Mechanisms of Disease

INTRAUTERINE INFECTION AND PRETERM DELIVERY

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PRETERM delivery is the chief problem in obstetrics today, accounting for 70 percent of perinatal mortality and nearly half of long-term neurologic morbidity.[1,2] Approximately 10 percent of all births are preterm, but most of the serious illness and death is concentrated in the 1 to 2 percent of infants who are born at less than 32 weeks of gestation and who weigh less than 1500 g. Approximately 20 percent of preterm births are the result of a physician's decision to bring about delivery for maternal or fetal indications, and the remainder follow the spontaneous onset of labor or rupture of the membranes.[3] The rate of preterm delivery has not decreased in the past several decades,[4] but the survival rate of infants delivered prematurely has increased, so that 80 percent of infants weighing 500 to 1000 g now survive. The percentage of survivors with handicaps, however, has changed little, so that the absolute number of surviving preterm infants with handicaps has increased.[2,5]

Bacterial infections within the uterus can occur between the maternal tissues and the fetal membranes (i.e., within the choriodecidual space), within the fetal membranes (the amnion and chorion), within the placenta, within the amniotic fluid, or within the umbilical cord or the fetus (Fig. 1). Infection of the fetal membranes, as documented by histologic findings or culture, is called chorioamnionitis; infection of the umbilical cord is called funisitis; and infection of the amniotic fluid is called amnionitis. Although the placental villi may be preferentially involved in blood-borne intrauterine infections such as malaria, bacterial infection within the placenta (villitis) is rare.

That preterm delivery may occur in association with leukocytosis of the amniotic fluid or chorioamnion has long been recognized.[6,7] However, the first substantial microbiologic evidence relating intrauterine infection before membrane rupture to preterm delivery was presented only in the late 1970s, when

bacteria were cultured from the amniotic fluid of 7 of 10 women in preterm labor who had intact membranes.[8] This review explores the evidence developed over the past two decades linking intrauterine infection and preterm delivery.

EPIDEMIOLOGY

Preterm delivery is not evenly distributed among women. The most obvious disparity is that the rate of preterm delivery among black women is twice that of any other racial group of women in the United States, with an even greater discrepancy in the rate of very early preterm delivery.[9] These differences are unexplained. However, more black women have bacterial vaginosis, histologically or clinically diagnosed chorioamnionitis, and postpartum endometritis; genital tract infection may explain much of the excess in preterm delivery among these women.[10-12] Another major risk factor for preterm delivery is a previous spontaneous preterm delivery, especially one that occurred in the second trimester.[13] Some women may have chronic intrauterine infections even between pregnancies, which could cause repeated spontaneous preterm deliveries.[14]

The relation between infection and preterm delivery is not consistent throughout gestation. Infection is rare in late preterm deliveries (at 34 to 36 weeks) but is present in most cases in which birth occurs at less than 30 weeks, as shown by histologic examination of the fetal membranes at delivery,[15-17] studies of amniotic fluid from women in labor with intact membranes,[18] and studies of fetal membranes from women with intact membranes who undergo cesarean section.[19-21]

ORGANISMS

Bacteria may invade the uterus by migration from the abdominal cavity through the fallopian tubes, inadvertent needle contamination at the time of amniocentesis or chorionic-villus sampling, hematogenous spread through the placenta, or passage through the cervix from the vagina.

