77 Urinary tract infections in pregnancy

Steven R. Allen

Urinary tract infections (UTIs) commonly complicate pregnancy, present in approximately 10% of gestations. Asymptomatic bacteriuria (ASB) is encountered most frequently. Symptomatic infections, cystitis and pyelonephritis, complicate pregnancy less frequently. Of these three infections, the primary impact on pregnancy outcome derives from acute pyelonephritis, which is commonly preceded by ASB rather than acute cystitis (1). Clinical presentation, risk factors, common complications, and treatment for these three forms of UTI are summarized in Table 1.

PATHOGENESIS

Female anatomy and the physiologic changes of normal pregnancy impart risk factors for UTIs. Because of the short length (approximately 4cm) of female urethra and its termination beneath the labia and relatively near the anus, it is at increased risk of colonization by Gram-negative colonic bacteria. Urethral and periurethral bacteria may intermittently enter the bladder, typically after intercourse (2). Once within the urinary tract, attachment of bacterial pili or fimbriae to carbohydrate components of urothelial cell surface glycolipids and glycoproteins enhances virulence (3).

Half of women with UTIs during pregnancy have an enlarged bladder capacity, and 15% have a significant post-void residual volume (50–150mL) (4). Normal physiologic changes of pregnancy include a mild hydronephrosis and hydroureter, potentially created by both the mechanical compression of the ureter by the enlarging uterus and pelvic blood vessels at the pelvic brim (right greater than left), and the relaxant effect of progesterone on ureteral smooth muscles. In combination, these factors account for the increased rate of both bladder and ascending infections during pregnancy.

Population-specific risk factors for UTIs in pregnancy include nonwhite race, younger maternal age, and antepartum genital tract infection (5).

The bacterial spectra responsible for all three types of UTIs in pregnancy are similar and also are similar to the spectra of bacteria causing UTIs in nonpregnant females. *Escherichia coli* is the most common isolate, present in 70% to 90% of positive urine cultures. Bacteria from other genres of Enterobacteriaceae are the next most common: *Klebsiella*, *Enterobacter*, *Citrobacter* and *Proteus*. Gram-positive organisms cause <10% of UTIs in pregnancy, with group B streptococcus the most common member of this group (1,6–9).

Beyond the fetal risks discussed below in relation to antibiotic exposure and the potential complications of pyelonephritis, maternal UTIs may also increase the risk of fetal anomalies. Analyses of data from the U.S. National Birth Defects Prevention Study show associations between the first-trimester maternal UTI and gastroschisis plus at least one other major anomaly (OR 3.1, 95% CI 1.4–6.7) (10) and

cardiovascular malformations (left ventricular outflow tract obstruction, OR 1.48, 95% CI 1.02, 2.14; atrioventricular septal defect, OR 2.55, 95% CI 1.19, 5.48) (11). For both of these noted associations, the risk appears to exist regardless of fever or antibiotic exposure.

ANTIBACTERIAL CONSIDERATIONS

Because of the similarity of bacterial spectra responsible for each of the three types of UTIs discussed within this chapter, similar antibacterial selection strategies can be applied for treating each. An understanding of the changing resistance pattern for *E. coli* is critical in selecting an appropriate antibiotic, since it is the predominant cause of UTIs. *E. coli* isolates from women with acute cystitis during an observation period ending in 1996 showed progressive resistance to ampicillin (34%), cephalothin (28%), trimethoprim (18%), and trimethoprim–sulfamethoxazole (18%). *E. coli* resistance to trimethoprim–sulfamethoxazole (TMP–SMX) had increased to over 20% in some regions of the United States (12). Results from a single institution in 2000 showed *E. coli* to be unacceptably resistant to ampicillin (75% incidence of sensitivity) and marginally more likely to be sensitive to TMP–SMX. In that study population, nitrofurantoin had the highest likelihood of success for treating uropathogens (100% susceptibility for *E. coli* and 89% overall) (13).

Several antibiotics have proven to be effective for treating UTIs. When treating UTIs in pregnancy, the safety considerations must obviously include potential fetal effects. The following drugs may be considered during pregnancy.

Penicillins and Cephalosporins

High likelihood of resistance prevents these agents from being ideal empiric choices.

