infants), neonatal sepsis (RR 0.86, 95% CI 0.64–1.16; 10 studies, 7386 infants), IVH (RR 0.76 95% CI 0.48–1.19; 5 studies, 6813 infants), chronic neonatal lung disease (on ultrasound before hospital discharge) (RR 1.17, 95% CI 0.78–1.76; 1 study, 6241 children) or mechanical ventilation (RR 1.02, 95% CI 1.02, 95% CI 0.84–1.24; 1 study, 6241 infants). Admissions to NICU were comparable in the two groups (RR 0.82, 95% CI 0.62–1.10; 5 studies, 6875 infants). Antibiotics were not associated with a significant reduction in the incidence of low birth weight (<2500 g) (RR 0.97, 0.81–1.15; 5 studies, 6628 infants). There was also no significant difference between groups in mean infant birth weight (MD 58.38 g, 95% CI -26.24 to 143.00; 12 studies, 7531 infants).

Long-term morbidity: One study in the United Kingdom followed up women and infants for 7 years. At age 7 years, there was no significant difference between children whose mothers had received antibiotics compared with those whose mothers had received placebo with respect to moderate or severe functional impairment (RR 1.07, 95% CI 0.89–1.28; 3052 children). There was a trend towards an increase in any functional impairment (including mild impairment) at age 7 (RR 1.10, 95% CI 0.99–1.23; 3052 children) and cerebral palsy (RR 1.82, 95% CI 0.99–3.34; 3173 children) for those children whose mothers had received antibiotics for preterm labour.

Specific classes of antibiotics versus no antibiotics

The review also examined subgroups comparing different types of antibiotics: betalactam antibiotics (e.g. ampicillin, amoxicillin, co-amoxiclav) alone versus no antibiotics macrolide antibiotics (e.g. erythromycin) alone versus no antibiotics combined macrolide and betalactam antibiotics versus no antibiotics antibiotics active against anaerobic bacteria (e.g. clindamycin) versus no antibiotics.

Pregnancy prolongation: There was no statistically significant evidence that any specific class of antibiotics reduced the number of preterm births (<37 weeks), or delayed birth by 48 hours compared with no antibiotics. While macrolide and betalactam antibiotics had no significant impact on the interval between randomization and birth, three small trials indicated that the mean interval between randomization and birth was increased in women receiving antibiotics active against anaerobic bacteria (MD 10.50 days, 95% CI 4.95–16.06; 293 women).

Adverse effects: There was no evidence that maternal adverse drug reactions were significantly increased with the use of any particular class of antibiotic.

Perinatal or infant death: For stillbirth, perinatal, neonatal and infant death, there were no statistically significant subgroup differences, although there were few events in some subgroups and many effect estimates were imprecise.

Severe neonatal morbidity: There was no evidence of subgroup differences for RDS, NEC or IVH.

Long-term morbidity: Long-term morbidity outcomes were measured in a single factorial study; there was no evidence that different antibiotics had a differential impact on moderate or severe functional impairment, or any functional impairment when children were 7 years of age. Compared with placebo, there was an increased risk of cerebral palsy observed at 7 years in association with macrolide and betalactam antibiotics combined (erythromycin plus co-amoxiclav) (RR 2.83, 95% CI 1.02–7.88; 1 study, 1052 children).

Further information and considerations related to this recommendation can be found in the WHO guidelines,
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 that further research on the following high-priority question is needed:

- What is the appropriate dose and regimen that should be used for prophylaxis (particularly in relation to combination therapy with betalactam and macrolide)?

Related links


Supporting systematic reviews:

Prophylactic antibiotics for inhibiting preterm labour with intact membranes

Other links of interest

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
References


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