

Review Article

Antimicrobials for Preterm Birth Prevention: An Overview

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Objective. Preterm birth (PTB) remains a major cause of neonatal morbidity and mortality. The association between PTB and infection is clear. The purpose of this report is to present a focused review of information on the use of antibiotics to prevent PTB. *Methods.* We performed a search of the PubMed database restricted to clinical trials or meta-analyses published in English from 1990 through May 2011 using keywords “antibiotics or antimicrobials” and “preterm.” *Results.* The search yielded 67 abstracts for review. We selected 31 clinical trials ($n = 26$) or meta-analysis ($n = 5$) for further full-text review. Discussion of each eligible clinical trial, its specific inclusion criteria, antibiotic regimen used, and study results are presented. Overall, trials evaluating antibiotic treatment to prevent preterm birth have yielded mixed results regarding any benefit. *Conclusion.* Routine antibiotic prophylaxis is not recommended for prevention of preterm birth.

1. Introduction

Preterm birth (PTB) continues to be a leading cause of neonatal morbidity and mortality. Defined as birth prior to 37 weeks of gestation, PTB accounts for over 35% of health care spending for infants and 10% of health care spending for children in the United States [1]. The incidence of PTB has been estimated to be 12-13% in the United States—or approximately 467,000 annual live births—significantly higher compared to European and other developed countries with incidence at 5–9% [2–4]. In fact, from 1996 to 2006, there was a steady increase in PTBs in the US to a peak at 12.8%—with the first decline in 2007 with a PTB rate of 12.7% [5, 6]. Moreover, despite advances in management of preterm labor and care of preterm infants, PTB still constitutes 75% of neonatal mortality and 50% of long-term neurologic impairment in children [7]. Spontaneous PTB (SPTB) accounts for the large majority (65–85%) of PTB and is strongly associated with infection [8]. As a result, considerable effort has been dedicated to evaluate antimicrobial therapy as an intervention to prevent PTB. The purpose of this

report is to review the role of infection in the epidemiology of PTB specifically focusing on the use antibiotics to prevent PTB.

2. Methods

We implemented a descriptive and analytic literature review of antimicrobial therapy to prevent PTB; our objective was not to conduct a synthetic meta-analysis (with summary estimates). Rather, it was to identify relevant contemporary articles on infection and antimicrobial therapy for PTB prevention. We searched the PubMed database restricted to clinical trials or meta-analyses published in English since 1990. Keywords for this search included “antibiotics or antimicrobials” and “preterm” yielding 67 abstracts for review by 2 authors. Of these 67 abstracts, only 31 eligible clinical trials ($n = 26$) or meta-analysis ($n = 5$) evaluated the use of antimicrobials to prevent PTB, and this was retrieved for further full-text review. For each eligible study we present its specific inclusion criteria, the antibiotic regimen used, and the study results.

3. Background

3.1. Epidemiologic Overview, Subtypes, and Mechanisms of Preterm Birth. Part of the difficulty in preventing PTB is its multifactorial etiology. The relative frequencies of the 3 major subcategories of preterm birth are the following: spontaneous preterm labor (50%), delivery for maternal or fetal indications (30%), and preterm premature rupture of membranes or PPRM (20%) [8, 9]. Compared with other ethnicities, black women are at disproportionately increased risk for PTB; risks are generally lower among Hispanic women [8]. Black women have double the rates of PTB as white women and women with a previous preterm delivery have a 15–50% recurrence risk [8]. Increasing prevalence of assisted reproductive technology and multiple gestations [10], as well as maternal and fetal indications including hypertension, diabetes, and intrauterine growth restriction contribute to rates of PTB [11].

Late preterm births (defined as birth between 34 and 36 weeks) contribute over 70% of PTB [6]. While these births carry less risk of neonatal morbidity and mortality than earlier births, they still carry a greater risk of neonatal impairment compared to term births.

Overall, key risk factors for preterm birth include age, race, nutritional status, a history of a previous PTB, multiple gestation, smoking, altered vaginal bacterial flora, and presence of infection [12]. Obesity itself is associated with hypertension and preeclampsia leading to indicated preterm birth but has been noted to be protective of spontaneous preterm birth [12].

How these risk factors contribute to the pathogenesis of spontaneous preterm labor and preterm premature rupture of membranes (PPROM) is largely unknown. Proposed mechanisms of term labor include progesterone withdrawal, oxytocin initiation, decidual activation, and activation of the fetal immune response [8]. The first two pathways have not been clearly elicited in humans, but inflammation-mediated decidual activation seems plausible. In this theory, infection, inflammation, or hemorrhage stimulates the innate immune system; chemokines and cytokines induce prostaglandins and other matrix degrading enzymes causing uterine contractility and degradation of extracellular matrix leading to labor and rupture of membranes [12, 13]. Activation of the fetal immune response could have a similar impact [12]. While this could similarly be implicated in preterm labor and PROM, other mechanisms include infection, inflammation, uteroplacental ischemia of hemorrhage, uterine overdistension, or psychosocial stress [12].