Trimethoprim–Sulfamethoxazole

Although TMP–SMX has been recommended as a primary treatment for uncomplicated UTIs (14), progressive bacterial resistance to it now potentially limits its effectiveness as an empiric therapy (13). The best predictor of resistance to TMP–SMX in urinary coliform bacteria is recent use of TMP–SMX (OR 5.9; 95% CI 2.4, 14.3); other predictors include diabetes, recent hospitalization, and current use of antibiotics (15). In addition to declining efficacy, safety features should also be considered before using TMP–SMX to treat UTIs during pregnancy. Both trimethoprim and sulfonamide antibiotics inhibit nucleic acid synthesis by interfering with bacterial production of folic acid. A case-control study of birth defects in the United States and Canada reported an increased likelihood of first-trimester exposure to dihydrofolate reductase inhibitors (including TMP–SMX) among women giving birth to babies with cardiovascular

Table 1 Summary of Urinary Tract Infections During Pregnancy

	Acute cystitis	Asymptomatic bacteriuria	Pyelonephritis
Symptoms	Urgency Frequency Dysuria	No symptoms	Back or flank pain Fever Chills
Unique risk factors	History of recurrent cystitis	Parity Nonwhite race Lower socioeconomic status Diabetes Prior UTI	Asymptomatic bacteriuria Younger age Nulliparity Sickle cell trait or disease
Complications	Recurrent acute cystitis	Pyelonephritis	Bacteremia Septic shock Pulmonary edema
Treatment	Oral broad-spectrum antibiotic, 3–7 days	Oral broad-spectrum antibiotic, 3–7 days	Broad-spectrum antibiotic, parenteral until clinically improved, then oral to complete 10- to 14-day course, followed by oral broad-spectrum antibiotic prophylaxis until 6 weeks postpartum

defects (OR 3.4; 95% CI 1.8–6.4) and oral clefts (OR 2.6; 95% CI 1.1–6.1) (16). The increased risk of cardiovascular defect associated with dihydrofolate reductase inhibitor consumption was offset in women who also took supplemental folic acid (400 µg/day). Although neonatal jaundice has occasionally been reported after fetal exposure to sulfonamides, a contemporary literature review shows no reported cases of kernicterus after such exposure (17). These findings support a recommendation to avoid TMP–SMX in both the first and late third trimesters, and to recommend a higher folic acid supplement dose (4mg/day) if TMP–SMX is prescribed in the first trimester (18).

Nitrofurantoin

This agent's primary benefit is its continued effectiveness against most strains of *E. coli*. It is also effective against many other gram-positive and gram-negative urinary pathogens, but has limited effectiveness against *Klebsiella*, *Enterobacter*, *Pseudomonas*, and *Proteus*. It reaches a high concentration in urine, but not in renal tissue, thus should not be used as primary treatment for pyelonephritis. Rare maternal complications include reversible sensory neuropathy (19) and reversible pneumonitis (occurring in fewer than 1/100,000 exposures) (20). Nitrofurantoin is not teratogenic and does not need to be avoided in the first trimester (21). The extremely low risk for fetal or neonatal hemolytic anemia due to impaired glutathione reductase activity or glucose-6-phosphate dehydrogenase deficiency (with an estimated risk of 0.001%) (22) need not prohibit its use near term. However, these concerns still prompt some recommendations against its use near anticipated delivery (23).

Gentamicin

Aminoglycosides attain high renal tissue levels, thus may be particularly beneficial in the treatment of pyelonephritis. Although ototoxicity has been reported with other aminoglycosides, there are no clear human data supporting fetal ototoxicity (24,25).

Fluoroquinolones

Although arthropathy may develop after fetal exposure in animals, limited human data have not shown arthropathy or other defects following fetal exposure (26). However, concerns about the potential development of drug resistance if this effective family of antimicrobials is overused logically keep fluoroquinolones from being first-line agents for the treatment of UTI in pregnancy.

Fosfomycin

Limited data for this agent in pregnancy preclude a specific recommendation for its use (27,28).

CYSTITIS

Acute cystitis in pregnancy has a clinical presentation not unlike that of symptomatic bladder infection outside of pregnancy. The diagnosis should be suspected in a woman with urgency, frequency, dysuria, or hematuria, and without evidence of upper UTI or systemic illness. A culture of catheterized or midstream urine positive for a single organism confirms the diagnosis. Although the traditional diagnosis of UTI is based upon a quantitative culture containing $\geq 10^5$ bacteria/mL, a lower threshold may be appropriate in the presence of bladder symptoms. Comparing cultures of urine obtained directly from the bladder via suprapubic aspiration or urethral catheterization with those of midstream specimens in acutely dysuric (nonpregnant) women, midstream samples with $\geq 10^2$ bacteria/mL have a sensitivity of 95% and a specificity of 85% for the detection of coliform bacteria (29).

Acute cystitis occurs much less frequently in pregnancy than asymptomatic UTIs. Harris and Gilstrap (6) found the incidence of cystitis to be 1.3% among a population of military dependents. Two-thirds developed their symptomatic infection after the initial clinic visit, and of these, 95% had negative urine cultures at their first prenatal visit. Although half of the patients with cystitis had a history of UTIs, after a 10-day course of antibiotic only 17% had recurrence, and no patients developed pyelonephritis.