In women in spontaneous preterm labor with intact membranes, the most commonly identified bacteria are *Ureaplasma urealyticum, Mycoplasma hominis, Gardnerella vaginalis,* peptostreptococci, and bacteroides species — all vaginal organisms of relatively low virulence.[20-25] The organisms often associated with genital tract infection in nonpregnant women, *Neisseria gonorrhoeae* and *Chlamydia trachomatis,* are rarely found in the uterus before membrane rupture, whereas those most often associated with chorioamnionitis and fetal infection after membrane rupture, group B streptococci and *Escherichia coli,* are found only occasionally. Rarely, non–genital tract organisms, such as mouth organisms of the genus capnocytophaga, are found in the uterus in association with preterm labor and chorioamnionitis[26]; these or-
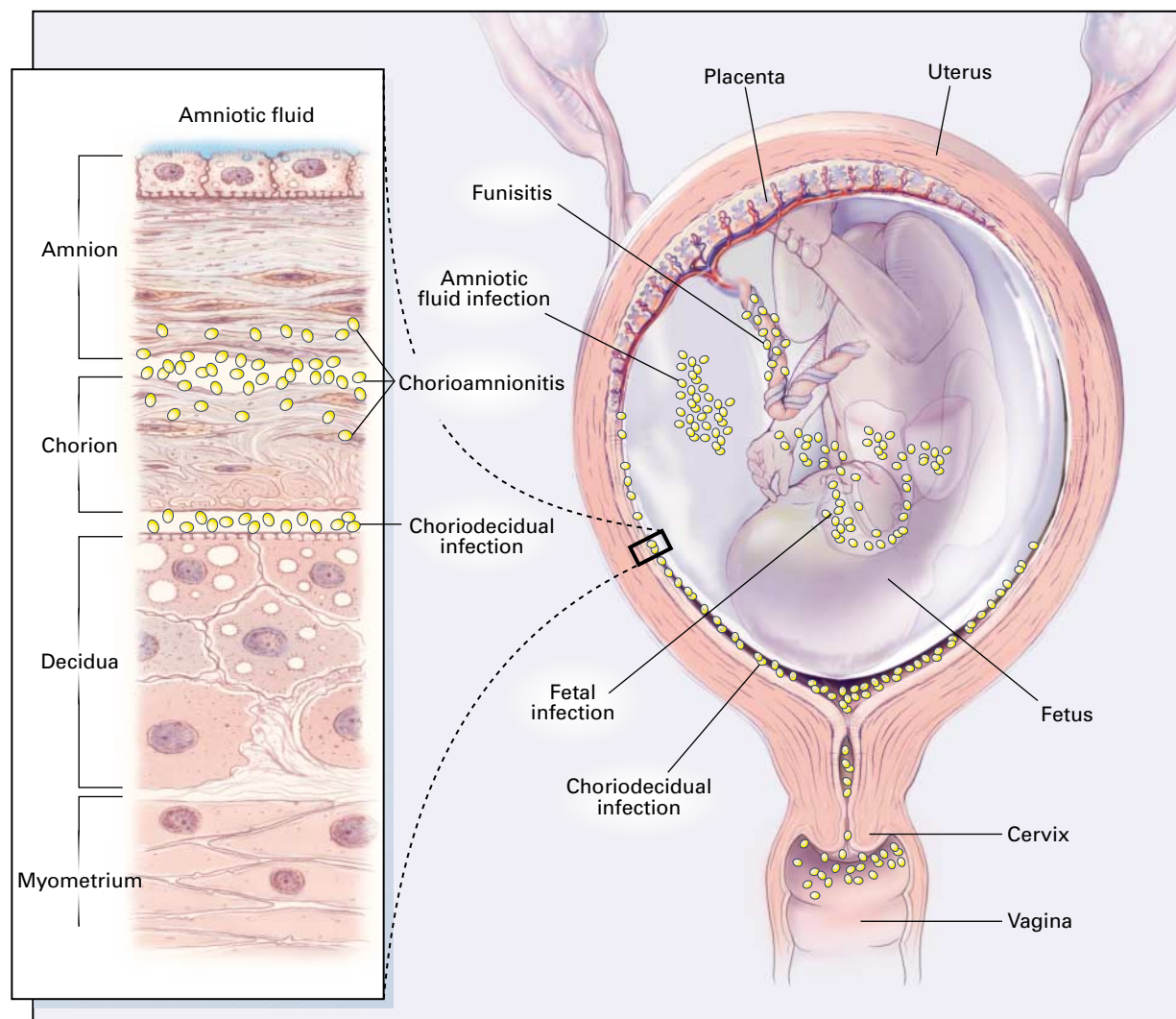
Figure 1. Potential Sites of Bacterial Infection within the Uterus.

