Asymptomatic Bacteriuria and Symptomatic Urinary Tract Infections During Pregnancy

Amanda M. Macejko, MD, Anthony J. Schaeffer, MD*

Department of Urology, Northwestern University, 303 East Chicago Avenue, Tarry 16-703, Chicago, IL 60611, USA

Urinary tract infections (UTIs), a common complication of pregnancy, may be classified as lower (cystitis and asymptomatic bacteriuria [ASB]) or upper (pyelonephritis) tract infections. Although the prevalence of cystitis and ASB are similar in pregnant and nonpregnant women, lower tract UTIs represent a significant risk factor for developing pyelonephritis in pregnant women [1]. The increased risk of pyelonephritis is thought to be secondary to the anatomic and physiologic changes that occur in pregnancy [2]. Because pyelonephritis during pregnancy may cause significant morbidity for both the mother and the fetus, proper screening and treatment of bacteriuria, regardless of the presence of symptoms, is necessary to prevent complications.

Pathogenesis

In normal circumstances, the genitourinary tract is sterile. Bacteriuria occurs when bacteria from a fecal reservoir gain access to the bladder by ascending the urethra [3]. Organisms causing bacteriuria are similar in both pregnant and nonpregnant women (Box 1) [2], with *E coli* being the most common pathogen [4]. Other microorganisms, including *Gardnerella vaginalis,* lactobacilli*, Chlamydia trachomatis* and *Ureaplasma urealyticum*, have been found in urine. Although the clinical significance of these organisms is not yet appreciated, a few small studies have reported improved outcomes following therapy [5,6].

Urinary tract changes in pregnancy

Although the incidence of bacteriuria in pregnant women is similar to that in their nonpregnant counterparts, the incidence of acute pyelonephritis in pregnant women with bacteriuria is significantly increased, compared with nonpregnant women [7]. Anatomic and physiologic urinary tract changes in pregnancy may cause pregnant women with bacteriuria to have an increased susceptibility to pyelonephritis [2]. These urinary tract changes involve nearly the entire tract, including the kidneys, collecting system, ureters, and bladder (Box 2). The kidneys increase in length by approximately 1 centimeters during pregnancy [8]. With this increase in renal size, the glomerular filtration rate increases by approximately 30% to 50% [9]. This change is important to consider when dosing medications because the rate of renal excretion may be increased, thus reducing the duration a particular drug is present in the urine [10]. The renal pelvis and ureters may begin to dilate as early as the seventh week of pregnancy [2]. This dilation progresses throughout the course of the pregnancy and is secondary to mechanical obstruction caused by the uterus, and smooth muscle relaxation caused by progesterone. This smooth muscle relaxation results in decreased peristalsis of the ureters [4], increased bladder capacity, and urinary stasis. The bladder itself is displaced superiorly and anteriorly during pregnancy [8].

Antimicrobials in pregnancy

In treating pyelonephritis in pregnant women, it is important to remember that therapy must be safe for both mother and fetus. Nearly all

* Corresponding author.
E-mail address: ajschaeffer@northwestern.edu
(A.J. Schaeffer).

urologic.theclinics.com

Box 1. Microbiology of bacteriuria in pregnancy

Enterobacteriaceae (90%): E coli, Klebsiella, Enterobacter
Other Gram-negatives
- *P. mirabilis*
- *Pseudomonas*
- *Citrobacter*

Gram-positives
- *Staphylococcus saprophyticus*
- *Group B streptococcus* (GBS)

Other organisms
- *Gardnerella vaginalis*
- *Ureaplasma urealyticum*

Data from Gilstrap 3rd LC, Ramin SM. Urinary tract infections during pregnancy. Obstet Gynecol Clin North Am 2001;28(3):581–91; Millar LK, Cox SM. Urinary tract infections complicating pregnancy. Infect Dis Clin North Am 1997;11(1):13–26; Le J, Briggs GG, McKeown A, et al. Urinary tract infections during pregnancy. Ann Pharmacother 2004;38(10):1692–701.

antimicrobials cross the placenta, and therefore agents that may be harmful to the developing fetus should be avoided. Penicillins, cephalosporins, and nitrofurantoin have been used for a number of years without adverse fetal outcomes (Table 1) [11]. Drugs that should be avoided during pregnancy because of adverse fetal effects include fluoroquinolones[1], chloramphenicol, erythromycin, and tetracycline.