The usual treatment for acute cystitis in pregnancy is with a short (3–7 days) course of broad-spectrum antibiotic. In nonpregnant women, without the cited physiologic genitourinary tract changes that predispose to UTI during pregnancy, multiple-dose regimens provide better treatment than a single dose of a broad-spectrum antibiotic (30). Logic predicts that multiple-dose regimens also will be more efficacious in pregnant women. Before the more common antimicrobial resistance patterns currently seen, a 10-day oral course of any one of the following—ampicillin 250mg four times a day, nitrofurantoin macrocrystals 100mg three times a day, sulfisoxazole 500mg four times a day, or cefazolin 250mg four times a day—demonstrated equal efficacy in pregnant women (6).

Taking into account the considerations listed in the prior section, any one of the typically effective drugs may be started empirically for the clinical diagnosis of cystitis, with appropriate changes in selection if directed by urine culture sensitivity results. Limited published data are available to specifically direct the best therapy for acute cystitis in pregnancy. Five days of twice-daily oral therapy with nitrofurantoin 100mg or ampicillin 500mg had similar cure rates (87% and 90%) in 1989 (31), before recent increases in ampicillin resistance, and similar cure rates have also been shown in a small study comparing a single 3-g dose of fosfomycin trometamol and a 3-day course of 400-mg ceftibuten per day (95% and 90%) (28). Given the predominance of *E. coli* as a uropathogen and its ongoing susceptibility to nitrofurantoin, that agent is likely to be the best primary therapy in most cases (13).

A follow-up urine culture may be obtained after initial treatment to confirm appropriate therapy for cystitis, but because of the low rate of recurrence and its typical symptomatic presentation, serial screening urine cultures are not recommended.

Sexual intercourse is a risk factor for recurrent cystitis in some women. Pfau and Sacks (32) showed a 99% reduction from the baseline (pre-pregnant) rate of recurrent cystitis among 33 pregnant women using post-coital cephalixin 250mg or nitrofurantoin 50mg. As compared with daily prophylaxis, this form of therapy provides most at-risk women with the convenience and cost benefit of less frequent antibiotic administration.

ASB

ASB, silent bacterial colonization of the urinary tract, is the most common UTI in pregnancy, with an incidence of 2% to 10% (7,33,34). Lower socioeconomic status, nonwhite race, increased parity (33), diabetes, and prior UTIs increase the risk (35).

For asymptomatic women, bacteriuria is diagnosed by quantitative urine culture: two consecutive voided specimens with isolation of the same bacterial strain in quantitative counts $\geq 10^5$ bacteria/mL or a single catheterized urine specimen containing $\geq 10^2$ bacteria/mL (36). Although only approximately 80% of women with a positive initial screening culture would have that confirmed on subsequent sampling, the detection of $\geq 10^5$ bacteria/mL in a single voided midstream urine is generally accepted as an adequate and more practical alternative to the requirement for serial positive samples (37).

The bacteria identified in ASB are generally similar to those of other UTIs, except that group B streptococcus is more common in this UTI, present in approximately one-quarter of positive screening cultures (8,38).

The significance of ASB during pregnancy lies not in the primary infection but rather in the potential secondary complications. Although ASB is no more common in pregnant women, the physiologic changes of pregnancy that lead to urinary stasis increase the likelihood of ASB progressing into an ascending infection. Subsequent pyelonephritis occurs in approximately 40% of untreated women with ASB (39). Fortunately, the risk of pyelonephritis is reduced to approximately 3% following the treatment for ASB (40). A meta-analysis evaluating the relationship between ASB and pregnancy outcomes showed low birth weight to be 3.4% more likely following ASB and preterm birth to be 3.8% more likely after untreated ASB (41). The same analysis showed a reversal of ASB's impact upon the risk of low birth weight with antibiotic treatment (OR for low birth weight if given antibiotics = 0.52, 95% CI 0.38–0.7).

The risks of untreated ASB and the inability to identify it clinically prompt recommendations for routine screening in pregnancy (36,42,43). As no rapid screening techniques have adequate sensitivity or predictive values, urine culture remains the recommended standard for detecting ASB (42,44).

Current published guidelines for ASB screening recommend that a urine culture be obtained at least once in early pregnancy (36), such as at 12 to 16 weeks of gestation (or at the first prenatal visit, if later) (42). Screening on that schedule will not identify all cases of ASB. A prospective cohort study in which participants had serial urine cultures performed showed that only 43% of the overall positives occurred at <20 weeks of gestation (38). However, early studies showing a great reduction in risk for pyelonephritis following primary antimicrobial therapy for ASB and an average risk for subsequent pyelonephritis in initially nonbacteriuric women of only 1.4% (40) together suggest that serial screening to identify ASB later in pregnancy would have a relatively low yield and not be cost effective.