ganisms may reach the uterus through the placenta from the circulation or perhaps by oral–genital contact. Nevertheless, most bacteria found in the uterus in association with preterm labor are of vaginal origin. Although it has not been studied extensively, intrauterine viral infection is probably not a common cause of spontaneous preterm delivery.[27]

Vaginal organisms appear to ascend first into the choriodecidual space (Fig. 1); in some women they then cross the intact chorioamniotic membranes into the amniotic fluid, and some of the fetuses ultimately become infected.[28] Evidence of infection by this route comes from a study of 609 women whose fetuses were delivered by cesarean section before membrane rupture (Fig. 2).[19-21,29] Half of the 121 women with positive membrane cultures also had organisms in the amniotic fluid. When cultures from both sites

were positive, the organisms usually were the same. A much smaller portion of the fetuses had positive blood or cerebrospinal fluid cultures at delivery. Women with positive membrane cultures had an active inflammatory response, as indicated by histologic findings of leukocytosis in the membranes and the presence of high concentrations of interleukin-6 in the amniotic fluid.[29] These findings may explain why women with negative amniotic fluid cultures but with high cytokine concentrations in the amniotic fluid are so resistant to tocolytic drugs. Apparently, these women often have an infection in the chorioamnion, a location not amenable to culture before delivery.

TIMING OF INFECTION

Why very early, but not later, preterm deliveries are associated with intrauterine infection has never been
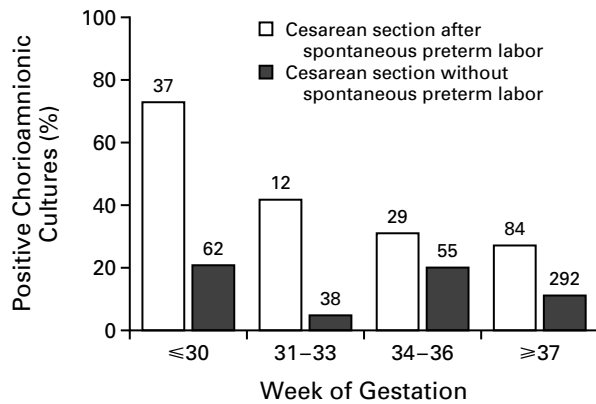
Figure 2. Frequency of Positive Cultures of Chorioamnionic Tissue as a Function of the Length of Gestation among Women Presenting in Spontaneous Labor with Intact Fetal Membranes and Who Deliver Their Infants by Cesarean Section.[19-21,29]

The controls were women with intact membranes who underwent cesarean section before the onset of spontaneous labor. The numbers above the bars are numbers of women.

satisfactorily explained. It is also not clear when the bacteria ascend from the vagina. However, recent evidence suggests that intrauterine infection may occur quite early in pregnancy and remain undetected for months. For example, *U. urealyticum* has been detected in some samples of amniotic fluid obtained for routine chromosomal analysis at 15 to 18 weeks of gestation. Most of these women had delivery at around 24 weeks.[30-32] Furthermore, high concentrations of interleukin-6 in the amniotic fluid at 15 to 20 weeks were associated with spontaneous preterm delivery as late as 32 to 34 weeks.[33,34]

In another example suggesting chronic infection, high fibronectin concentrations in the cervix or vagina at 24 weeks (considered a marker of upper genital tract infection) were associated with the development of chorioamnionitis an average of 7 weeks later.[35] Finally, some nonpregnant women with bacterial vaginosis have intrauterine colonization associated with chronic plasma-cell endometritis.[14,36] It is therefore possible that the intrauterine colonization associated with spontaneous preterm labor is present at conception. It is important to emphasize that most of these chronic upper genital tract infections remain asymptomatic and are not associated with fever, a tender uterus, or peripheral-blood leukocytosis.

If intrauterine organisms are not cleared within four to eight weeks after the expanding membranes seal the endometrial cavity near mid-pregnancy, the infection often becomes symptomatic and results in spontaneous preterm labor or rupture of the membranes. According to this scenario, once the organisms already in the uterus are destroyed by the mother's immune system, few new intrauterine infections occur as long as the membranes remain intact, since organisms no longer ascend from the vagina to the uterus. Although unproved, this hypothesis may explain the frequent association between infection and early preterm delivery and the relative rarity of intrauterine infection as women approach term. An alternative hypothesis to explain this association is related to the timing of the initiation of the fetal immune response. It may be that only with a maturing immune system is the fetus able to generate the cytokine or hormonal response necessary to initiate labor.