3.2. Infection and Preterm Birth. Intrauterine infection is estimated based on studies of amniotic fluid and cultures to be associated with approximately 25–40% of PTB—the association stronger, the earlier the gestation at birth [12]. The different types of infection involving the maternal fetal interface include deciduitis, chorioamnionitis, villitis, and funisitis [12]. Although infection is noted to be extremely common in preterm delivery, it is often chronic, subclinical, and asymptomatic (apart from labor). In one study of 602 women delivered by cesarean section prior to membrane rupture,

121 (20.1%) had positive membrane culture; 50% of these women also had positive amniotic fluid culture—often with the same organism [12]. In another study of the placentas of 446 mother-infant pairs, women with a SPTB were significantly more likely to have acute inflammation of the membranes, chorionic plate, and the umbilical cord than women with indicated preterm births [13].

The pathogenesis of SPTB in the setting of subclinical infection is not fully elucidated—the current understanding is presented in Figure 1 [12]. Bacterial invasion of maternal and fetal tissues causes release of endo and exotoxins. These substances activate both a maternal response stimulating the release of cytokines such as tumor necrosis factor alpha (TNF-alpha), interleukin-1alpha, interleukin-1 β , interleukin-6, interleukin-8, granulocyte colony-stimulating factor (G-CSF), and other factors [12, 14–18]. These active substances stimulate the production and release of prostaglandins—causing uterine contractility—and neutrophil activity and thereby synthesis and release of metalloproteinases—causing rupture of membranes and remodeling of collagen in the cervix [19–21]. A fetal response also may occur, in which infection stimulates the production of corticotropin-releasing hormone (from the fetal hypothalamus and placenta) causing an increase in fetal corticotropin and thereby fetal cortisol also stimulating prostaglandins [22].

Multiple inflammatory markers have been noted to be elevated in amniotic fluid, the serum, or vaginal and cervical secretions. These include amniotic fluid interleukin-6 concentration interleukin-1, interleukin-8, G-CSF, and TNF-alpha, ferritin, and fetal fibronectin; however, none of these markers have been found useful in predicting preterm delivery in routine clinical practice [12, 23].

Given the strong association between SPTB and infection, prophylactic antibiotics seem a logical preventative strategy for PTB. This review focuses on the specific infections associated with PTB and the effectiveness and safety of antibiotic prophylaxis.

3.3. Organisms and Mechanisms of Infection. In order to evaluate the effectiveness of specific antibiotics used to prevent PTB, it is important to consider the microbes implicated in associated intrauterine infections. Organisms most commonly gain access to the uterus and pregnancy by ascending from the vagina and cervix [12]. Less frequent pathways include iatrogenic inoculation during amniocentesis or chorionic villus sampling, hematogenous spread through uterine and placental blood flow or through descending infection from the abdominal cavity and fallopian tubes to the chorioamnion. Ascending infection extends to the choriodecidual space and may ultimately invade the membranes, amniotic fluid, and fetus [12]. The exact timing of infection in relation to pregnancy is not fully elucidated but has been hypothesized to occur early in gestation or even in the preconceptual period [24].

The most commonly isolated organisms include microbes with low virulence: *Ureaplasma urealyticum*, *Mycoplasma hominis*, *Gardnerella vaginalis*, *peptostreptococcus*, and *bacteroides* species—all organisms of vaginal flora [25–28]. *Ureaplasma* and *Mycoplasma* species are the most