To accurately interpret the results of a quantitative urine culture, it must have been obtained under conditions that minimize contamination. Vulval cleansing with chlorhexidine may reduce the bacterial colony counts of a midstream urine sample, and cleansing with water provides more representative results. Additionally, the quantity of bacteriuria correlates with the time interval between episodes of voiding; although a first morning void is not necessary, the practice of having patients drink fluid to speed diuresis should be avoided (45).

Although early protocols used continuous treatment until delivery, by 1977 Whalley and Cunningham (46) had shown that short-term treatment (14 days) combined with surveillance for recurrent bacteriuria provided similar results. In 2000, a Cochrane systematic review concluded that published data are insufficient to determine the optimal duration of therapy for ASB in pregnancy (47). In 2005, the Infectious Diseases Society of America recommended 3 to 7 days of antimicrobial therapy for ASB, but did not identify an optimal drug for therapy (36).

A Cochrane systematic review of antibiotic treatments for ASB in pregnancy published in 2007, which included

randomized controlled trials of a variety of antibiotics (sulfonamides, nitrofurantoin, penicillin, and ampicillin), concluded that antibiotic treatment is effective in reducing the risk of pyelonephritis, but no single antibiotic choice is superior (48). According to that review, the number of women needed to treat to prevent one case of pyelonephritis is seven.

Since the diagnosis of bacteriuria is made by urine culture and no optimal drug choice had been identified, antimicrobial selection for the treatment of ASB in pregnancy may be guided by susceptibility results and fetal safety considerations.

In response to the potential silent recurrence of ASB, the Infectious Diseases Society of America recommends periodic screening after initial therapy in pregnancy (36). Urine cultures obtained 1 to 2 weeks after initiation of therapy and additional screening per trimester would meet these guidelines.

Following a recurrent UTI, broad-spectrum antibiotic suppression for the remainder of the pregnancy may be helpful, such as with nitrofurantoin 100mg every day. For women with recurrent infections, urologic examination should be scheduled for 3 to 6 months postpartum, as up to half of these women will have a urinary tract structural abnormality (4). Although pyelographic abnormalities are more common in women with a history of ASB, it is unclear whether these are primarily or secondarily associated.

PYELONEPHRITIS

Affecting 1% to 2% of all pregnancies, pyelonephritis is one of the most common serious medical problems encountered during pregnancy. It will develop in 36% to 42% of untreated women with ASB; this risk falls to $\leq 3\%$ with the treatment for bacteriuria (39,49). Only approximately 1.4% of women without bacteriuria early in a pregnancy will subsequently develop pyelonephritis before delivery (40). Pyelonephritis occurs most commonly during the second or third trimester, although up to one-quarter of infections are diagnosed intrapartum or postpartum (1,50,51). In addition to other risk factors for UTIs in general, younger age, nulliparity (51), and sickle cell trait (52) or disease (OR 1.3, 95% CI 1.0–1.8) (53) make pyelonephritis more likely. It is usually an ascending infection, more likely to occur during pregnancy because of the physiologic changes predisposing to urinary stasis. Conditions unique to the renal medulla make the kidney particularly vulnerable to infection in the presence of stasis: high urine osmolarity, high urea and sodium concentrations, and low pH impair chemotaxis and inhibit polymorphonuclear leukocyte phagocytosis.

Unlike its usual precursor ASB, pyelonephritis is nearly always diagnosed clinically. Patients typically present with the symptoms of back pain and chills (82%); approximately one-quarter have nausea and vomiting. An elevated temperature is uniformly present, with a temperature of $\geq 40^\circ\text{C}$ in 12% of patients. The majority of patients have costovertebral angle tenderness (predominantly right sided or bilateral) (1). Because none of these signs or symptoms is pathognomonic for pyelonephritis, the final diagnosis should depend on a urine culture positive for a known uropathogen.

To speed up diagnosis and treatment while awaiting the urine culture results, microscopic examination of uncentrifuged urine can be performed. One bacterium per high power

field indicates a bacterial concentration of at least $10^5/\text{mL}$. One or more white blood cells per high power field will also usually be seen in pyelonephritis. Although indicative of a UTI, none of these findings are specific for pyelonephritis. If the diagnosis of pyelonephritis is suspected, blood cultures may also be obtained before antibiotic treatment is begun. However, the additional cost of blood cultures may not be substantiated by clinical benefit, as the blood culture results of the patients with pyelonephritis who develop bacteremia usually parallel the urine culture results; MacMillan and Grimes changed antibiotic treatment based on blood cultures in only 2% of pregnant patients with pyelonephritis (54).