BACTERIAL VAGINOSIS

Women who have bacterial vaginosis, defined as a decrease in the normally occurring lactobacillus species and a massive increase in other organisms, including *G. vaginalis,* bacteroides species, mobiluncus species, *U. urealyticum,* and *M. hominis,* have a doubled risk of spontaneous preterm delivery.[37-41] It is unknown whether bacterial vaginosis can actually cause preterm labor and delivery if the organisms do not ascend into the uterus. Bacterial vaginosis is associated with increased concentrations of elastase, mucinase, and sialidase in the vagina and cervix.[42,43] However, since the vast majority of women who have early spontaneous preterm delivery have organisms in the uterus, it may not be necessary to invoke the local action of vaginal infection as the cause of the preterm delivery. It is more likely that bacterial vaginosis is a marker of intrauterine colonization with similar organisms.[25,44,45] If vaginal infection alone (in the absence of ascending infection) or infections such as periodontitis[46] and urinary tract infection[47] actually cause spontaneous preterm delivery, the mechanisms are unknown. One possible explanation is activation of a local inflammatory response by cytokines or endotoxins carried in the blood from the vagina to the uterus.

MECHANISMS OF PRETERM DELIVERY DUE TO INFECTION

Data from animal, in vitro, and human studies all provide a consistent picture of how bacterial infection results in spontaneous preterm delivery (Fig. 3).[28,29,48-58] Bacterial invasion of the choriodecidual space, acting in part through release of endotoxins and exotoxins, activates the decidua and the fetal membranes to produce a number of cytokines, including tumor necrosis factor α, interleukin-1α, interleukin-1β, interleukin-6, interleukin-8, and granulocyte colony-stimulating factor.[28,29,48-58] Furthermore, cytokines, endotoxins, and exotoxins stimulate prostaglandin synthesis and release and also initiate neutrophil chemotaxis, infiltration, and activation, culminating in the synthesis and release of metalloproteases and other bioactive substances. The prostaglandins stimulate uterine contractions while the metalloproteases attack the chorioamniotic membranes, leading to rupture. The metalloproteases also remodel the collagen in the cervix and soften it.[57-59]
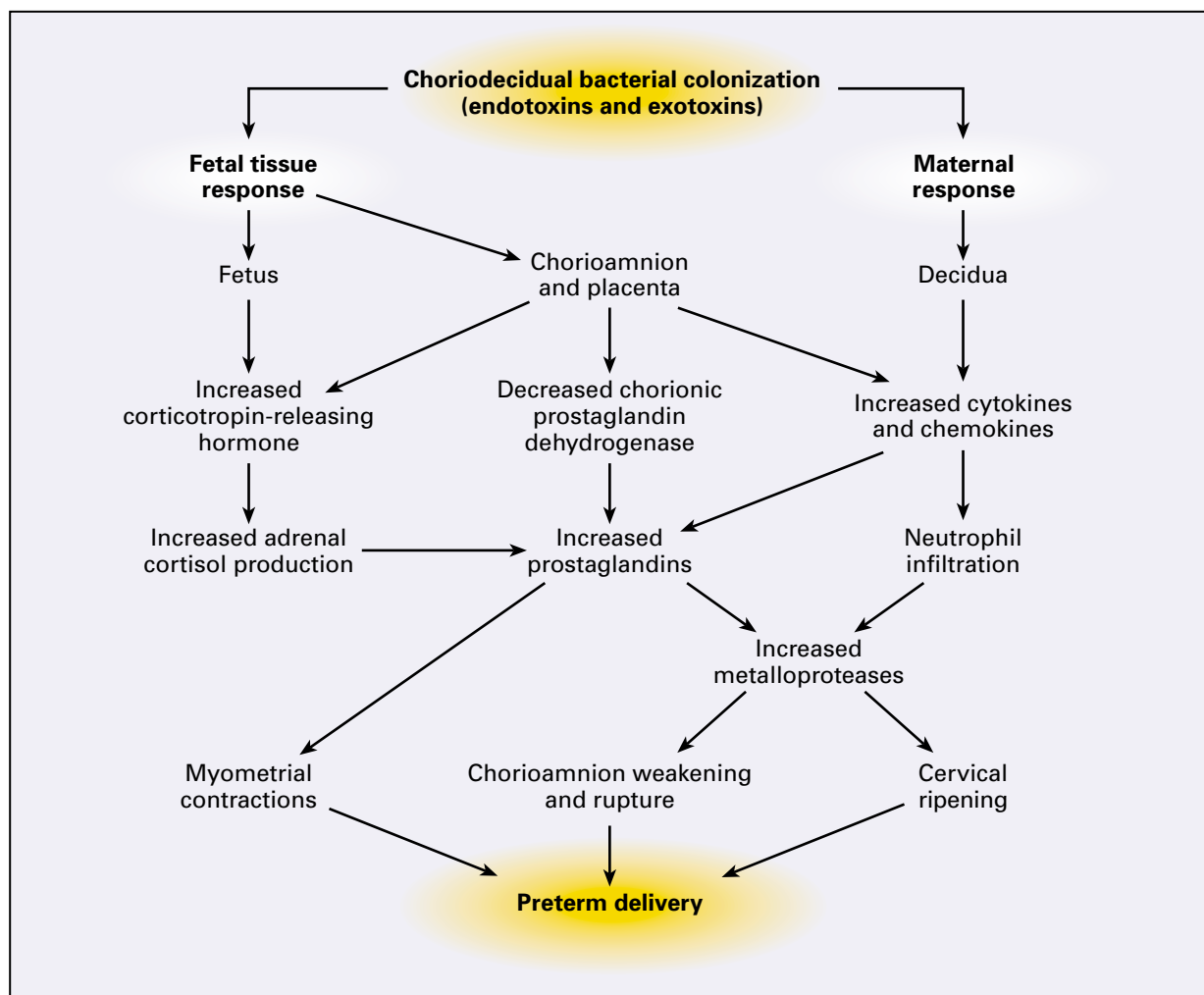
Figure 3. Potential Pathways from Choriodecidual Bacterial Colonization to Preterm Delivery.