The treating physician must also remain aware that serum and tissue drug concentrations may be lowered because of the physiologic changes of pregnancy. These changes include increased maternal fluid volume, drug distribution to the fetus, increased renal blood flow, and increased glomerular filtration [3,11].

Penicillins

Penicillins have been used for a number of years, are mostly well tolerated, and are not

known to be teratogenic [10]. Ampicillin is given parenterally and may require an increased dose or frequency in pregnant women because it is rapidly excreted renally [12]. Ampicillin's oral counterpart, amoxicillin, does not require increased dosage and has been a mainstay of UTI treatment in pregnancy. However, increasing resistance to both ampicillin and amoxicillin has been observed, and therefore one should use susceptibility testing to guide treatment [13]. Penicillin G is effective and remains the drug of choice for group B streptococci bacteriuria [11].

Cephalosporins

Cephalosporins are also used commonly in pregnancy. These agents are a good choice for pyelonephritis, especially when there is resistance to first-line therapy [14]. Cephalexin, a first-generation cephalosporin, is the most commonly used oral cephalosporin [15]. Third-generation cephalosporins have excellent coverage against gram-negative, and some gram-positive, organisms. It is important to note however, that cephalosporins are not active against *Enterococcus* [11]. The clinician should also keep in mind that doses may need to be altered because cephalosporins may have a shorter half-life in pregnancy owing to increased renal clearance [16].

Box 2. Urinary tract changes in pregnancy

Kidneys
- Increased renal length
- Increased glomerular filtration rate by 30% to 50%

Collecting system
- Decreased peristalsis

Ureters
- Decreased peristalsis
- Mechanical obstruction

Bladder
- Displacement superiorly and anteriorly
- Smooth muscle relaxation

Data from Waltzer WC. The urinary tract in pregnancy. J Urol 1981;125(3):271–6.

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[1] It is generally recommended that fluoroquinolones be avoided during pregnancy, as described in this article. However, a different opinion is given by Shrim and colleagues in their article on pharmaceutical agents in pregnancy, elsewhere in this issue.

Table 1
Antimicrobials in pregnancy

Drug	Fetal toxicity	Comments
Safe in pregnancy		
Penicillins		
Penicillin G		Used for GBS
Ampicillin		Increasing bacterial resistance
Amoxicillin		Increasing bacterial resistance
Cephalosporins		Not active against *Enterococcus*
Cephalexin		Used extensively
Cefaclor		Effective against gram-negatives
Clindamycin		Used for GBS in penicillin-allergic patients
Use cautiously in pregnancy		
Nitrofurantoin	3rd trimester: theoretical risk of fetal hemolytic anemia when mother has G6PD deficiency	Not effective in pyelonephritis
Not active against *Proteus*
Hemolytic anemia in maternal G6PD deficiency
Rare maternal pulmonary reaction
Aminoglycosides	Theoretical risk of fetal oto- and nephrotoxicity	May cause maternal oto- and nephrotoxicity
Sulfisoxazole	1st trimester: antifolate metabolism associated with theoretical increased risk of neural tube defects
3rd trimester: may lead to neonatal hyperbilirubinemia with kernicterus	Increasing *E coli* resistance
Hemolytic anemia in G6PD deficiency
Trimethoprim	1st trimester: antifolate metabolism associated with theoretical increased risk of neural tube defects	Increasing *E coli* resistance
May cause maternal megaloblastic anemia
Avoid in pregnancy		
Fluoroquinolones	Irreversible arthropathy in animal studies	
Chloramphenicol	"Gray baby syndrome"	
Erythromycin		May cause maternal cholestasis
Tetracycline	Discoloration of deciduous teeth	May cause maternal acute fatty liver degeneration

Abbreviation: G6PD, glucose-6-phosphare dehydrogenase.

Data from Schaeffer AJ. Infections of the urinary tract. In: Walsh PC, Retik AB, Vaughan ED Jr, editors. Campbell's Urology. 8th edition. Philadelphia: WB Saunders; 2002. p. 516–602; Dashe JS, Gilstrap 3rd LC. Antibiotic use in pregnancy. Obstet Gynecol Clin North Am 1997;24(3):617–29.

