Antibiotics for Preterm Labor

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Abstract

Since intrauterine infection is the most frequent cause of preterm birth, numerous trials have been attempted on the antibiotic treatment of various conditions. There is insufficient evidence to recommend treatment of genital tract infection in early pregnancy to reduce the prevalence of preterm birth. Routine antibiotics in pregnant women with preterm labor and intact membranes can have harmful effects on the neonatal outcome. Thus, antibiotic administration should be withheld unless obvious infection signs are observed. The efficacy of antibiotic administration has been established in prelabor premature rupture of membranes. However, clinicians should be cautious regarding the development of resistant organisms after prophylactic antibiotics. Once a pregnant woman is diagnosed with or suspected to have intrauterine infection, immediate initiation of antibiotic therapy is recommended. Since intrauterine infection is usually polymicrobial involving both aerobic and anaerobic bacteria, antibiotics should cover these microorganisms. The optimal antibiotic regimen has not been well-studied. Amniotic fluid sample obtained by transabdominal amniocentesis in pregnant women with suspected intrauterine infection can determine antibiotic susceptibility and the efficacy of an antibiotic treatment. Expectant management with antibiotic treatment may contribute to prolongation of pregnancy duration; however, strict observation of the fetal condition is necessary.

Keywords

Chorioamnionitis · Preterm birth · Antibiotics · Prelabor premature rupture of membranes

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13.1 Antibiotics for the Prevention of Preterm Birth

Maternal genital tract colonization with various pathogens including Ureaplasma species [1, 2], *Chlamydia trachomatis* [3–6], and *Trichomonas vaginalis* [4, 7] can be associated with preterm birth. Antibiotic treatment against these pathogens during pregnancy has been attempted to prevent preterm birth.

Erythromycin treatment in pregnant women with vaginal Ureaplasma species colonization in the third trimester decreased the prevalence of low-birth-weight infants in a randomized double-blind study [8]. However, a large, randomized, double-blind, multicenter clinical trial showed that erythromycin treatment for pregnant women with *Ureaplasma urealyticum* colonization in the vagina between 26 and 30 weeks of gestation did not prevent preterm birth [9]. The Cochrane Review including one trial and 1071 patients concluded that the evidence was insufficient to assess whether Ureaplasma colonization in the genital tract should be treated to prevent preterm birth [10].

A double-blind, randomized, placebo-controlled trial showed that treatment of a chlamydia infection during pregnancy had little effect on reducing preterm delivery [11]. However, a systematic review and meta-analysis including 24 studies revealed that pregnant women with chlamydia infection had a significantly higher prevalence of preterm delivery with an odds ratio (OR) of 2.28 [95% confidence interval (CI), 1.64–3.16] [12], although some recent studies resulted in negative [13, 14].

Interestingly, metronidazole treatment for asymptomatic Trichomonas infection at 24–29 weeks of gestation increased the risk of preterm delivery with a relative risk (RR) of 3.0 (95% CI, 1.5–5.9) [15]. The authors hypothesized that a dying Trichomonas caused an inflammatory response, resulting in preterm labor.

Additionally, whether vaginal candidiasis treatment reduces the prevalence of preterm birth remains controversial. A systematic review and meta-analysis using two studies and 685 patients showed that treatment of asymptomatic candidiasis may reduce the risk of preterm birth, although the evidence was insufficient because the result included unplanned subgroup analysis [16].

Treatment of bacterial vaginosis is discussed in Chap. 18.

There are some trials on the antibiotic treatment of pregnant women with a specific condition. A randomized clinical trial showed that metronidazole plus erythromycin for pregnant women with a positive fetal fibronectin between 21 and 25 weeks of gestation did not reduce the risk of preterm delivery [17]. Moreover, another randomized controlled trial revealed that metronidazole for pregnant women with a positive fibronectin and a risk of preterm birth, including mid-trimester loss or preterm delivery, uterine abnormality, cervical surgery, or cerclage, between 24 and 27 weeks of gestation did not reduce the prevalence of preterm birth [18].