Other pathways may have a role as well. For example, prostaglandin dehydrogenases in chorionic tissue inactivate prostaglandins produced in the amnion, preventing them from reaching the myometrium and causing contractions.[60-62] Chorionic infection decreases the activity of these dehydrogenases, allowing increasing quantities of prostaglandins to reach the myometrium. Another pathway by which infection may cause preterm delivery involves the fetus itself. In fetuses with infections, increases in both fetal hypothalamic and placental production of corticotropin-releasing hormone cause an increase in fetal corticotropin secretion, which in turn increases fetal adrenal production of cortisol. The increase in cortisol secretion results in increased production of prostaglandins.[63] Also, when the fetus itself is infected, the fetal production of cytokines is increased and the time to delivery is markedly decreased.[64] However, the relative contributions of the maternal and the fetal compartments to the overall inflammatory response are unknown.

MARKERS OF INFECTION

Intrauterine infection is often chronic, and it is usually asymptomatic until labor begins or the membranes rupture. Even during labor, most women who are later demonstrated (by histologic findings or culture) to have chorioamnionitis have no symptoms other than preterm labor — no fever, abdominal pain, or peripheral-blood leukocytosis, and there is usually no fetal tachycardia.[65] Therefore, identifying women with intrauterine infections is a major challenge. Substances found in abnormal quantities in amniotic fluid and at other sites in women with intrauterine infection are listed in Table 1.[66]

The best-studied site of infection is the amniotic fluid. As well as containing bacteria, amniotic fluid from women with intrauterine infections has lower