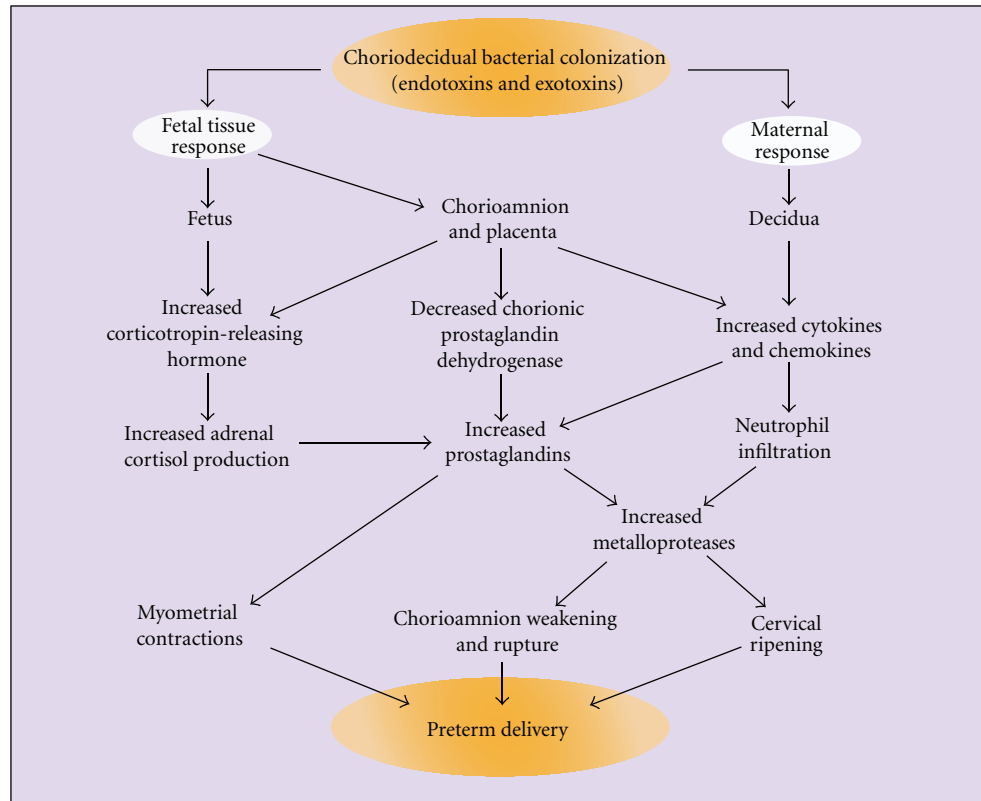


FIGURE 1: Potential Pathways from choriodecidual bacterial colonization to preterm delivery [12].

common microbes cultured from placental tissue and fluids obtained from patients with histologic and clinical chorioamnionitis. In a study of umbilical cord blood in preterm 23–32-week births, Goldenberg et al. showed that *Ureaplasma urealyticum* and/or *Mycoplasma hominis* were present in 23% of cultures—especially in women undergoing spontaneous compared to indicated preterm delivery (34.7% versus 3.2%, $P < 0.001$) [29].

Bacterial vaginosis (BV) is also commonly associated with PTB. Due to an interruption in normal vaginal flora, it is characterized by a reduction in lactobacillus and an overgrowth of other anaerobic bacteria such as *gardenerella*, *bacteroides*, and *mobiluncus*. Its diagnosis is based on either Amsel's criteria (taking into account vaginal pH, presence of discharge, amine odor, or presence of clue cells) or Nugent's score (a gram stain scoring system). Bacterial vaginosis is present in 15–42% of pregnant women and confers a 2 to 4-fold independent increase in the risk of spontaneous preterm birth and PROM [30–33]. In a meta-analysis including 18 studies, Leitich et al. shows that the associated risk is greater when BV is diagnosed at earlier gestation [33]. The alterations in vaginal flora by bacterial vaginosis may also increase susceptibility to other ascending genital tract infections.

Sexually transmitted infections including *Trichomonas vaginalis*, *Neisseria gonorrhoeae*, *Chlamydia trachomatis* and syphilis have also been associated with preterm delivery and intrauterine infection [34–36]. Numerous small studies have shown adverse outcomes associated with trichomoniasis

including PTB, PROM, and low birth weight [34]. In the largest study of trichomoniasis during pregnancy, Cotch et al. studied over 12,000 women and noted a modest 1.3 odds ratio of preterm delivery (95% CI 1.1–1.4) [34]. Other genitourinary microbes such as *Group B streptococcus* and *Escherichia coli* have also been described in intrauterine infection and consequent preterm delivery [12].

Nongynecologic infections have also been studied in PTB including pneumonia, pyelonephritis, periodontitis, and gastrointestinal infections [37, 38]. The mechanism of action of these infections is thought to be an acute inflammatory response, but for periodontal disease it is hypothesized to be transient bacteremia and hematogenous spread to the placenta, chorioamnion, and fetus [8]. Viral infections such as varicella and influenza have been associated with PTB; however, the role of viral infection in PTB but has been inadequately studied [8, 39, 40].

4. Results and Comments

4.1. Antibiotic Therapy to Prevent PTB. Given the abounding data associating various infections with PTB, it is natural to consider the use of antibiotic and other antimicrobial therapy to prevent PTB. Studies have investigated the use of different antimicrobials both as empiric therapy providing broad coverage to prevent or treat infection and as targeted therapy against specific infections. In addition, the timing of

antibiotic therapy in relation to pregnancy varies. Characteristics and findings from individual studies are presented below and summarized in Tables 1 and 2.