Traditional management recommendations for acute pyelonephritis in pregnancy include hospitalization and intravenous antibiotic administration until significant clinical improvement allows conversion to oral antibiotics, completing a 10- to 14-day course of therapy (55). Van Dorsten and associates showed the importance of appropriate initial antibiotic selection, demonstrating a 67% rate of successful treatment with an antibiotic proven effective by routine sensitivity methods, as compared with a 42% rate of successful treatment with an antibiotic to which the isolated bacteria were resistant (56). Although ampicillin has been used for primary therapy, the increasing resistance of *E. coli* to ampicillin compromises its status as the drug of choice. Gentamicin is nearly uniformly effective but because of associated costs for monitoring serum levels and the lack of an oral equivalent, it is not most commonly used for primary therapy. Gentamicin and ampicillin may be combined for efficacious empiric therapy of pyelonephritis in pregnancy; the half of women with ampicillin-resistant uropathogens have no higher rate of complications (anemia, renal dysfunction, respiratory insufficiency, or preterm birth) than the half with ampicillin-sensitive uropathogens (57). A variety of successful protocols may be used to treat pyelonephritis in pregnancy (Table 2).

Sanchez-Ramos and coworkers reported the single-daily intravenous administration of ceftriaxone 1g to be equally effective and less costly than three-daily 2-g doses of cefazolin intravenously (58). Wing and colleagues randomized gravidas with pyelonephritis to receive initial parenteral treatment with ampicillin (2g IV every 4 hours) plus gentamicin (2mg/kg IV loading then 1.75mg IV every 8 hours), cefazolin (2g IV every 8 hours), or ceftriaxone (1g IM every 24 hours) and identified no difference in the duration of fever, time to resolution of costovertebral angle tenderness, duration of hospitalization, or birth outcomes (59).

Table 2 Pyelonephritis Antibiotic Protocol Options

Antimicrobial agent	Suggested regimen
Cefazolin $\pm$ gentamicin (dose as below)	1–2g IV q6–8h
Cefuroxime	0.75–1.5g IV q8h
Ceftriaxone	1–2g IV or IM q24h
Ampicillin $\pm$ gentamicin (dose as below)	2g IV q4h
Gentamicin	2mg/kg IV loading dose, then 1.75mg/kg q8h or per pharmacokinetic dosing
Cephadrine	1g IV q6h

In addition to parenteral antibiotics, some gravidas with pyelonephritis also will initially require hydration to correct intravascular volume deficits and electrolyte imbalances, antipyretic treatment, and tocolysis.

Recognizing that outpatient oral treatment of acute pyelonephritis in nonpregnant patients has been proven safe and effective (60), successful trials of outpatient treatment for pregnant women with uncomplicated pyelonephritis also have been published (61–63). Angel and colleagues compared oral and intravenous cephalosporin treatments of pyelonephritis in pregnancy, reporting excellent results for both forms of administration (91% and 93% success rates, respectively) (61). Millar and colleagues demonstrated the efficacy of outpatient treatment for pyelonephritis in women with pregnancies of gestational age both less than 24 weeks and after 24 weeks (62,63). Their protocol at less than 24 weeks compared initial parenteral ceftriaxone for outpatient treatment with cefazolin for inpatient treatment (both followed by oral cephalexin 500mg four times daily for 10 days), with similar culture-negative success rates (78–80%) at follow-up 2 weeks after completion of therapy. However, inpatients receiving initial cefazolin were more likely to remain febrile for more than 3 days or require a change in antibiotic. Millar's subsequent study of women with pyelonephritis after 24 weeks of gestational age treated all participants with ceftriaxone 1g IM twice (24 hours apart), then cephalexin 500mg orally four times daily for 10 days, and led to 91% culture-negative success at 2-week follow-up. The majority of the women randomized to outpatient treatment were discharged with follow-up within 2 to 3 days, but 28% remained hospitalized for complications including sepsis or preterm labor. The cited studies comparing inpatient and outpatient therapy for pyelonephritis in pregnancy share comparable success rates and lack of complications for both strategies. Furthermore, the published outpatient strategies, limiting the outpatient option to otherwise uncomplicated patients, share a conservative approach of initial hospital observation and prompt outpatient follow-up.

A meta-analysis of randomized control studies of treatments for symptomatic UTIs during pregnancy reviewed six pyelonephritis studies and concluded that data are insufficient to recommend any specific best strategy among the study protocols (64). Factors to consider in selecting an empiric regimen may then include local resistance patterns and costs.

The benefit of chronic antibiotic prophylaxis after primary treatment for pyelonephritis has been demonstrated by Harris and Gilstrap (9), who reduced the 60% risk of recurrent pyelonephritis in their population to 3% by continuing broad-spectrum antibiotic prophylaxis after primary therapy throughout the duration of pregnancy. Nitrofurantoin macrocrystals 50mg every day is an excellent choice for prophylaxis. Note, however, that such prophylaxis is effective only if the primary antibiotic therapy is appropriate for the etiologic organism (56). Although most early studies on the potential benefit of prophylactic antibiotics following acute pyelonephritis in pregnancy ended prophylaxis at the time of delivery (9,65), Sandberg extended the prophylaxis for a month postpartum (66), and many subsequent studies have extended prophylaxis until 6 weeks postpartum (62,63).