TABLE 1. MARKERS OF INTRAUTERINE INFECTION
IN PREGNANT WOMEN.*

WOMEN PRESENTING IN LABOR

AMNIOTIC FLUID	CERVIX OR VAGINA	SERUM
Bacteria	Bacterial vaginosis	High G-CSF
Low glucose	High G-CSF	High interleukin-6
High white-cell count	High TNF-α	High TNF-α
High G-CSF	High interleukin-1	High C-reactive protein
High TNF-α	High interleukin-6	
High interleukin-1	High interleukin-8	
High interleukin-6	High fetal fibronectin	

ASYMPTOMATIC WOMEN IN ROUTINE PRENATAL CARE

AMNIOTIC FLUID	CERVIX OR VAGINA	SERUM
High interleukin-6	Bacterial vaginosis	High G-CSF
	High interleukin-6	High ferritin
	High ferritin	
	High fetal fibronectin	

*G-CSF denotes granulocyte colony-stimulating factor, and TNF-α tumor necrosis factor α.

glucose concentrations, higher white-cell counts, and higher concentrations of complement C3 and various cytokines than fluid from uninfected women.[29,67,68] However, detecting bacteria or measuring cytokines and other analytes in amniotic fluid requires amniocentesis, and it is not clear that amniocentesis improves the outcome of pregnancy, even in women with symptoms of preterm labor. At present, it is not appropriate to obtain amniotic fluid routinely to test for intrauterine infection in women who are not in labor.

Positive results on tests of vaginal secretions for bacterial vaginosis, whether done by Gram's staining[69] or by the use of Amsel's criteria (homogeneous vaginal discharge, white cells ringed by bacteria, an amine odor when vaginal fluid is combined with potassium hydroxide, and pH above 4.5),[70] are associated with intrauterine infection and predict preterm delivery.[37-41] In women with preterm labor and asymptomatic women, a positive result on the test of vaginal or cervical secretions for fibronectin, a protein of the placental membranes, not only is the best predictor of spontaneous preterm delivery, but also is strongly associated with subsequent chorioamnionitis and neonatal sepsis.[35,71-73] It is believed that intrauterine infection disrupts the extracellular choriodecidual basement membrane, causing leakage of this protein into the cervix and vagina.[72,73]

In women with symptoms of preterm labor, high concentrations of many cytokines in the vaginal or cervical secretions, including tumor necrosis factor α, interleukin-1, interleukin-6, and interleukin-8, are associated with early preterm delivery.[74,75] In women receiving routine prenatal care, high cervical concentrations of interleukin-6 also predict subsequent pre-

term delivery and add to the predictive value of measurements of fibronectin.[76] However, other than testing for bacterial vaginosis, no vaginal or cervical test is commonly used to predict intrauterine infection.

A short cervix, as determined by ultrasonography, correlates with several markers of infection and chorioamnionitis.[77,78] Although a short cervix might facilitate the ascension of bacteria into the uterus, it is also likely that in some women, the cervix shortens in response to an upper genital tract infection that has already occurred. However, since an early preterm delivery due to infection may be indistinguishable from one due to a structurally inadequate cervix, it remains uncertain whether the length of the cervix shortens before or after a silent uterine infection.

Women with symptoms of preterm labor who later have a preterm delivery have high serum concentrations of interleukin-6, interleukin-8, and tumor necrosis factor α.[79] Among women without symptoms of preterm labor who are screened routinely, granulocyte colony-stimulating factor is the only cytokine whose circulating concentrations in serum have been found to be high before the onset of preterm labor.[80] Noncytokine markers of infection include high serum C-reactive protein and ferritin concentrations.[81-83] In women receiving routine prenatal care, low serum ferritin concentrations are indicative of low iron stores, but high serum ferritin concentrations appear to represent an acute-phase reaction and predict preterm delivery. Serum ferritin concentrations also double within a week after membrane rupture, probably indicating progressive intrauterine infection.[84] High cervical concentrations of ferritin also predict subsequent spontaneous preterm delivery.[85]

Among the markers of intrauterine infection, bacterial vaginosis and a history of early preterm delivery can be determined before pregnancy. Before 20 weeks of gestation, bacterial vaginosis, high concentrations of fibronectin in the vaginal fluid,[86] and a short cervix have all been associated with chronic infection. Soon after mid-pregnancy, in women not in labor, high cervical or vaginal fibronectin concentrations, a short cervix, high concentrations of several cytokines in the vaginal or cervical fluid, and high serum granulocyte colony-stimulating factor and ferritin concentrations have all been associated with an increased risk of spontaneous preterm delivery. Finally, preterm labor between 20 and 28 weeks of gestation is itself highly correlated with intrauterine infection, and this relation is even stronger among women with a short cervix, high cervical or vaginal fibronectin concentrations, or high concentrations of various cytokines in the amniotic, cervical, or vaginal fluids or in the serum.

