

The role of antibiotics in the prevention of preterm birth

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Abstract

There are multiple uses for antibiotics during pregnancy: treatment of intercurrent bacterial infections such as urinary or respiratory tract infections, maternal treatment to prevent fetal or neonatal disease, prophylactic treatment for surgical procedures, and treatment of puerperal infections. This report will summarize the current recommendations for the use of antibiotics specifically to reduce the risk of preterm birth.

Introduction and context

Preterm delivery, the leading cause of perinatal morbidity and mortality worldwide, occurs in 12–13% of births in the US and 5–9% of births in many other developed countries [1]. Spontaneous preterm labor and preterm premature rupture of membranes together account for 80% of preterm births [2]. There is substantial evidence that infection and inflammatory mediators are implicated in the pathogenesis of preterm birth. Of all premature births, 25% or more occur in women with evidence of infection of the amniotic cavity [3]. Furthermore, proinflammatory cytokines, such as interleukin-1-beta and tumor necrosis factor-alpha, have been identified as mediators in the pathophysiology of preterm labor [4]. Specific maternal bacterial infections that have been shown to be associated with an increased risk of preterm birth include urinary tract infection [5], lower genital tract infection [6], and periodontal infection [7]. The specific pathophysiologic mechanisms by which these infections cause preterm birth include direct ascending infection of the placenta and fetus, transplacental blood-borne infection, and systemic activation of proinflammatory cytokines that activate prostaglandin production.

There is no controversy about the treatment of symptomatic bacterial infections during pregnancy, such as pyelonephritis, vaginitis, cervicitis, pneumococcal

pneumonia, or listeriosis. A high index of clinical suspicion, the use of appropriate laboratory measures to confirm the diagnosis and identify the specific organism, and prompt treatment with appropriate antibiotics will reduce maternal morbidity, forestall preterm birth, and prevent fetal infections as in the case of listeriosis. What is controversial is the extent to which screening for and treatment of asymptomatic infection or antibiotic treatment of asymptomatic women at increased risk of preterm birth will reduce the risk of preterm birth or otherwise decrease perinatal morbidity.

In prescribing antibiotics (or any other drugs), for whatever indication, to women who are pregnant, physicians must keep in mind the potential untoward effect on the developing embryo and fetus. This is particularly important in the first 56 days of pregnancy, when the developing embryo is at the greatest risk of teratogenic effects of medications. If there is any doubt about the safety of a medication, a reliable reference should be consulted, such as that by Briggs *et al.* [8].

Recent advances

Asymptomatic bacteriuria

Screening for and antibiotic treatment of asymptomatic bacteriuria during pregnancy are widely accepted as means of preventing pyelonephritis and reducing the risk

of preterm birth [5]. The mechanism of action involved in the reduction of the risk of preterm birth is not entirely clear. Screening for bacteriuria in prenatal patients is advised. A meta-analysis by Devillé *et al.* [9], which included 70 studies, found the urine dipstick method of screening to be useful in excluding the presence of infection, especially in pregnant women. However, the rapid tests are less reliable in detecting infection and their use should not replace urine culture for detecting asymptomatic bacteriuria [9].

Bacterial vaginosis

Bacterial vaginosis (BV) is characterized by an overgrowth of a variety of anaerobic organisms, including *Gardnerella vaginalis*, *Mycoplasma hominis*, *Mobiluncus species*, *Atopobium vaginae*, and other organisms, and an associated reduction in normal vaginal *Lactobacillus* species [10]. A recent meta-analysis of 15 controlled trials, which included 5,888 women, found that antibiotic treatment was highly effective in eradicating BV in pregnancy [11]. However, a meta-analysis of seven recent randomized controlled trials of screening and treatment of pregnant women who were asymptomatic for BV evidence found that screening and treatment of pregnant women for BV did not result in a reduction in preterm birth. Also, there was concern about the potential for unintended harm from the treatment [12]. That study resulted in the recommendation by the US Preventive Services Task Force that current evidence is insufficient to support a policy of screening for BV in pregnant women at high risk for preterm delivery [13]. The use of probiotics (live organisms, especially *Lactobacillus* species) has been shown to be effective in treating BV, but evidence that probiotic treatment reduces the risk of preterm birth is lacking [14].

Antibiotic treatment for patients in preterm labor

Although the role of inflammation in the pathophysiology of spontaneous preterm birth is well documented, there is no evidence that the routine use of antibiotics in the management of patients with preterm labor has reduced the incidence of preterm birth. The most important study showing that lack of effectiveness of antibiotic therapy for preterm labor was the ORACLE II randomized controlled trial [15]. Women with intact membranes and in spontaneous premature labor ($n = 6,295$) were randomly assigned to treatment with various combinations of erythromycin, amoxicillin, and clavulanic acid and a placebo four times daily for 10 days. Although antibiotic treatment was associated with a lower occurrence of maternal infection, none of the antibiotic regimens were associated with a lower incidence of preterm birth. A meta-analysis by King and Flenady [16] of 11 controlled trials, which included the

data from the ORACLE II trial, confirmed these findings. A follow-up study of 3,196 children from the ORACLE II trial at 7 years of age found that those who had received erythromycin either alone or in combination with amoxiclav were significantly more likely to have developed cerebral palsy [17]. In an evaluation of this study, Faculty of 1000 member Michael Marsh raised the possibility that the use of antibiotics might mask the signs of intrauterine infection thereby leading to the delayed delivery of an affected infant [18].

