WHO recommendation on antibiotic administration for women with preterm prelabour rupture of membranes

17 November 2015

Recommendation

Antibiotic administration is recommended for women with preterm prelabour rupture of membranes.

*(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

- In order to avoid inadvertent antibiotics administration to women with intact amniotic membranes, antibiotics should not be prescribed unless a definite diagnosis of preterm prelabour rupture of membranes (PPROM) has been made. Therefore, a policy of prescribing antibiotics for women with PPROM should be accompanied by a protocol for reliably diagnosing PPROM.
- Women should be monitored for signs of clinical chorioamnionitis.

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. gestational 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 women should be offered antenatal prophylactic antibiotics? (considering women with preterm rupture of membranes)
  - Which antibiotics (and regimens) should be used in eligible women?

Evidence summary

Evidence on the use of antibiotics for women with PPROM was extracted from a Cochrane review that included 22 RCTs and a total of more than 7000 women (13).

Data were mainly for women cared for in high-resource settings: 14 trials in the USA, and one trial each in
Denmark, Finland, Germany, Spain, Turkey, Zimbabwe, as well as two multicentre trials, one mostly recruiting women from Chile and the other one from the United Kingdom. Most of the results were dominated by the findings of the United Kingdom trial with data for more than 4800 women (the ORACLE I trial) (14). Most women recruited into the trials were not in active labour. Trials recruited women between 20 and 37 weeks of gestation. For the 16 placebo-controlled trials, women received oral antibiotics in three trials, IV antibiotics in four trials, and IV therapy followed by oral antibiotics in the remaining trials. Ten of these trials examined broad-spectrum antibiotics and five compared macrolide antibiotics (erythromycin) with placebo. In some trials combinations of different drugs were used. The duration of the course of antibiotics varied considerably across trials, from two doses through to continued antibiotic therapy until delivery.

Any prophylactic antibiotic versus placebo or no antibiotics

Maternal outcomes

**Pregnancy prolongation:** Compared with placebo, there was no statistically significant evidence that antibiotics reduced the likelihood of preterm birth (< 37 weeks) (RR 1.00, 95% CI 0.98–1.03; 3 studies, 4931 women). Antibiotics were associated with a reduction in the chances of women giving birth within 48 hours (RR 0.71, 95% CI 0.58–0.87; 7 studies, 5927 women) and within 7 days (RR 0.79, 95% CI 0.71–0.89; 7 studies, 5965 women).

**Maternal death:** There were no maternal deaths in any of the three trials that reported this outcome (763 women). Maternal infectious morbidity: Fewer women in the group receiving antibiotics developed chorioamnionitis (RR 0.66, 95% CI 0.46–0.96; 11 studies, 1559 women). Four studies with data for 5547 women reported on maternal infection following delivery (before hospital discharge); there was no significant difference between groups for this outcome (RR 0.91, 95% CI 0.8–1.02).

**Maternal adverse effects:** No women were reported to have suffered a major adverse drug reaction (3 studies, 5487 women).

Infant outcomes

**Perinatal death:** There was no significant difference between groups in terms of perinatal death (RR 0.89, 95% CI 0.74–1.08; 18 studies, 6872 infants). In a sensitivity analysis including only placebo-controlled trials, the difference between groups remained nonsignificant (RR 0.93, 95% CI 0.76–1.14; 12 studies, 6301 infants).

**Severe neonatal morbidity:** Infants whose mothers received antibiotics had a reduced risk of infection, including pneumonia (RR 0.67, 95% CI 0.52–0.85; 12 studies, 1680 infants), and a reduced risk of having a positive blood culture (RR 0.79, 95% CI 0.63–0.99; 3 studies, 4961 infants). Infants whose mothers received antibiotics were also at reduced risk of major cerebral abnormality (RR 0.81, 95% CI 0.68–0.98; 12 studies, 6289 infants). In one study, antibiotics slightly reduced the risk of the infant requiring treatment with a surfactant (RR 0.83, 95% CI 0.72–0.96; 1 study, 4809 infants). There were no significant differences between groups receiving or not receiving antibiotics with regard to RDS (RR 0.95, 95% CI 0.83–1.09; 12 studies, 6287 infants), NEC (RR 1.09, 95% CI 0.65–1.83; 11 studies, 6229 infants) or need for mechanical ventilation (RR 0.90, 95% CI 0.80–1.02; 2 studies, 4924 infants). There were no instances of neonatal encephalopathy in one trial with a small sample size reporting this outcome. Admissions to the NICU were similar in the two groups (RR 0.98, 95% CI 0.84–1.13; 4 studies, 5023 infants). Data on length of NICU stay were reported in three trials with small sample sizes; infants in the group whose mothers received antibiotics, on average, had five fewer days in special care (MD -5.05 days, 95% CI -9.77 to -0.33; 225 infants). Antibiotics were not associated with a reduction in the incidence of low birth weight (< 2500 g) (RR 1.00, 0.96–1.04; 2 studies, 4876 infants). Mean birth weight was slightly increased in those infants whose mothers had received antibiotics (MD 53.83 g, 95% CI 7.06–100.60; 12 studies, 6374 infants).
Long-term morbidity: One study followed up women and infants for seven years. At age 7, there were no significant differences in serious disability between children whose mothers had received antibiotics in pregnancy versus placebo (RR 1.01, 95% CI 0.91–1.12; 3171 children).

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 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:

References


Citation: WHO Reproductive Health Library. WHO recommendation on antibiotic administration for

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