Genitourinary Infections and Their Association with Preterm Labor

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Genitourinary tract infections are one cause of preterm delivery. Prematurity is one of the leading causes of perinatal mortality in the United States. Uterine contractions may be induced by cytokines and prostaglandins, which are released by microorganisms. Asymptomatic bacteriuria, gonococcal cervicitis and bacterial vaginosis are strongly associated with preterm delivery. The role of *Chlamydia trachomatis*, *Trichomonas vaginalis* and *Ureaplasma urealyticum* is less clear. By adopting a rational approach to the diagnosis and treatment of genitourinary infections, family physicians can substantially decrease a patient's risk of preterm delivery. (Am Fam Physician 2002;65:241-8. Copyright© 2002 American Academy of Family Physicians.)

Preterm delivery, defined as delivery occurring before 37 complete weeks of gestation, causes the majority of neonatal deaths unrelated to congenital anomalies and also accounts for more than one half of nursery costs.[1-3] Furthermore, premature infants who survive often have significant morbidities including necrotizing enterocolitis, retinopathy of prematurity, intraventricular hemorrhage, chronic lung disease and developmental delay.[1]

Approximately one in 10 deliveries in the United States occurs preterm.[1] Identifying and treating the underlying cause of preterm labor would potentially decrease perinatal morbidity and mortality. Unfortunately, the etiology in most cases of preterm labor is unknown. Some identified factors include anatomic abnormalities of the uterus and cervix, premature rupture of the membranes (PROM), placenta previa or abruption, trauma, excessive uterine enlargement, as in multiple gestation and hydramnios, and infection. This article discusses the relationship between genitourinary infections and preterm labor.

Approximately one in 10 births in the United States results in a preterm delivery, and 40 percent of preterm deliveries are thought to be the result of infection.

Mechanism of Action

One mechanism by which microorganisms might cause preterm labor is through ascension from the cervical/vaginal area and replication in the placenta, decidua and membranes.[4] In one study,[5] the amniotic membranes of pregnant Rhesus monkeys were inoculated with group B streptococci (GBS). Subsequent samples of the monkeys' amniotic fluid showed elevated levels of cytokines, such as interleukin-1β (IL-1β), interleukin-6 (IL-6), and prostaglandins, such as PGE_2 and PGF_{2a}.[5]

IL-1β is thought to promote the synthesis of IL-6 and IL-8, which then triggers the production of prostaglandins E_2 and F_{2a}; these prostaglandins are known to stimulate uterine contractions.[6] Because IL-1β is not present in the membranes of term-laboring patients, it may be the unique mediator by which intrauterine infection induces preterm labor.[7]

Infection and Preterm Labor

Approximately 40 percent of spontaneous premature births are thought to be caused by infection.[8] Systemic maternal febrile infections such as pyelonephritis have been associated with preterm delivery. A model of successful intervention in the prevention of preterm delivery is screening and treatment for asymptomatic bacteriuria early in gestation, which prevents pyelonephritis during pregnancy.[9]

Preterm delivery is more likely to occur in pregnant women with untreated asymptomatic bacteriuria than in women without bacteriuria.

ASYMPTOMATIC BACTERIURIA

Asymptomatic bacteriuria, defined as more than 100,000 colonies of a single bacterial species per mL of urine, cultured from midstream sample, is present in 2 to 7 percent of pregnant women.[10] The most commonly isolated bacteria is *Escherichia coli*. Pregnancy does not increase the incidence of asymptomatic bacteriuria; however, pyelonephritis develops in 20 to 40 percent of pregnant women with untreated asymptomatic bacteriuria.[11]

Results of multiple studies have shown that women with asymptomatic bacteriuria have a higher preterm delivery rate than women without bacteriuria.[12] Approximately 40 to 80 percent of the pregnancy complications caused by acute pyelonephritis could be prevented by treating asymptomatic bacteriuria.[13] Therefore, identifying and treating asymptomatic bacteriuria could decrease the risk of preterm delivery in affected patients.

Treatment of GBS bacteriuria has been shown to decrease the rate of preterm delivery.[14] Moreover, GBS bacteriuria has been associated with heavy GBS genitourinary colonization.[15] The Centers for Disease Control and Prevention (CDC) recommends that pregnant women with GBS bacteriuria be treated at the time of diagnosis and during labor.[15] Intrapartum antibiotic prophylaxis is used to prevent early GBS infection in newborns.