Despite these correlations, none of these markers have been found useful in the development of strategies to reduce prematurity or delay delivery among women with or without symptoms of labor, except

that women at high risk who have bacterial vaginosis may benefit from antibiotic treatment. For this reason, measurements of the other markers in an effort to reduce the frequency of preterm delivery are not indicated.

TREATMENT OF INFECTION TO PREVENT PRETERM DELIVERY

In the early 1970s, a prolonged course of tetracycline, beginning in the middle trimester, was found to reduce the frequency of preterm delivery both in women who had asymptomatic bacteriuria and in those who did not.[7] This treatment fell into disuse, probably because of tetracycline-related tooth and bone dysplasias in the infants. The results of treatment with erythromycin, targeting ureaplasma or mycoplasma in the vagina or cervix, have been mixed.[87] It should be noted that ureaplasma is part of the vaginal microflora in many women, and its presence in the lower genital tract, unlike its presence in the upper genital tract, has not been associated with an increased risk of spontaneous preterm delivery.[88]

In recent years, trials of prenatal treatment for the prevention of preterm delivery have focused on bacterial vaginosis, with intriguing but mixed results.[89-94] The overall results suggest that in women with a previous preterm delivery and with bacterial vaginosis diagnosed in the second trimester, treatment for one week or more with oral metronidazole, and perhaps with erythromycin, results in a significant reduction in the incidence of preterm delivery.[89-91] There was no significant reduction in preterm delivery when antibiotics were administered vaginally, when shorter courses of antibiotics or antibiotic regimens not including metronidazole were used, or when the women treated were at low risk (usually defined as not having had a prior preterm delivery).[91-94]

For women with intact membranes and with symptoms of preterm labor, antibiotic treatment does not usually delay delivery, reduce the risk of preterm delivery, or improve the neonatal outcome.[95] In these trials, the women were usually treated with penicillin and cephalosporin derivatives or erythromycin. However, in two small, randomized trials, a prolonged course of metronidazole plus ampicillin resulted in a substantial delay until delivery, an increase of 200 to 300 g in the mean birth weight, a reduction in the incidence of preterm delivery, and in lower neonatal morbidity, as compared with placebo.[96,97] Because of our concern about the excessive use of antibiotics in pregnancy and the small samples in both studies, we are reluctant to recommend changes in practice at this time.

For women who present with preterm rupture of the membranes, preventing preterm delivery is not a reasonable goal. However, there is substantial evidence that antibiotic treatment of these women for a week or more significantly increases the time to delivery and reduces the incidence of chorioamnionitis and improves various measures of neonatal morbidity.[98] Similarly, in women who test positive for group B streptococcus in the vagina, there is now evidence that penicillin treatment during labor reduces the rate of neonatal group B streptococcal sepsis, but not that of spontaneous preterm delivery.[99]

CONCLUSIONS

The recent increase in knowledge about infection and preterm delivery has raised many questions and suggested new strategies for prevention. It is not known how and when bacteria invade the uterus and whether additional, as yet undocumented, infections with viruses, protozoa, or bacteria other than those already described are involved in preterm delivery.[100] Having more information about the chronicity of uterine infections both before and during pregnancy and the mechanisms by which the mother and fetus respond to bacterial infection is crucial to developing a better understanding of these infections. Because chronic upper genital tract infections are largely asymptomatic, more discriminating markers to identify women with these infections for study and intervention are needed. Finally, a deeper understanding of the relation between intrauterine infection and spontaneous preterm delivery will permit the clinical investigation of treatments to reduce spontaneous preterm delivery and its associated long-term morbidity and mortality.

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