Nitrofurantoin

Nitrofurantoin attains therapeutic levels in urine and is an acceptable agent for ASB or cystitis; however, it does not achieve adequate tissue penetration, and therefore should not be used in pyelonephritis. Nitrofurantoin is a good choice for penicillin-allergic patients or for those with resistant organisms, but it is not active against *Proteus* sp [10]. Rare, but serious, complications of nitrofurantoin include pneumonitis or pulmonary reaction and hemolytic anemia in mothers with glucose-6-phosphate dehydrogenase deficiency [1]. Nitrofurantoin has not been associated with fetal malformations [17].

Macrolides

Clindamycin is recommended for group B streptococci in pregnant women who are allergic to penicillin. It is unnecessary to increase the dose in pregnancy and teratogenicity has not been reported [18].

Aminoglycosides

This group of antimicrobials is often used in combination with ampicillin for the treatment of acute pyelonephritis during pregnancy. Aminoglycosides are particularly effective because they achieve high renal parenchymal concentrations [14]. Gentamicin is the most commonly used aminoglycoside in pregnancy. Because aminoglycosides are known to cross the placenta, they could cause ototoxicity and nephrotoxicity in the fetus [11]. However, no congenital anomalies, or ototoxicity or nephrotoxicity, after in utero exposure to aminoglycosides, have been reported [11].

Sulfonamides

This class of antimicrobials is not recommended as first-line agents because of the incidence of *E coli* resistance and toxicity. Sulfonamides may also be associated with antifolate teratogenicity in the first trimester [19]. Additionally, in the third trimester, sulfonamides can displace bilirubin from albumin, and have been reported to cause hyperbilirubinemia with kernicterus [11]. Hemolytic anemia in a fetus with a mother with glucose-6-phosphate dehydrogenase deficiency has also been reported.

Trimethoprim

Resistance of *E coli* to trimethoprim (TMP) is common, decreasing its efficacy as a first-line agent. Studies have not demonstrated teratogenicity; however, because TMP inhibits folate metabolism, theoretically it could increase the risk of neural tube defects [12]. Therefore, TMP should not be used in the first trimester [20].

Quinolones

Although quinolones achieve high concentrations within renal tissue and are appropriate for treatment of pyelonephritis in nonpregnant women, they are not recommended for pregnant women. Fluoroquinolones have been shown to impair cartilage development in animal studies. Although this adverse effect has not been described in humans, quinolones should be avoided in pregnancy [3].

Tetracycline

Tetracycline is not an appropriate agent to use in pregnancy because it leads to discoloration of deciduous teeth if given after 5 months' gestation [1,11]. Early reports suggested that tetracycline also caused enamel hypoplasia and inhibition of fibula growth; however, Porter and colleagues [21] have reported evidence that refutes these claims. Despite this, tetracyclines are Food and Drug Administration category D, and therefore should not be used in pregnancy. High doses of tetracycline in the treatment of pyelonephritis have also been reported to cause acute fatty liver degeneration [22].

Asymptomatic bacteriuria of pregnancy

Definition

ASB is essentially an asymptomatic UTI. In other words, it is the presence of significant bacteriuria without symptoms or signs, such as frequency, urgency, dysuria, pyuria, or hematuria. Significant bacteriuria is defined as greater than or equal to 10^5 colony-forming units of a single pathogen per milliliter of urine in two consecutive midstream urine samples [23]. Counts as low as 10^2 colony-forming units per milliliter should be considered significant bacteriuria if the specimen is catheterized urine or if the patient is symptomatic.

Epidemiology

Pregnancy itself is not a risk factor for ASB because ASB occurs in 4% to 6% of pregnant and nonpregnant women [24]. Socioeconomic status is a significant risk factor for ASB; it has been reported that indigent women have a fivefold greater incidence of bacteriuria, compared with nonindigent populations [25,26]. Other risk factors include diabetes, sickle cell disease and trait, multiparity, history of UTI, and anatomic or functional urinary tract abnormalities [1,25].