4.1.1. Empiric Antibiotic Therapy. Macrolides (commonly erythromycin, azithromycin), beta-lactams, clindamycin, and metronidazole have been used in isolation or in combination as empiric therapy to prevent PTB. Macrolides and other bacteriostatic agents have been advocated since they suppress bacterial virulence as opposed to bactericidal agents such as penicillins, which theoretically may worsen outcomes for preterm infants by releasing bacterial endotoxins [60]. Combination antimicrobials provide empiric coverage against the common microbes including ureaplasmas, gram-negative rods, and anaerobes.

Beta-Lactams. Three randomized controlled studies have focused solely on the penicillin family of antimicrobials and PTB. Newton et al. failed to show any benefit in terms of days gained, neonatal outcome, or gestational age in a double-blind trial of the combination of ampicillin/sulbactam with indomethacin—a nonsteroidal anti-inflammatory tocolytic—in the setting of magnesium tocolysis [41]. Similarly, Cox et al. randomized 78 women in preterm labor with intact membranes at 24 to 34 weeks of gestation to either parenteral ampicillin (2 grams) + sulbactam (1 gram) for 2 days followed by oral amoxicillin-clavulanic acid (250 mg) for 5 days ($n = 39$), or to similar placebo ($n = 39$). Steroids or tocolysis were not administered. There was no difference in the mean gestational age at delivery (34.2 ± 0.7 versus 34.1 ± 0.9 , not significant); other perinatal outcomes were similar [42]. Finally, Gordon described similar findings among 117 women in preterm labor randomized to receive 2 grams of parenteral ceftizoxime or placebo for 5 days [43]. The primary outcome of interest, mean interval to delivery, was not significantly different between the two groups (34.5 ± 21.1 days versus 34.6 ± 24.5 days, $P = 0.99$). In these three studies, regardless of the use of tocolysis or steroid administration, no significant benefit was associated with the use of penicillins.

Clindamycin. While studies of beta-lactams have not been promising, a small-randomized trial by McGregor et al. showed some benefit of clindamycin. Women on tocolysis for preterm labor at gestational age less than 34 weeks were randomized to receive either placebo versus parenteral followed by oral clindamycin for 7 days. Patients treated with clindamycin at gestational ages less than 32 weeks were more likely to have increased duration of pregnancies (35 versus 25 days, $P = 0.02$). Moreover, in a subgroup analysis, those women diagnosed with bacterial vaginosis and then treated with clindamycin were more likely to have longer pregnancy latency, increased birth weights, and increased gestational age at delivery [44]. Lamont et al. described up to a 60% reduction of PTB with the use of 2% clindamycin cream in patients with abnormal genetic flora (4% versus 10%; $P < 0.03$) [45]. However, other studies of vaginal clindamycin specifically for bacterial vaginosis—discussed below—have been contradictory [46]. Some studies have even suggested

increased risk of bacterial resistance and neonatal morbidity [61, 62]. Given the disparity of findings, the role of clindamycin in PTB prevention remains inconclusive.

Azithromycin. Few studies have been performed solely on macrolides. In the large 2200 patient APLe study conducted in Southern Malawi, van den Broek et al. conducted a placebo-controlled trial of oral azithromycin (1 gram) given at 16–24 and again at 28–32-weeks, gestation to unselected women. Findings showed no significant differences in outcomes between the two groups regarding PTB (16.8% versus 17.4%, odds ratio 0.96 (0.76–1.21)) or other perinatal outcomes including perinatal mortality. Further inclusion of this study in a meta-analysis with seven other studies also failed to show any salutary effect on PTB [47].

Combination Antibiotic Regimens. It seems that, regardless of the antibiotic of choice, gestational age at administration, route of administration, days of therapy, or repeat dosages of antibiotics, no single agent has been noted to be efficacious in the prevention of PTB. Thus, trials involving empiric combination antibiotic regimens are more prevalent in the obstetric literature.

Beta-lactams Plus Metronidazole. Norman et al. randomized 81 women in preterm labor to receive parenteral ampicillin or oral amoxicillin and metronidazole for 5 days ($n = 43$) versus no antibiotic treatment ($n = 38$). All women were treated with indomethacin and hexoprenaline for tocolysis and betamethasone for fetal lung maturity. Women receiving antibiotics had significantly prolonged pregnancies (median 15 versus 2.5 days, $P = 0.04$). In addition, patients in the control group had significantly increased risks of necrotizing enterocolitis (5 versus 0, $P = 0.02$) [48].