Pregnant women with amniotic fluid sludge detected by ultrasonography are potential candidates for antibiotic prophylaxis. A historically controlled observational study has shown that antibiotic treatment reduced the prevalence of preterm birth at <34 weeks in women at high risk for preterm birth (i.e., cervical length ≤25 mm, history of spontaneous preterm birth, previous spontaneous loss in the

second trimester, uterine malformations, or cervical conization) with an OR of 0.24 (95% CI, 0.06–0.99) [19], although its evidence level is low. Hence, further research is needed.

Overall, the Cochrane Review including eight trials and approximately 4300 patients reviewed the effect of prophylactic antibiotic treatment for women in the second or third trimester and concluded that antibiotic prophylaxis during pregnancy did not reduce the risk of preterm prelabor rupture of membranes (relative ratio (RR), 0.31; 95% CI, 0.06–1.49) or preterm delivery (RR, 0.88; 95% CI, 0.72–1.09) [20].

In conclusion, there is an insufficient evidence to recommend treatment of genital tract infection to reduce the prevalence of preterm birth. However, the use of antibiotic treatment to prevent the spread of sexual transmitted infection or for symptomatic patients is justified.

13.2 Antibiotics for Preterm Labor with Intact Membranes Without Evidence of Infection

Some clinicians favor the use of antibiotics in pregnant women with preterm labor because intrauterine infection is an important cause of preterm labor. However, routine prophylactic antibiotics should be avoided in those with preterm labor and intact membranes.

The ORACLE II study is the largest trial involving 6295 patients which compared erythromycin (n = 1611), co-amoxiclav (amoxicillin and clavulanic acid; n = 1550), both (n = 1565), or placebo (n = 1569) for 10 days or until delivery among pregnant women with preterm labor and intact membranes, but without any signs of clinical infection. This study failed to demonstrate the benefits of antibiotic use for the reduction of neonatal composite outcome including neonatal death, chronic lung disease, or major cerebral abnormality on ultrasonography [21].

Furthermore, the Cochrane Review reviewed 14 studies and concluded that the use of prophylactic antibiotics in pregnant women with preterm labor and intact membranes had no beneficial effects on the neonatal outcome. It is important to note that the incidence of neonatal death increased in women who received prophylactic antibiotics compared to those without antibiotics (RR, 1.57; 95% CI, 1.03–2.40). In a subgroup analysis, cerebral palsy significantly increased in infants born to women with combined macrolide and beta-lactam antibiotics compared to those receiving placebo (RR, 2.83; 95% CI, 1.02–7.88). The prevalence of neonatal death (RR, 1.52; 95% CI, 1.05–2.19), any functional impairment (RR, 1.11; 95% CI, 1.01–1.20), and cerebral palsy (RR, 1.90; 95% CI, 1.20–3.01) increased in infants whose mothers received any macrolide antibiotics compared to those who received no macrolide antibiotics (including placebo and co-amoxiclav alone) [22].

These findings suggest that routine antibiotics should be withheld in pregnant women with preterm labor and intact membranes, unless obvious infection signs are manifested.

13.3 Antibiotics for Prelabor Premature Rupture of Membranes (pPROM) Without any Sign of Infection

In contrast to preterm labor with intact membranes, the efficacy of antibiotic administration has been established in pPROM.

The first large randomized controlled trial conducted by the National Institute of Child Health and Human Development Maternal-Fetal Medicine Units Network in 1997 demonstrated the impact of antibiotic prophylaxis on pPROM management [23]. A total of 614 pregnant women with pPROM between 24 and 32 weeks of gestation were included and randomly assigned to receive intravenous ampicillin (2 g every 6 h) and erythromycin (250 mg every 6 h) for 48 h, followed by oral amoxicillin (250 mg every 8 h) and erythromycin (333 mg every 8 h) for 5 days or placebo. Group B streptococcus (GBS) carriers were identified and treated. Tocolytics and corticosteroids were withheld after randomization. The prevalence of neonatal composite adverse outcomes (i.e., fetal or infant death, respiratory distress, severe intraventricular hemorrhage, stage 2 or 3 necrotizing enterocolitis, or sepsis) (44.1% vs 52.9%), respiratory distress (40.5% vs 48.7%), and necrotizing enterocolitis (2.3% vs 5.8%) was significantly lower in the antibiotics group than that in the placebo group. Among the GBS negative women, the antibiotics group had a prolonged median time to delivery compared to the placebo group (6.1 days vs 2.9 days). About half of antibiotics group remained pregnant at 7 days after treatment, while about 25% of placebo group did.