Significance

ASB is not considered clinically significant in most patient populations; however, this is not the case with pregnant women. The number of pregnant women who develop pyelonephritis is significantly higher than their nonpregnant counterparts. If untreated, as many as 20% to 40% of pregnant women with ASB will develop pyelonephritis [2,4,27]. Treatment of bacteriuria early in pregnancy has been shown to decrease the incidence of pyelonephritis by 90% [28]. Although it is known that bacteriuria can lead to pyelonephritis in pregnancy, other adverse effects of bacteriuria are less well-established. In various studies, untreated bacteriuria has been linked with prematurity, low birth weight, intrauterine growth

retardation, and neonatal death [29]. However, poor outcomes may be the result of coexisting risk factors, such as low socioeconomic status, rather than of bacteriuria alone. To date, this suggestion remains controversial [2].

Group B streptococcus has been linked to premature rupture of membranes, preterm delivery, neonatal sepsis, meningitis, and pneumonia. Women with group B streptococcal bacteriuria should be treated at initial diagnosis and at the onset of labor [1].

Screening

The American College of Obstetricians and Gynecologists currently recommends screening for ASB in all pregnant women. A study of 3254 pregnant women determined that the optimal timing for bacteriuria screening was at 16 weeks gestation [4,30]. Urine culture is the gold standard, and all pregnant women should provide a urine specimen for culture during the first trimester [1]. A single voided specimen with 10^5 bacteria per milliliter of urine is 80% specific, whereas two specimens with the same organism are 95% specific for bacteriuria [23,31]. Using a single specimen to diagnose bacteriuria may lead to an overestimation because women with either contamination or transient bacteriuria will be included [32]. Therefore, a confirmatory culture is desirable for most cases of ASB. However, considering the risks of bacteriuria in pregnancy, in this setting it is appropriate to treat without the confirmatory culture.

If the initial negative urine culture is negative, repeat cultures are not recommended [33] because only 1% to 2% of women with initial negative cultures will go on to develop pyelonephritis during pregnancy [34]. Exceptions include women with a history of recurrent UTI, or those with known urinary tract abnormalities. These women should undergo follow-up urine cultures throughout the remainder of pregnancy.

Because urine cultures are expensive, efforts to find a more cost-effective method of detecting bacteriuria have been evaluated. However, these other methods fail to be as reliable as urine culture. For example, pyuria is not always present in bacteriuria, nor is it specific for bacteriuria. McNair and colleagues [35] reported a 53% false-negative rate with dipstick screening of nitrite and leukocyte esterase in pregnant patients. A cost analysis by Wadland and colleagues [36] found that screening with urine culture was cost-effective, and it remains the recommended method of screening.

Treatment

Screening and treatment for ASB significantly decreases the risk of symptomatic UTI and its complications. Sweet [7] reported that treatment of ASB decreases the incidence of pyelonephritis during pregnancy from 13.5% to 65% down to 5.3% to zero. The duration of therapy has been a topic of debate, and treatment duration varies from a single dose to one week (Table 2). Single-dose therapy cure rates have been reported at 50% to 60% [37]. Efficacy rates of 70% to 80% have been shown following 3-day courses of antimicrobials. Cure rates do not improve with longer courses of therapy [38] and thus, 3-day therapy is recommended [2].

A follow-up culture 1 week following therapy to ensure that bacteriuria is eliminated should be obtained. In 20% to 30% of patients, short-course therapy will fail. In these cases, a repeat 7- to 10-day course with a culture-specific antimicrobial is appropriate [39].

Prevention

After a negative culture is obtained, daily antimicrobial suppression should be considered, which may consist of 50 to 100 mg of nitrofurantoin orally nightly [1,40]. Without prophylaxis, as many as one third of women will experience recurrent infections during pregnancy [2,32]. If suppression is not used following treatment of ASB, women should have frequent urine cultures throughout the remainder of pregnancy to identify recurrent bacteriuria. In women with recurrent or persistent bacteriuria, follow-up cultures should also be obtained after delivery. Additionally, a urologic evaluation 3 to 6 months postpartum is appropriate [41].

Symptomatic UTI

Lower UTI (acute cystitis)

Incidence of cystitis during pregnancy has been approximated at 1% to 2%. Diagnosis of cystitis is based on a combination of bacteriuria and signs and symptoms of frequency, urgency, dysuria, hematuria, and pyuria. Treatment of cystitis is the same as treatment for ASB (see Table 2). Again, follow-up as outlined above is important because up to one third of women may experience recurrent UTI during pregnancy [1].