Frequent follow-up urine cultures may suffice as an alternative to chronic antibiotic prophylaxis following pyelonephritis in pregnancy. In a study tracking urine cultures every 2 weeks and comparing the option of chronic nitrofurantoin following treated pyelonephritis, gravidas not receiving prophylaxis were no more likely to get recurrent symptomatic UTI (14% vs. 8%); however, they were nearly twice as likely to have a subsequent positive urine culture (59% vs. 33%, $p < 0.02$) (66). The cost of multiple urine cultures will probably exceed the cost of prophylactic nitrofurantoin.

Following appropriate parenteral antimicrobial therapy, clinical improvement occurs quickly, with resolution of fever anticipated within 48 hours in 85% of patients (67). In the uncommon event of no improvement after 48 to 72 hours of appropriate antibiotic therapy, consideration should be given to complicating factors such as obstruction, cortical abscess, papillary necrosis, or perinephric abscess. A renal ultrasound scan will detect many of the treatable complications that could delay response to therapy. However, ultrasonography has only one-quarter of the sensitivity of non-enhanced helical computed tomography for the detection of renal calculi (68).

Transient renal dysfunction has been demonstrated during acute pyelonephritis, with a reduction of endogenous creatinine clearance to ≤ 80 mL/min in 27% of patients, and an incidence of approximately 20% for elevated blood urea nitrogen (>11 mg/dL) and serum creatinine (>1 mg/dL) (1,69). The urinary tract is the most common site of origin for gram-negative sepsis, and bacteremia occurs in up to 17% of patients with pyelonephritis. Bacteremia in the presence of pyelonephritis is usually an incidental finding, but it may also present as septic shock. Cunningham and co-workers reported a 3% incidence of septic shock among gravidas with acute pyelonephritis (67). Septic shock occurs secondary to endotoxemia or exotoxemia, and may lead to diffuse organ failure. Acute renal failure secondary to acute tubular necrosis may further compromise the transient renal dysfunction commonly seen with pyelonephritis. Pulmonary insufficiency, including dyspnea, tachypnea, hypoxemia, and pulmonary infiltrates, complicates 7% of gravidas with pyelonephritis (51). Septic shock complicating pyelonephritis may also cause hemolysis, thrombocytopenia, hepatic dysfunction, and adult respiratory distress syndrome. A syndrome of noncardiogenic pulmonary edema, with or without renal, hepatic, or hematopoietic dysfunction, has been reported in 2% of pregnant patients with pyelonephritis (70). This syndrome typically appears within 30 hours of admission and manifests as dyspnea, tachypnea, hypoxemia, and pulmonary effusions and consolidation; 20% of patients require mechanical ventilation, and most recover within 2 to 3 days.

An association between pyelonephritis and both preterm delivery and increased perinatal mortality was recognized in the pre-antibiotic era; however, appropriate antibiotic therapy appears nearly to eliminate these risks. Gilstrap and co-workers reported a higher rate of low birth weight for women with pyelonephritis (<2500 g, 15% incidence vs. 10% in controls) (71), but no increase in perinatal mortality rate, and Fan and associates found no increase in low birth weight, size small for gestational age, or preterm delivery (50).