The second impact trial was the ORACLE trial in 2001 [24]. This is the largest trial which included a total of 4826 pregnant women with pPROM at less than 37 weeks of gestation. They were randomly assigned to oral 250 mg erythromycin ($n = 1197$), 325 mg co-amoxiclav (250 mg amoxicillin and 125 mg clavulanic acid; $n = 1212$), both ($n = 1192$), or placebo ($n = 1225$) four times daily for 10 days or until delivery. The prevalence of neonatal composite adverse outcomes (i.e., neonatal death, chronic lung disease, or major cerebral abnormality) was lower in the erythromycin only group than that in the placebo group, although it was not statistically significant (12.7% vs 15.2%, $p = 0.08$). Importantly, the co-amoxiclav only group had a higher incidence of necrotizing enterocolitis than the placebo group (1.9% vs 0.5%). Additionally, the any co-amoxiclav group had a higher incidence of necrotizing enterocolitis than the no co-amoxiclav group (1.8% vs 0.7%). Therefore, co-amoxiclav is not recommended for pregnant women with pPROM.

The Cochrane Review included 12 studies and reported that antibiotic treatment in pregnant women with pPROM statistically significantly reduced the prevalence of chorioamnionitis (RR, 0.66; 95% CI, 0.46–0.96), prolonged the latency period for 48 h (RR, 0.71; 95% CI, 0.58–0.85) and 7 days (RR, 0.79; 95% CI, 0.71–0.89), neonatal infection (RR, 0.67; 95% CI, 0.52–0.85), surfactant use (RR, 0.83; 95% CI, 0.72–0.96), oxygen therapy (RR, 0.88; 95% CI, 0.81–0.96), and abnormal cerebral ultrasound scan (RR, 0.81; 95% CI, 0.68–0.98). Co-amoxiclav was associated with an increased risk of neonatal necrotizing enterocolitis (RR, 4.72; 95% CI, 1.57–14.23) [25].

The most optimal regimen and duration of antibiotics have yet to be established. The combination of ampicillin/amoxicillin and erythromycin following the NICHD trial is commonly used.

Clinicians should be cautious on the development of resistant organisms following the use of prophylactic antibiotics. Basically, single antibiotic and short-term is favorable. Only small studies have revealed three-day regimen had no difference in outcomes, compared with seven-day regimen [26, 27]. Hence, a larger study is necessary.

13.4 Antibiotics for Diagnosed or Suspected Intrauterine Infection

13.4.1 Timing of Antibiotic Treatment

If a pregnant woman is diagnosed with or suspected to have intrauterine infection, immediate initiation of antibiotic therapy is recommended. There is only one small randomized prospective trial involving 45 pregnant women [28] which compared intrapartum treatment and immediate postpartum treatment. The antibiotics were intravenous ampicillin 2 g every 6 h plus gentamicin 1.5 mg/kg every 8 h. In addition, patients delivered by cesarean section received clindamycin 900 mg every 8 h. The incidence of neonatal sepsis was lower (0% vs 21%) and the neonatal hospital stay was shorter (3.8 days vs 5.7 days) in the intrapartum antibiotic group than that in the postpartum antibiotic group. Similarly, the intrapartum antibiotic group had significantly shorter maternal postpartum hospital stay (4.0 days vs 5.0 days) and febrile days (0.44 days vs 1.5 days) than the postpartum antibiotic group. A retrospective study also showed that intrapartum antibiotic treatment had a lower incidence of neonatal sepsis ($p = 0.06$) [29].

13.4.2 Antibiotic Regimen

Intra-amniotic infection is usually polymicrobial involving both aerobic and anaerobic bacteria. Therefore, antibiotics should cover these microorganisms. The optimal antibiotic regimen has not been well-studied.