Similar benefit of ampicillin plus metronidazole was noted by Svare et al. in a randomized study of 112 women in preterm labor with intact membranes between 26- and 34-weeks gestation. Women receiving parenteral ampicillin for 24-hour followed by penicillin agent pivampicin 500 milligrams orally for 7 days) and metronidazole for 7 days were compared to controls receiving placebo. Those receiving antibiotics had prolonged pregnancy (47.5 days versus 27 days, $P < 0.05$), higher mean gestational age at delivery (37 versus 34 weeks, $P < 0.05$), decreased incidence of preterm birth <37 weeks (42% versus 65%, $P < 0.05$), and lower rates of admission to neonatal intensive care unit (40% versus 63%, $P < 0.05$) [49]. Although both studies noted some benefit with the beta-lactam plus metronidazole antibiotic regimens, no larger studies have been performed. Moreover, improved outcomes could have been secondary to tocolysis and/or antenatal steroid therapy.

Beta-Lactams and Macrolides. Trials of beta-lactams combined with macrolides have yielded mixed results. In a blinded study by Newton et al., 103 women between 24–35 weeks' gestation in preterm labor undergoing tocolysis were randomized to receive either parenteral ampicillin and oral erythromycin for 7 days or placebo. No statistical differences

TABLE 1: Summary of studies of empiric use of antibiotics for PTB prevention.

Study	N	Antibiotic regimen	Gestational age at treatment(wks)	Days treatment	Primary outcomes	Benefit
<i>Beta lactams</i>						
Newton et al. (1991) [41]	91	IV ampicillin/sulbactam + PO indomethacin	Less than 36	3	(1) Gestational age at delivery (2) Number of term deliveries (3) Days gained	No
Cox et al. (1995) [42]	78	IV ampicillin/sulbactam + PO amoxicillin-clavulanate	24–34	7	Mean gestational age at delivery	No
Gordon et al. (1995) [43]	117	IV ceftizoxime	24–35	5	Prolongation of gestation	No
<i>Clindamycin</i>						
McGregor et al. (1991) [44]	117	IV and PO clindamycin	Less than 34	7	Interval to delivery	Yes (35 versus 25 days latency, $P = 0.02$)
Lamont et al. (2003) [45]	409	2% clindamycin cream (vaginal)	13–20	3	Incidence of preterm birth	Yes (4% versus 10% rate of PTB $P < 0.03$)
Kekki et al. (2001) [46]	5432	2% clindamycin cream (vaginal)	10–17	7	(1) Rates of preterm delivery (2) Peripartum infection	No
<i>Azithromycin</i>						
Van de Broek et al. (2009) [47]	2297	PO azithromycin	16–24 and 28–32	2 doses	Incidence of preterm birth	No

TABLE 1: Continued.

Study	N	Antibiotic regimen	Gestational age at treatment(wks)	Days treatment	Primary outcomes	Benefit
<i>Combination regimens</i>						
Norman et al. (1994) [48]	81	IV ampicillin/PO amoxicillin + PO metronidazole	26–34	5	(1) Days gained (2) Perinatal mortality (3) Perinatal morbidity	Yes (15 versus 2.5 days latency, $P = 0.04$)
Svare et al. (1997) [49]	112	IV ampicillin/PO pivampicin + PO metronidazole	26–34	7	(1) Days to delivery (2) Gestational age (GA) at delivery (3) Rates of preterm delivery (4) Low birth weight (5) Maternal infection (6) Neonatal infection	Yes (1) (47.5 versus 27 days latency, $P < 0.05$) (2) (37 versus 34 weeks GA at delivery, $P < 0.05$) (3) (42% versus 65% preterm birth rate, $P < 0.05$)
Newton et al. (1989) [50]	103	IV Ampicillin/PO erythromycin	24–35	7	(1) Rate of preterm birth (2) Time to delivery (3) Birthweight (4) Episodes of recurrent preterm Labor	No
Romero et al. (1993) [51]	277	IV Ampicillin/erythromycin + PO amoxicillin/erythromycin	24–34	7	(1) Time to delivery (2) Frequency of preterm delivery (3) Frequency of PROM (4) Maternal outcomes (5) Episodes of recurrent preterm labor	No
Oracle II (2001) [52]	6295	PO erythromycin or PO amoxicillin-clavulanate or both	Less than 37	10	Composite neonatal morbidity or mortality	No

TABLE 2: Studies of specific use of antibiotics for preterm birth prevention.