REFERENCES

- Gilstrap LC III, Cunningham FG, Whalley PJ. Acute pyelonephritis in pregnancy: an anterospective study. *Obstet Gynecol* 1981; 57: 409–13.
- Buckley RM Jr, McGuckin M, MacGregor RR. Urine bacterial counts after sexual intercourse. *N Engl J Med* 1978; 298: 321–4.
- Lomberg H, Cedergren B, Leffler H, et al. Influence of blood group on the availability of receptors for attachment of uropathogenic *Escherichia coli*. *Infect Immun* 1986; 51: 919–26.
- Diokno AC, Compton A, Seski J, Vinson R. Urologic evaluation of urinary tract infection in pregnancy. *J Reprod Med* 1986; 31: 23–6.
- Schieve LA, Handler A, Hershow R, et al. Urinary tract infection during pregnancy: its association with maternal morbidity and perinatal outcome. *Am J Public Health* 1994; 84: 405–10.
- Harris RE, Gilstrap LC III. Cystitis during pregnancy: a distinct clinical entity. *Obstet Gynecol* 1981; 57: 578–80.
- Campbell-Brown M, McFadyen IR, Seal DV, Stephenson ML. Is screening for bacteriuria in pregnancy worthwhile? *Br Med J* 1987; 294: 1579–82.
- Wood EG, Dillon HC Jr. A prospective study of group B streptococcal bacteriuria in pregnancy. *Am J Obstet Gynecol* 1981; 140: 515–20.
- Harris RE, Gilstrap LC III. Prevention of recurrent pyelonephritis during pregnancy. *Obstet Gynecol* 1974; 44: 637–41.
- Feldkamp ML, Reefhuis J, Kucik J, et al. Case-control study of self reported genitourinary infections and risk of gastroschisis: findings from the national birth defects prevention study, 1997–2003. *BMJ* 2008; 336: 1420–3.
- Cleves MA, Malik S, Yang S, et al. Maternal urinary tract infections and selected cardiovascular malformations. *Birth Defects Res (Part A)* 2008; 82: 464–73.
- Karlowsky JA, Jones ME, Thornsberry C, et al. Prevalence of antimicrobial resistance among urinary tract pathogens isolated from female outpatients across the US in 1999. *Int J Antimicrob Agents* 2001; 18: 121–7.
- Jamie WE, Edward RK, Duff P. Antimicrobial susceptibility of Gram-negative uropathogens isolated from obstetric patients. *Infect Dis Obstet Gynecol* 2002; 10: 123–6.
- Treatment of urinary tract infections in nonpregnant women. ACOG Practice Bulletin No. 91, American College of Obstetricians and Gynecologists. *Obstet Gynecol* 2008; 111: 785–94.
- Wright SW, Wrenn KD, Haynes ML. Trimethoprim-sulfamethoxazole resistance among urinary coliform isolates. *J Gen Intern Med* 1999; 14: 606–9.
- Hernandez-Diaz S, Werler MM, Walker AM, Mitchell AA. Folic acid antagonists during pregnancy and the risk of birth defects. *N Engl J Med* 2000; 343: 1608–14.
- Forna F, McConnell M, Kitabire FN, et al. Systemic review of the safety of trimethoprim-sulfamethoxazole for prophylaxis in HIV-infected pregnant women: implications for resource-limited settings. *AIDS Reviews* 2006; 8: 24–36.
- Sivojelezova A, Einarson A, Shuhaiber S, Koren G. Trimethoprim-sulfonamide combination therapy in early pregnancy. *Can Fam Physician* 2003; 49: 1085–6.
- Kammire LD, Donofrio PD. Nitrofurantoin neuropathy: a forgotten adverse effect. *Obstet Gynecol* 2007; 110: 510–12.
- D'Arcy PF. Nitrofurantoin. *Drug Intell Clin Pharm* 1985; 19: 540–7.
- Ben David S, Einarson T, Ben David Y, et al. The safety of nitrofurantoin during the first trimester of pregnancy: meta-analysis. *Fundam Clin Pharmacol* 1995; 9: 503–7.
- Gait JE. Hemolytic reactions to nitrofurantoin in patients with glucose-6-phosphate dehydrogenase deficiency: theory and practice. *Ann Pharmacother* 1990; 24: 1210–13.
- Cimolai N, Cimolai T. Nitrofurantoin and pregnancy. *Can Med Assoc J* 2007; 176: 1860–1.
- Kirkwood A, Harris C, Timar N, Koren G. Is gentamycin ototoxic to the fetus? *J Obstet Gynaecol Can* 2007; 29: 140–5.
- Czeizel AE, Rockenbauer N, Olsen J, Sorensen HT. A teratological study of aminoglycoside antibiotic treatment during pregnancy. *Scand J Infect Dis* 2000; 32: 309–13.
- Larsen H, Nielsen GL, Schonheyder HC, et al. Birth outcome following maternal use of fluoroquinolones. *Int J Antimicrob Agents* 2001; 18: 259–62.
- Bayrak O, Cimentepe E, Inegöl I, et al. Is single-dose fosfomycin trometamol a good alternative for asymptomatic bacteriuria in the second trimester of pregnancy? *Int Urogynecol J Pelvic Floor Dysfunct* 2007; 18: 525–9.
