Prevention of Intrauterine Growth Restriction and Preterm Birth with Presumptive Antibiotic Treatment of Pregnant Women: A Literature Review

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Introduction

Intrauterine growth restriction (IUGR) and preterm birth (PTB) account for a large share of global child mortality, morbidity and developmental loss. Of the numerous risk factors for these conditions, maternal infections have been most consistently identified [1, 2]. Because of the assumed causative role of infections, there has been a wide interest to study the efficacy of presumptive or targeted treatment of pregnant women with antimicrobial agents as a means to promote fetal growth and prevent PTB. In malaria-endemic areas, especially in Sub-Saharan Africa, intermittent preventive treatment of malaria in pregnancy has proven beneficial in this respect [3], but data from studies with antibacterial drugs have yielded more conflicting results. We carried out a systematic literature search and review in order to summarize the current data on presumptive antibiotic treatment of pregnant women and to identify predictors of its efficacy in preventing PTB or IUGR.

Methods

We performed a computerized search for clinical trials from Ovid MEDLINE® database (1946 to February 2014). We searched for both subject headings and their corresponding keywords that are related to pregnancy, premature birth, birthweight, fetal growth and antimicrobial agents.

We included randomized, controlled, trials that compared early treatment of asymptomatic pregnant women with oral or injectable broad-spectrum antibiotics and measured birthweight or the duration
of pregnancy as outcomes. Antibiotics having antimicrobial activity against both Gram-negative and Gram-positive aerobic and anaerobic bacteria were considered broad-spectrum. Early treatment was defined as starting before 32 gestation weeks and asymptomatic meant that the participants did not have signs of acute illness or imminent delivery at enrolment.

**Results**

From the 374 initially identified articles, we selected 14 trials for review. The total number of participants in these trials was 15,787. Six trials were conducted in Sub-Saharan Africa (10,790 participants), 2 in India, 5 in the United States and one in the UK. The assumed mechanism leading to improved outcomes was almost universally an effect of the antibiotic treatment on maternal reproductive tract infections, bacterial vaginosis, or chorioamnionitis. The tested antibiotic regimens included erythromycin alone, erythromycin + metronidazole, erythromycin + cephalexin, clindamycin, ceftriaxone, cefetamet-pivoxil, azithromycin + cefexime + metronidazole, and azithromycin alone.

Of the six trials in Africa, all but one reported a positive effect on birthweight or the duration of pregnancy or both. All of these trials tested a wide-spectrum antibiotic regimen, i.e., azithromycin, third general cephalosporin, a combination of them, or a combination of erythromycin and metronidazole (table 1). The only trial where no effect was found was conducted in Malawi and tested the effect of azithromycin given in combination with a possibly insufficient malaria prophylaxis. Two studies from India suggested no intervention effect, and trials in the US or Europe yielded both positive and negative findings.

**Discussion**

In almost all reports, antibiotics were assumed to improve birth outcomes by affecting infections or bacterial colonization in the maternal reproductive tract. Local spread is, however, only one of the pathogenic mechanisms associated with infection-related adverse birth outcomes. Two alternative pathways include hematogenic dissemination of bacteria from elsewhere in the body and a systemic inflammatory response that can lead to PTB and IUGR through a multitude of processes [4, 5].

We conclude that presumptive antimicrobial treatment of pregnant women may improve birth outcomes in some but not all contexts. An effect is more likely if the intervention targets maternal infections in general, not only those in the reproductive tract. Another precondition is that
a high fraction of IUGR and PTB in the target population is attributable to infectious etiology [2]. This situation is more common in Sub-Saharan Africa than in Asia, USA or Europe.

**References**