Study	N	Antibiotic regimen	Gestational age at treatment (wks)	Days treatment	Primary outcomes	Benefit
Hauth et al. (1995) [53]	624	PO metronidazole + PO erythromycin	22–24	7/14	Gestational age at delivery Rate of preterm delivery	Yes (26% versus 36% rate of preterm delivery, $P = 0.01$)
McDonald et al. (1997) [54]	897	PO metronidazole	24–29	2 doses	Reduction in Spontaneous birth less than 37 weeks	Yes (9.1% versus 41.7% reduction, OR 0.14, CI 0.01–0.84)
Carey et al. (2000) [67]	1953	PO metronidazole	16–24 24–30	2 doses	Rate of delivery before 37 weeks	No
Ugumadu et al. (2003) [56]	6210	PO clindamycin	12–22	5	Spontaneous preterm delivery and late miscarriage	Yes (10.4% reduction in miscarriages and PTD, $P = 0.0003$)
<i>Trichomonas vaginalis</i>						
Klebanoff et al. (2001) [55]	617	PO metronidazole	16–23 24–29	2 doses	Rate of delivery before 37 weeks	No
Kigozi et al. (2003) [57]	206	PO azithromycin, cefixime, metronidazole	Any gestation	1 dose	(1) Birth weight (2) Rate of preterm birth (3) 2-year mortality rate	No
<i>Other relevant studies</i>						
Interconception Andrews et al. (2006) [69]	124	PO azithromycin + PO metronidazole	4 months after delivery	2 doses/7 days every 4 months until next pregnancy	Subsequent rate of preterm birth or miscarriage	No
Fetal Fibronectin + Andrews et al. (2003) [58]	703	PO metronidazole + PO erythromycin	21–25.6	10	Spontaneous delivery less than 37 weeks	No
Fetal Fibronectin + Shennan et al. (2006) [59]	109	PO metronidazole	24–27	7	Spontaneous preterm delivery less than 30 weeks	No

were noted between groups in terms of time to delivery, frequency of preterm birth, or birth weight [50].

Similarly no differences were noted by Romero et al. in a multicenter, randomized trial from the Maternal Fetal Medicine Units Network [51]. In this study of 277 women at six centers, 133 received intravenous ampicillin and erythromycin for 48 hours followed by oral amoxicillin and erythromycin for 5 days; the control group received placebo. No statistically significant differences were noted in time to delivery, frequency of preterm delivery <37 weeks, frequency of premature rupture of membranes, or neonatal outcomes including Neonatal Intensive Care Unit (NICU) admission, respiratory distress, and sepsis. Further trials by Watts et al. and Oyarzún et al. have also failed to demonstrate benefit to penicillins combined with macrolides [63, 64]. Furthermore, in the Oracle II trial with over 6000 women in preterm labor, erythromycin, amoxicillin-clavulanic acid as compared with placebo was not associated with any maternal or fetal benefit [52]. Results of the longterm followup on women in the Oracle II trial suggest an increase in cerebral palsy—indicating that routine beta-lactam and macrolide antibiotics solely for PTB prevention may be ill-advised.

Macrolides and Metronidazole. One large-scale study has directly evaluated metronidazole with macrolides. Hauth et al. in a double blind, randomized controlled study evaluated the efficacy of treating patients with bacterial vaginosis in the 2nd trimester of pregnancy (22–24 weeks). 624 women with a history of a prior spontaneous preterm birth were allocated in a 2:1 ratio in an antibiotic group ($n = 433$) or placebo (191). The antibiotic regimen consisted of metronidazole 250 milligrams three times a day for 7 days and erythromycin 333 milligrams three times a day for 14 days. Patient receiving antibiotics had a lower rate of preterm delivery (26% versus 36%, $P = 0.01$). Among the women with bacterial vaginosis included in the Hauth trial, antibiotics significantly reduced the incidence of PTB (31% versus 49%, $P = 0.006$) leading to the conclusion that antibiotic therapy may reduce preterm delivery in patients at risk for premature delivery with bacterial vaginosis [53]. These patients, however, were treated earlier in pregnancy than any of the earlier discussed trials and were all known to have documented infection with bacterial vaginosis.

Meta-Analyses. In a Cochrane Review, King et al. included 11 studies (the largest of which was the Oracle II trial) and a total of 7428 women. There was a reduction in maternal infection (relative risk 0.74, 95% CI 0.64–0.87), but no statistically significant differences in mean gestational age at delivery, frequency of preterm birth, and neonatal outcomes including mortality. In addition, no differences were noted in a subgroup analysis between the types of antibiotics [65]. Furthermore, no subgroup analysis was presented for patients receiving metronidazole in the first half of pregnancy.

Similarly, a more recent meta-analysis performed by Simcox et al. in 2007 identified 17 randomized controlled trials comparing antibiotics to placebo in asymptomatic nonlaboring women with a risk of PTB (previous PTB, positive fetal

fibronectin, or abnormal vaginal flora). No significant association was noted in the reduction of PTB, the antimicrobial administered, or gestational age at treatment [66]. In summary, while small-scale studies have shown some benefit to antibiotic prophylaxis—especially in the case of beta-lactams and metronidazole—no advantages, efficacy, or prevention of PTB has been consistently presented to support routine antibiotic therapy. The question then arises if there is any efficacy to treating specific infections with targeted therapy.