Usually, women who do not have asymptomatic bacteriuria at the initial prenatal visit will not develop bacteriuria later in the pregnancy.[13] Accordingly, routine screening for asymptomatic bacteriuria should be performed at the initial prenatal visit. Treatment options include a three- to seven-day course of (1) oral amoxicillin, 250 mg three times daily; (2) 100 mg of nitrofurantoin macrocrystals (Macrobid), 100 mg twice daily; or (3) cephalexin (Keflex), 250 mg four times daily[13] *(Table 1[16,17] and Table 2[18])*. After therapy is completed, a urine culture should be repeated to ensure eradication of infection. This repeat culture will also identify patients with persistent or recurrent bacteriuria.

For patients who have persistent or recurrent bacteriuria, consideration should be given to administering suppressive doses of antibiotics, such as 100 mg of nitrofurantoin taken orally once a day at bedtime, or 250 mg of cephalexin taken orally once a day at bedtime until delivery.[19]

NEISSERIA GONORRHOEAE

Neisseria gonorrhoeae is a gram-negative intracellular diplococcal organism that is sexually transmitted. This bacterium causes infections in the genital tract that may disseminate to organs. *N. gonorrhoeae* cervicitis is strongly associated with premature delivery.[20]

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TABLE 1
Antibiotics Commonly Used in Pregnancy

Agent	*Risk category*	*Fetal effects*	*Maternal effects*	*Excretion route*	*Half-life in nonpregnant women (hours)**
Considered safe					
Aminopenicillin (i.e., ampicillin)	B	None known	Allergic reaction, rash (5% to 7%)	Renal	1
Cephalosporin (1st, 2nd, 3rd and 4th generations)	B	None known	Allergic reaction; bleeding if methylthiotetrazole side chain	Renal, hepatic	0.5 to 8
Erythromycin (base, stearate or ethyl-succinate)	B	None known	GI upset; allergic reaction	Hepatic	2 to 4
Clindamycin (Cleocin)	B	None known	Pseudomembranous colitis	Hepatic	2.4
Probably safe—use with caution					
Azithromycin (Zithromax)	B	None known	Occasional GI symptoms	Hepatic	68
Metronidazole (Flagyl)	B	None known†	GI; reversible neuropathy; intolerance to alcohol	Renal	8
Nitrofurantoin (Furadantin)	B	None known	Hemolysis if G6PD-deficient; neuropathy	Renal	0.3 to 1
Contraindicated					
Doxycycline (Vibramycin)	D	Bone and teeth	Occasional GI symptoms; photosensitivity, hepatotoxicity	Renal	8 to 19

GI = gastrointestinal; G6PD = glucose-6-phosphate dehydrogenase.

**—Half-life varies with gestational age. Data during pregnancy are generally unavailable.*
†—Metronidazole is usually withheld in the first trimester because of theoretic teratogenic effects.[19]

Information from Briggs GG, Freeman RK, Yaffe SJ. Drugs in pregnancy and lactation: a reference guide to fetal and neonatal risk. 4th ed. Baltimore: Williams & Wilkins, 1994, and ACOG educational bulletin. Antimicrobial therapy for obstetric patients. Number 245—March 1998 (replaces no. 117, June 1988). American College of Obstetricians and Gynecologists. Int J Gynaecol Obstet 1998;61:299-308.

Risk factors for gonococcal infection include a history of multiple sexual partners, sexually transmitted diseases or illicit drug use.[21]

Women with gonococcal cervicitis are commonly asymptomatic but may have vaginal discharge, vaginal spotting or dysuria.[10] Physical examination frequently reveals a mucopurulent cervical discharge and a hyperemic cervix. Other infected sites may include the pharynx, anal canal and urethra. Culture of the affected site remains the gold standard for diagnosis. Results from recent

TABLE 2
Treatment Regimen

Infection	*Treatment options*	*Treat partner*
Asymptomatic bacteriuria	Amoxicillin, 250 mg orally three times daily for three to seven days *or* Nitrofurantoin (Furadantin), 100 mg orally twice daily for three to seven days *or* Cephalexin (Keflex), 250 mg orally four times daily for three to seven days	Routine treatment of sexual partners is not recommended.
Neisseria gonorrhoeae	Ceftriaxone (Rocephin), 125 mg intramuscular single dose *or* Cefixime (Suprax), 400 mg orally as a single dose *plus* Erythromycin base, 500 mg orally three times daily for seven days *or* Amoxicillin, 500 mg orally three times daily for seven days *or* Azithromycin (Zithromax), 1 g oral single dose	Refer sexual partners for evaluation and treatment.
Bacterial vaginosis	First trimester: Clindamycin (Cleocin), 300 mg orally twice daily for seven days After first trimester: Metronidazole (Flagyl), 250 mg orally three times daily for seven days *or* Clindamycin, 300 mg orally twice daily for seven days *or* Metronidazole, 250 mg orally three times daily for seven days *plus* Erythromycin base, 333 mg orally three times daily for 14 days	Routine treatment of sexual partners is not recommended.
Chlamydia trachomatis	Erythromycin base, 500 mg orally four times daily for seven days *or* Amoxicillin, 500 mg orally three times daily for seven days *or* Azithromycin,1 g oral single dose	Refer sexual partners for evaluation and treatment.
Trichomonas vaginalis	After first trimester: Metronidazole, 2 g orally *or* Metronidazole, 500 mg orally twice a day for seven days	Sexual partners should be treated.