Table 2
Treatment regimens for ASB and cystitis

Antimicrobial	Single-dose regimens	Short-course regimens
Amoxicillin	3 g OR	250–500 mg tid × 3 or 7 d
	2 g + 1 g probenecid	3 g × two doses 12 h apart
Amoxicillin/clavulanic acid	–	250/125 tid × 7 d
Nitrofurantoin	200 mg	100 mg qid × 3 or 7 d
Sulfisoxazole	2 g	1 g then 500 mg qid × 7 d
Cephalexin	2–3 g OR	250–500 mg qid × 7 d
	2 g + 1 g probenecid	
Trimethoprim/Sulfamethoxazole	320/1600	320/1600 bid × 3 d

Data from Patterson TF, Andriole VT. Detection, significance, and therapy of bacteriuria in pregnancy. Update in the managed health care era. Infect Disclin North Am 1997;11(3):593–608; Le J, Briggs GG, Mckeown A, et al. Urinary tract infections during pregnancy. Ann Pharmacother 2004;38(10):1692–701; Connolly A, Thorp JM Jr. Urinary tract infections in pregnancy. Urol Clin North Am 1999;26(4):779–87; Ovalle A, Levancini M. Urinary tract infections in pregnancy. Curr Opin Urol 2001;11(1):55–9.

Upper UTI (acute pyelonephritis)

Epidemiology

Incidence of pyelonephritis during pregnancy is approximately 1% to 2%. However, 20% to 40% of women with untreated bacteriuria will develop pyelonephritis during pregnancy [1]. Pyelonephritis is seen most commonly during the third trimester, when stasis and hydronephrosis are most evident [3].

Diagnosis

Bacteriuria and clinical signs and symptoms establish a diagnosis of pyelonephritis. The signs and symptoms are similar to those of nonpregnant women, and include fever, nausea, vomiting, chills, and costovertebral tenderness.

Significance

In the preantimicrobial era, between 20% to 50% of children born to women with pyelonephritis were premature [42]. It has been theorized that the mechanism of preterm labor is associated with microorganism production of phospholipase A2 and subsequent prostaglandin activation [26]. Other reported complications of pyelonephritis have included low birth weight and neonatal death [42]. Although the complications of untreated pyelonephritis in pregnancy are well-known, there is debate in the literature as to whether antibiotic-treated pyelonephritis leads to adverse pregnancy outcomes.

Multiple maternal complications of pyelonephritis have also been reported, including anemia, hypertension [42], transient renal failure, acute respiratory distress syndrome, and sepsis [1].

Treatment

All patients who have pyelonephritis during pregnancy should be admitted and treated with parenteral agents [3]. Initial antimicrobial therapy is typically ampicillin plus gentamicin or cephalosporins. Second- or third-generation cephalosporins may also be considered for single-agent therapy [1]. With these treatment regimens, more than 95% of women will respond within 72 hours [43,44]. Resistant organisms must be considered in women who do not respond appropriately to treatment, and antimicrobials should be changed according to culture results. If treatment response is suboptimal despite culture-specific treatment, an ultrasound should be obtained to rule out nephrolithiasis, structural abnormality, or renal abscess [45].

Once afebrile, women may be switched to a 2-week outpatient course of an oral antimicrobial. This course should be followed by suppressive therapy until delivery [46,47]. As with ASB and cystitis, follow-up after treatment is important. Women should be monitored closely throughout their pregnancy because there is an increased risk of recurrent pyelonephritis [42].

Summary

UTIs are common complications of pregnancy and may lead to significant morbidity for both mother and fetus. During pregnancy, ASB is the major risk factor for developing a symptomatic UTI. Screening and treatment of pregnant women for ASB may prevent morbidity associated with symptomatic UTIs. Bacteriuria should be treated

with short-course therapy with appropriate antimicrobials. Women should be followed closely after treatment of bacteriuria because recurrence may occur in up to one third of patients.

Key points in this article may be summarized as follows:

- Urine culture is the gold standard for screening for bacteriuria in pregnancy.
- All pregnant women should be screened for bacteriuria in the first trimester.
- Women with a history of recurrent UTI or urinary tract anomalies should have repeat bacteriuria screening throughout pregnancy.
- All bacteriuria should be treated during pregnancy.
- Treatment should be effective, and nontoxic to the fetus.
- Antimicrobial prophylaxis or close follow-up after treatment of ASB and symptomatic UTI is necessary throughout the remainder of pregnancy.

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