4.1.2. Specific Antibiotic Therapy

Bacterial Vaginosis. Several studies have specifically evaluated the role of antibiotics prophylaxis for preterm delivery in the setting of bacterial vaginosis. Hauth et al. in a double blind, randomized controlled study described above concluded that antibiotic therapy may reduce preterm delivery in patients at risk for premature delivery with bacterial vaginosis [53].

McDonald et al. revisited the possibility of a reduction in the risk of SPTB with metronidazole treatment of women with heavy growth of *Gardnerella* during mid-pregnancy. Patients identified with heavy growth of *Gardnerella* or a gram stain indicative of bacterial vaginosis were randomized to receive oral metronidazole 400 milligrams or placebo twice daily for two days at 24-week gestation and then again at 29 weeks [54]. No differences were noted in overall PTB or SPTB; however, in a subgroup analysis of women with a previous PTB, a significant reduction in SPTB (9.1% versus 41.7%, OR 0.14 CI 0.01–0.84) was noted [54].

Given these positive results, a larger Maternal Fetal Medicine Units Network trial ($n = 1953$) was performed using metronidazole to prevent PTB by treating asymptomatic bacterial vaginosis between 16 and 24 weeks of gestation [67]. Asymptomatic bacterial vaginosis (absence of itching, odor or discharge) was diagnosed by Nugent's criteria and treated with two doses of metronidazole (2 grams) or placebo. There were no differences in the rates of preterm delivery (12.2% versus 12.5%, relative risk 1.0, 95% CI 0.8–1.2), spontaneous rupture of membranes (4.2% versus 3.7%), delivery before 32 weeks (2.3% versus 2.7%), or neonatal outcomes [67]. A meta-analysis of 15 trials with over 5800 women with bacterial vaginosis that examined the effect of metronidazole to treat bacterial vaginosis on preterm birth <37 weeks showed no risk reduction (odds ratio 0.91, 95% CI: 0.78–1.06) [68]. In this meta-analysis, however, there were no results presented regarding comparison between patients with symptomatic versus asymptomatic infection.

Trials have also yielded mixed results regarding intravaginal clindamycin for bacterial vaginosis. While Lamont showed some benefit regarding PTB in patients with abnormal vaginal flora, in a study of over 5000 women by Kekki et al., vaginal clindamycin did not decrease the rate of preterm deliveries (OR 1.3, 95% CI 0.5,3.5) [45, 46]. Trials have similarly yielded mixed results on the role of oral clindamycin for antibiotic prophylaxis in the setting of bacterial vaginosis. Ugwumadu et al. studied patients at high risk for late miscarriage or SPTB-randomized women between 12

and 22 weeks of gestation with bacterial vaginosis receiving oral clindamycin 300 mg twice daily for five days or placebo. Women receiving clindamycin had significantly fewer late miscarriages or preterm deliveries (10.4% percentage difference, $P < 0.001$) [56]. No subgroup analysis of solely preterm birth was reported.

It is evident that there is no convincing data to support the routine use of metronidazole or clindamycin in the 2nd trimester of pregnancy in patients with bacterial vaginosis. While few small studies have shown some possible efficacy, larger trials have refuted any benefit. In fact, other trials have even noted deleterious effects of clindamycin on neonatal morbidity—especially noted to be infectious morbidity [61, 62].

Trichomonas Vaginalis. No benefit for PTB prevention has been shown for treatment of asymptomatic or symptomatic trichomoniasis. Klebanoff et al. randomly assigned 617 patients with asymptomatic trichomoniasis (defined as trichomonas on culture of vaginal secretions) to metronidazole (two doses of 2 grams 48 hours apart) versus placebo between 16 to 23 weeks of gestation and then again at 24–29-week gestation. Delivery prior to 37 weeks occurred in 19% of women treated with antibiotics and 10.7% of patients receiving placebo (relative risk 1.8, 95% CI: 1.2–2.7, $P = 0.004$) [55]. Thus, not only did they observe no benefit for treatment of asymptomatic trichomoniasis, intervention was found to be harmful.

Kigozi et al. similarly noted no benefit to treatment of trichomonas during pregnancy. In their randomized controlled trial women presumptively diagnosed with trichomonas were randomized to receive oral 1 gram azithromycin, 400 milligrams cefixime, and 2 grams metronidazole. Increased rates of low birth weight, preterm birth, and 2-year mortality were noted in patients treated for infection [57]. Again, intervention was noted to be harmful. However, it should be emphasized that these patients were treated at any gestational age at pregnancy and were not a high-risk population for PTB.