A recent meta-analysis of 17 controlled trials of the use of antibiotics in patients at risk of premature birth because of abnormal vaginal flora, previous preterm birth, or positive fetal fibronectin, found that there was no association between antibiotic treatment and reduction in preterm birth irrespective of the criteria used to assess risk, the antimicrobial agent administered, or gestational age at the time of treatment [19]. These data would be in accord with the recommendation of the American College of Obstetricians and Gynecologists (ACOG) that women in preterm labor should not be treated with antibiotics for the sole purpose of preventing preterm delivery [20].

At least two recent trials have found that preconception use of antibiotics to treat patients at increased risk of preterm birth has not been effective in reducing the subsequent risk of delivering a preterm infant for these patients, and in some instances, the treatment actually increased the risk of subsequent preterm birth [21,22]. In an evaluation of the study by Tita *et al.* [22], Faculty of 1000 member Bryan Larsen suggested that the destruction of bacteria by antibiotics may release toxic mediators leading to adverse outcomes or that the cause of preterm birth is more complex than has been suggested by research to date and will require a different set of measures applied to the intrauterine environment [23].

Antibiotics in patients with preterm premature rupture of membranes

The cause of preterm premature rupture of the membranes (PPROM), which occurs in 2 to 4% of all singleton pregnancies and in a higher proportion of twin pregnancies, is not known. Most cases of PPROM occur in otherwise healthy women without identifiable risk factors. However, ascending choriodecidual infection has been identified in some cases, although it is not known whether this is a cause or a consequence of PPROM. Nevertheless, the use of antibiotics in women with PPROM has been shown to increase the latency period, defined as the period between the rupture of membranes and the onset of labor. A meta-analysis by

Ananth *et al.* [24] of nine placebo-controlled randomized trials of the use of antibiotics in patients with PPROM found a significant increase in the latency period and a reduction in neonatal sepsis in subjects who received antibiotic treatment as compared with those who received placebos. These studies suggested that broad-spectrum antibiotic coverage (for example, ampicillin-sulbactam) was more effective than a narrow-spectrum antibiotic (ampicillin). Subsequent trials in patients with PPROM, including the trial conducted by the ORACLE Collaborative Group, have confirmed the efficacy of broad-spectrum antibiotic treatment in prolonging the latency period, prolonging gestation, and reducing the incidence of chorioamnionitis and of neonatal infection and intraventricular hemorrhage [25].

A number of different broad-spectrum antibiotic regimens have been used to treat patients with PPROM. Although there is no conclusive evidence demonstrating a single regimen that is superior, a 5-day course of antibiotic therapy including a macrolide (erythromycin or azithromycin) is effective [26].

The mechanism of action of the prolongation of the latency period achieved by antibiotic treatment of women with PPROM may be more complex than simply prevention of chorioamniotic infection. A recent study by Gomez *et al.* [27] analyzed two amniocentesis specimens taken 5 days apart in women with PPROM and found that antibiotic treatment (ceftriaxone, clindamycin, and erythromycin) failed to eradicate microbial invasion of the amniotic cavity or eliminate host inflammatory response. In an evaluation of this study, Faculty of 1000 member Austin Ugwumadu pointed out that the findings were consistent with existing evidence that antibiotics administered to the mother do not reach therapeutic levels within the fetal compartment to inhibit common pathogens [28].

Based on the information in two large multicenter clinical trials [29,30], ACOG recommends a 48-hour course of ampicillin and erythromycin followed by 5 days of amoxicillin and erythromycin during expectant management of PPROM remote from term to prolong pregnancy and to reduce infectious and gestational age-dependent neonatal morbidity [31]. The use of ampicillin-clavulanic acid is not recommended because of its association with an increased rate of neonatal necrotizing enterocolitis [30]. Also, the ACOG recommendation notes that women with PPROM and who are known carriers of Group B Streptococcus, and those who give birth before carrier status can be delineated, should receive intrapartum prophylaxis (penicillin) to prevent vertical transmission regardless of earlier treatments. The

guidelines of the Royal College of Obstetricians and Gynaecologists for the treatment of women with PPROM differ from those of the ACOG in the antibiotic regimen recommendation only: erythromycin (250 mg orally every 6 hours) for 10 days following the diagnosis of PPROM [32].

Implications for clinical practice

Screening for bacteriuria in prenatal patients is advised. However, rapid screening tests should not replace urine culture for detecting asymptomatic bacteriuria. Routine screening for and treatment of asymptomatic BV are not indicated. The use of antibiotics to treat women at high risk of preterm birth or those with idiopathic spontaneous preterm labor does not significantly decrease the incidence of preterm birth and may result in an increased risk of neonatal developmental abnormalities. This does not preclude the need for prophylaxis against early-onset Group B streptococcal disease when indicated. Patients with preterm premature rupture of membranes should receive a 7- to 10-day course of antibiotic therapy. Antibiotic regimens should include a macrolide (erythromycin or azithromycin) but not ampicillin-clavulanic acid.

Abbreviations

ACOG, American College of Obstetricians and Gynecologists; BV, bacterial vaginosis; PPROM, preterm premature rupture of the membranes.

Competing interests

The author declares that he has no competing interests.

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