Adapted from Centers for Disease Control and Prevention. 1998 guidelines for treatment of sexually transmitted diseases. MMWR Morb Mortal Wkly Rep 1998;47(RR-1):1-115.

studies have shown that gonococcal DNA tests have excellent sensitivity and specificity, and they are easier to perform than cultures.[10]

Epidemiologic studies have demonstrated that the treatment of gonococcal cervicitis is associated with a decreased rate of preterm delivery.[9] Because coinfection with chlamydia is common, the recommended treatment for pregnant women with gonorrhea is a single 125-mg intramuscular dose of ceftriaxone (Rocephin) or a 400-mg oral dose of cefixime (Suprax), and either a single 600-mg oral dose of azithromycin (Zithromax) or 500 mg of erythromycin base taken orally four times a day for seven days.[18,21]

The use of doxycycline (Vibramycin), which has a Category D pregnancy rating, should be avoided in pregnant women *(Table 1[16,17] and Table 2[18])*. While a follow-up culture to establish cure is no longer recommended after completion of treatment, testing for reinfection one to two months after cessation of therapy is advisable.[21] Sexual partners should be referred for evaluation and treatment.[18]

Pregnant women with gonococcal cervicitis should be treated with antibiotics that are also effective in the treatment of chlamydial infections because coinfection commonly occurs.

BACTERIAL VAGINOSIS

Recent studies have shown that bacterial vaginosis, a noninflammatory overgrowth of anaerobic species (including Bacteroides species, Peptostreptococcus species and *Gardnerella vaginalis*), is associated with preterm delivery in high-risk patients.[20,22,23] Up to 40 percent of pregnant women may have bacterial vaginosis.[24] Patients are usually asymptomatic but may report a nonpruritic malodorous vaginal discharge.[25]

On examination, a malodorous, thin, homogeneous discharge is typically seen. The diagnosis of bacterial vaginosis rests on the presence of three of the following four findings: (1) a thin, dark or dull gray homogenous malodorous discharge that adheres to the vaginal walls; (2) an elevated vaginal pH level (≥4.5); (3) a positive Whiff test (fishy odor is noted on adding KOH to the discharge); or (4) the presence of clue cells (epithelial cells with adherent organisms) on wet mount microscopic evaluation. These diagnostic criteria combined are approximately 90 percent sensitive and almost 90 percent specific.[25]

In some studies, the treatment of bacterial vaginosis has been shown to reduce the preterm delivery rates in women who have a history of preterm delivery or who weigh less than 50 kg (110 lb) before pregnancy.[23,26] However, treatment of bacterial vaginosis in low-risk women does not decrease the risk of preterm birth.[27] There is currently insufficient evidence to suggest that screening and treating all pregnant patients will decrease the risk of preterm birth.

Metronidazole is usually not prescribed in the first trimester because of theoretic teratogenic effects.[18] After the first trimester, 250 mg of metronidazole taken orally three times a day for seven days is recommended. This regimen has been shown to decrease the preterm delivery rate in high-risk patients.[28]

Metronidazole intravaginal gel (one application twice a day for five days) is an effective treatment for bacterial vaginosis, but treatment has not been shown to affect preterm delivery rates.[29] Metronidazole plus erythromycin was found to be as effective in the treatment of bacterial vaginosis and could be considered an alternative treatment option[26] *(Table 1[16,17] and Table 2[18])*. Routine treatment of sexual partners of women who have bacterial vaginosis is not recommended.[18]

TRICHOMONAS VAGINALIS

Trichomoniasis is a common vaginal infection caused by the protozoan *Trichomonas vaginalis*.[18] Although *T. vaginalis* may be associated with preterm delivery, treatment does not appear to decrease the risk.[9] Up to one third of infected women are asymptomatic.[25]

Amoxicillin appears to be equally as effective as erythromycin for the treatment of chlamydial cervicitis in pregnancy.