Timing of Antibiotic Administration. In addition to type and specificity of antibiotic regimens, the timing of antibiotic administration is an important consideration. Uterine infection may occur prior to conception, early in pregnancy or at later gestational age. Therefore, it has been postulated that the lack of benefit in some trials, may in part be due to late treatment when the mechanisms leading to PTB may already be established. Based on this hypothesis, Andrews et al. performed an interconceptional antibiotic randomized trial. Women with a SPTB prior to 34 weeks were randomized four months postpartum to receive oral azithromycin 1 gram twice (4 days apart) plus metronidazole 750 milligrams daily for 7 days ($n = 59$) or placebo ($n = 65$). The regimen was repeated every 4 months until next pregnancy. No statistical differences were observed between subsequent SPTB at less than 37, 35, or 32 weeks. Interestingly, patients in the antibiotic group were noted to have decreased mean birth weight and earlier mean delivery gestational age, albeit

not statistically significant [69]. Therefore, additional well-tailored trials are needed to further clarify this issue.

Antibiotics for Other Indications Associated with PTB. PTB may occur not only as a result of intrauterine subclinical infection, but also from systemic infection and PROM. In a Cochrane review of PROM, Kenyon analyzed 6800 subjects in 22 randomized controlled clinical trials. Antibiotics were associated with decreased rates of chorioamnionitis, delivery within 48 hours, and delivery within 7 days. Neonatal short-term outcomes were also improved [70]. A similar benefit was noted with the utilization of antibiotics for asymptomatic bacteriuria in a 14 study meta-analysis conducted by Smail et al. While there was no clear reduction in preterm delivery, asymptomatic bacteriuria, pyelonephritis, and low birthweight were reduced [71]. As a result of this evidence supporting antibiotic treatment for these two conditions—as least for short-term outcomes—antibiotic prophylaxis and treatment is now routinely employed.

In addition, positive fetal fibronectin (FFN) is strongly associated with both infection and PTB. FFN leaks into the genital tract with disruption of the maternal-fetal interface through mechanisms such as infection, inflammation, and hemorrhage. Therefore randomized trials have evaluated the potential benefit of antibiotic therapy among those with a positive fetal fibronectin test. Andrews et al. randomized women to metronidazole or placebo. No differences were noted in SPTB <37 weeks (OR 1.17, 95% CI: 0.8–1.70) or at earlier gestational age cutoffs [58].

In another trial by Shennan et al., asymptomatic women with positive fetal fibronectin were randomized to a one-week course of metronidazole or placebo. Previous studies regarding metronidazole showed mixed results with regard to benefit in terms of preterm labor especially in patients with bacterial vaginosis. However, Shennan chose to study the effect of this antimicrobial in patients between 24–27 weeks of gestational age and with positive vaginal FFN. Patients randomized to metronidazole had an increased risk of preterm delivery less than 30 weeks (21% versus 11%, odds ratio 1.9, 95% CI: 0.72–5.09, $P = 0.18$) as well as prior to 37 weeks (62% versus 39%, odds ratio 1.6, 95% CI: 1.05–2.4, $P = 0.02$). The trial was prematurely stopped. Thus, similar to the findings for BV, treatment may increase the risk of preterm delivery [59].

5. Conclusions

There is no doubt that preterm birth continues to be an obstetrical and neonatal priority in the 21st century—with infection as a major cause. Trials evaluating antibiotic treatment to prevent PTB have yielded mixed results regarding benefit. No identifiable patterns regarding timing of antibiotic administration, gestational age at administration, antibiotic of choice, repeat dosages of antibiotics, the presence of documented underlying infection, or positive fetal fibronectin have emerged to suggest a role for these prophylactic antibiotics at this time. Moreover, a number of studies have suggested harm, and antibiotics should be avoided

for prophylaxis for asymptomatic bacterial vaginosis and trichomoniasis. As such, routine antibiotic prophylaxis is not recommended for prevention of PTB. Based on the review, there may be promise of further studying the timing of antibiotic administration—even before conception—as well as more directed antimicrobial therapy. Studies targeted at timing of antibiotic therapy could be undertaken by treating patients not only during early pregnancy, but between pregnancies or shortly in the postpartum period with specific evaluation of the microbial = human flora interaction. Further studies aimed at elucidating the exact mechanism of decidual activation and the most-implicated microbes may be helpful to delineate specific antimicrobial agents and their optimal mode of delivery (oral versus vaginal versus parenteral). Furthermore, molecular receptor analysis, genetics, and proteomics may be the other steps needed to elucidate the black box that occurs between infection and preterm delivery.

Conflict of Interests

No financial conflict of interests are noted by the authors.

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