A combination of intravenous ampicillin and gentamicin is traditionally preferred since GBS and *Escherichia coli* are the most common pathogens of neonatal sepsis. These agents have lack of activity against anaerobic coverage. Therefore, addition of clindamycin is recommended for the treatment of women undergoing cesarean section. However, a randomized controlled study failed to demonstrate the benefit of adding clindamycin to ampicillin and gentamicin in the prevalence of endometritis, neonatal sepsis, or mortality [30]. On the other hand, the Cochrane Review reported that the combination of clindamycin and gentamicin is the most effective agent for the treatment of endometritis [31].

Gentamicin is traditionally administered in small doses every 8 h. A high dose of gentamicin given every 24 h is recently recommended. It has the advantages of possible concentration-dependent killing, post-antibiotic effect, and decreased nephrotoxicity. Several studies have been conducted on adults and children with various conditions.

Once-daily high-dose administration gives optimal fetal serum peak level that is closer to optimal neonatal values with shorter time below the toxicity threshold, suggesting a decreased risk of fetal nephrotoxicity and ototoxicity, compared with the conventional three times daily administration (Locksmith). However, there is no evidence that showed a significant difference in maternal or neonatal outcomes [32, 33].

A randomized double-blind trial comparing piperacillin to cefoxitin showed a similar effect on postpartum endometritis. This study did not evaluate the neonatal outcome [34].

Although Ureaplasma species are the most common organism in women with intrauterine infection, it is not well-known whether the maternal administration of antibiotic should cover them. The addition of macrolide or clindamycin is reasonable if genital mycoplasma is identified.

13.4.3 Duration of Antibiotic Treatment

Some studies have evaluated the optimal duration of antibiotic treatment from the standpoint of maternal postpartum outcome. Single-dose cefotetan was associated with a shorter hospital stay, with a similar incidence of failed treatment, compared with multiple-dose cefotetan in a randomized controlled trial [35]. A randomized controlled study has shown that single additional postpartum antibiotic treatment had the same effect on treatment failure, compared with those with no additional treatment. The authors concluded that if intrapartum antibiotic treatment is promptly initiated, additional postpartum treatment is unnecessary [36]. Further oral antibiotic is also not beneficial [37.]

13.4.4 Antibiotic Treatment for Confirmed Intra-Amniotic Infection

Whether antepartum antibiotic treatment in women with preterm labor or pPROM can eradicate the microorganism is not well-understood. Obtaining the amniotic fluid by transabdominal amniocentesis in pregnant women with suspected intrauterine infection for the identification of microorganisms can determine antibiotic susceptibility and the efficacy of an antibiotic treatment.

One study has shown that the antibiotic treatment for pregnant women with pPROM and confirmed intra-amniotic infection failed to eradicate the microorganisms. Among the seven pregnant women with a positive amniotic fluid culture at admission, six of them still had a positive amniotic fluid culture after 10–14 days of antibiotic treatment. Moreover, intra-amniotic inflammation developed in one-third

of women without intra-amniotic infection and inflammation at admission despite antibiotic treatment [37]. A recent study has shown that among 50 pregnant women with preterm labor and intact membranes who had a confirmed intra-amniotic infection/inflammation, only 16 of them (32%) had a successful eradication of microorganisms (15/50) or delivery after 37 weeks of gestation (1/50). Interestingly, 29 of 50 women (58%) were still pregnant for more than 7 days. The median amniocentesis-to-delivery interval was significantly longer among women who received a combination of antibiotics than those who did not receive such treatment (11 days vs 3 days) [38]. Expectant management with antibiotic administration under strict observation of the fetal well-being may be an option to prolong the pregnancy duration.

Identification of microorganisms by amniotic fluid culture obtained through transabdominal amniocentesis may be necessary for choosing the appropriate antibiotic which may prolong the pregnancy [39]. However, its effect on the neonatal outcome is not established. Careful fetal monitoring is required for the prolongation of pregnancy with antibiotic treatment. Clinicians should consider the risk of prematurity and severity of fetal infection/inflammation.

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