The clinical presentation of trichomoniasis is a copious yellow-gray homogenous discharge and an alkaline vaginal pH. An inflamed "strawberry cervix" may occasionally be seen. The diagnosis is confirmed on wet mount microscopy by observing mobile flagellated organisms and numerous leukocytes; however, in one fourth of infected patients, the wet mount will be unrevealing.[25]

Treatment consists of a single 2-g oral dose of metronidazole or, alternatively, 500 mg of metronidazole taken twice daily for seven days *(Table 1[16,17] and Table 2[18])*. During the first trimester, intravaginal clotrimazole (Lotrimin) may be used, which has been shown to have a 48 percent cure rate.[25] No follow-up or repeat testing is recommended if the patient was initially symptomatic or becomes asymptomatic. Sexual partners should be treated.[18]

CHLAMYDIA TRACHOMATIS

Chlamydia trachomatis, an obligate intracellular bacteria, is considered to be the most commonly isolated sexually transmitted organism. The prevalence of *C. trachomatis* in pregnant patients ranges from 5 to 26 percent.[21] Conflicting evidence exists regarding the relationship of chlamydial cervicitis and preterm labor.[9] Patients infected with *C. trachomatis* are often asymptomatic, but they may present with a mucopurulent vaginal discharge or cervicitis. Diagnosis is made by culture or by DNA probe, which is 90 percent sensitive and 97 percent specific.[21]

Multiple treatment regimens exist, including a 500-mg erythromycin base taken orally four times a day for seven days, 1 g of azithromycin taken orally as one dose or 500 mg of amoxicillin taken three times a day for seven days.[18,21] Amoxicillin and erythromycin appear to be equally efficacious[30,31] *(Table 1[16,17] and Table 2[18])*. However, amoxicillin is dosed less frequently and has fewer side effects than erythromycin. A test for cure is recommended three weeks after completion of therapy, followed by repeat testing in the third trimester. Sexual partners of women who have *C. trachomatis* should be referred for evaluation.

UREAPLASMA UREALYTICUM

Ureaplasma urealyticum is a mycoplasma bacterium that commonly inhabits the genitourinary membranes. No consensus exists on whether *U. urealyticum* is a genital tract pathogen or on its role in preterm delivery.[32,33] Currently, screening for or treatment of this organism is not justified because of insufficient information.

OTHER INFECTIONS

Routine screening for other infections such as hepatitis B, human immunodeficiency virus (HIV) and syphilis is important to prevent maternal and fetal-neonatal complications; however, the role of these infections in preterm labor is unclear.

Recommendations

The U.S. Preventive Services Task Force recommends screening every pregnant patient for asymptomatic bacteriuria using a urine culture. The American Academy of Family Physicians (AAFP) recommends periodic screening with urine semiquantitative dipstick evaluation, and the American College of Obstetricians and Gynecologists (ACOG) recommends screening at the initial prenatal visit using a urinalysis and additional investigations as clinically indicated. It is the authors' opinion that screening at the initial prenatal visit should be undertaken using a urine culture because urine dipstick testing may have up to a 50 percent false-negative rate.[10] Furthermore, the culture would identify group B streptococcus bacteriuria.

The CDC advises that every pregnant

woman undergo gonococcal screening at the initial visit, whereas the Clinical Services Task Force (CSTF), ACOG and AAFP recommend screening for patients with risk factors for gonorrhea. The CDC, CSTF and ACOG also recommend repeating cultures in the third trimester for high-risk patients. These recommendations are aimed at preventing neonatal complications.

It is our opinion that patients with a high risk for contracting sexually transmitted diseases, with previous preterm delivery and with current preterm PROM or preterm labor, should be screened for gonococcal infection. Repeat testing should be performed in the third trimester for women determined to be at high risk for gonococcal infection. The use of the DNA probe should be considered because of its ability to screen for chlamydia and gonorrhea, and because of its easier handling characteristics.

The CDC, ACOG and AAFP recommend screening for chlamydia for at-risk pregnant patients. These formal recommendations are intended to decrease maternal postnatal and neonatal complications. The optimal timing of such screening is unclear. Most guidelines recommend screening at the initial visit and/or during the third trimester. The authors recommend using the same criteria as those used to screen for gonorrhea.

Final Comment

There is insufficient evidence to support routine screening for bacterial vaginosis. But for those patients who do have an infection and are beyond the first trimester, a 250-mg oral dose of metronidazole taken three times a day for seven days is the recommended treatment. Although no formal recommendations exist, assessing for *T. vaginalis* in symptomatic patients is also recommended.

To decrease vertical transmission and maternal complications, screening for infections such as HIV, hepatitis B and syphilis should be performed at the initial visit and possibly at delivery, according to state law.

Available data are insufficient to justify screening or treating pregnant women infected with Ureaplasma urealyticum.

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