- Krcmery S, Hromec J, Demesova D. Treatment of lower urinary tract infection in pregnancy. *Intl J Antimicrob Agents* 2001; 17: 279–82.
- Stamm WE, Counts GW, Running KR, et al. Diagnosis of coliform infection in acutely dysuric women. *N Engl J Med* 1982; 307: 463–8.
- Greenberg RN, Reilly PM, Luppen KL, et al. Randomized study of single-dose, three-day, and seven-day treatment of cystitis in women. *J Infect Dis* 1986; 153: 277–82.
- Jaimes EC, Garcia JLA, Salinas JO, et al. Cistourethritis aguda durante la gestacion. *Ginec Obst Mex* 1989; 57: 57–63.
- Pfau A, Sacks TG. Effective prophylaxis for recurrent urinary tract infections during pregnancy. *Clin Infect Dis* 1992; 14: 810–14.
- Turck M, Goffe BS, Petersdorf RG. Bacteriuria of pregnancy. Relation to socioeconomic factors. *N Engl J Med* 1962; 266: 857–60.
- Van Dorsten JP, Bannister ER. Office diagnosis of asymptomatic bacteriuria in pregnant women. *Am J Obstet Gynecol* 1986; 155: 777–80.
- Golan A, Wexler S, Amit A, et al. Asymptomatic bacteriuria in normal and high-risk pregnancy. *Eur J Obstet Gynecol Reprod Biol* 1989; 33: 101–8.
- Nicolle LE, Bradley S, Colgan R, et al. Infectious Diseases Society of America guidelines for the diagnosis and treatment of asymptomatic bacteriuria in adults. *Clin Inf Dis* 2005; 40: 643–54.
- Smaill F. Asymptomatic bacteriuria in pregnancy. *Best Pract Res Clin Obstet Gynaecol* 2007; 21: 439–50.
- McIsaac W, Carroll JC, Biringer, et al. Screening for asymptomatic bacteriuria in pregnancy. *J Obstet Gynaecol Can* 2005; 27: 20–4.
- Kincaid-Smith P, Bullen M. Bacteriuria in pregnancy. *Lancet* 1965; 1: 395–9.
- Sweet RL. Bacteriuria and pyelonephritis during pregnancy. *Semin Perinatol* 1977; 1: 25–40.
- Romero R, Oyarzun E, Mazor M, et al. Meta-analysis of the relationship between asymptomatic bacteriuria and preterm delivery/low birth weight. *Obstet Gynecol* 1989; 73: 576–82.
- US Preventive Services Task Force. Screening for asymptomatic bacteriuria in adults: US Preventive Services Task Force reaffirmation recommendation statement. *Ann Intern Med* 2008; 149: 43–7.
- American Academy of Pediatrics, American College of Obstetricians and Gynecologists. Guidelines for Perinatal Care, 6th edn. Elk Grove Village, IL, and Washington, DC: American Academy of Pediatrics and American College of Obstetricians and Gynecologists 2007: 100–1.
- Kacmaz B, Kahir O, Aksoy A, Biri A. Evaluation of rapid screening tests to detect asymptomatic bacteriuria in pregnancy. *Jpn J Infect Dis* 2006; 59: 261–3.
- Roberts AP, Robinson RE, Beard RW. Some factors affecting bacterial colony counts in urinary infection. *Br Med J* 1967; 1: 400–3.
- Whalley PJ, Cunningham FG. Short-term versus continuous antimicrobial therapy for asymptomatic bacteriuria in pregnancy. *Obstet Gynecol* 1977; 49: 262–5.
- Villar J, Widmer M, Lydon-Rochelle MT, et al. Duration of treatment for asymptomatic bacteriuria during pregnancy. *Cochrane Database Syst Rev* 2000; (2): CD000491. DOI:10.1002/14651858.CD000491.
- Smaill F, Vazquez JC. Antibiotics for asymptomatic bacteriuria in pregnancy. *Cochrane Database Syst Rev* 2007; (2): CD000490. DOI:10.1002/14651858.CD000490.pub2.
- Kass EH. Bacteriuria and pyelonephritis of pregnancy. *AMA Arch Int Med* 1960; 105: 194–8.
- Fan Y, Pastorek JG II, Miller JM Jr, et al. Acute pyelonephritis in pregnancy. *Am J Perinatol* 1987; 4: 324–6.
- Hill JB, Sheffield JS, McIntire DD, Wendel GD. Acute pyelonephritis in pregnancy. *Obstet Gynecol* 2005; 105: 18–23.
- Thurman AR, Steed LL, Hulsey T, Soper DE. Bacteriuria in pregnancy women with sickle cell trait. *Am J Obstet Gynecol* 2006; 194: 1366–70.
- Villers MS, Jamison MG, DeCastro LM, James AH. Morbidity associated with sickle cell disease in pregnancy. *Am J Obstet Gynecol* 2008; 199: 125.e1–5.
- MacMillan MC, Grimes DA. The limited usefulness of urine and blood cultures in treating pyelonephritis in pregnancy. *Obstet Gynecol* 1991; 78: 745–8.
- Duff P. Pyelonephritis in pregnancy. *Clin Obstet Gynecol* 1984; 27: 17–31.

56. Van Dorsten JP, Lenke RR, Schiffrin BS. Pyelonephritis in pregnancy. The role of in-hospital management and nitrofurantoin suppression. *J Reprod Med* 1987; 32: 895–900.
57. Greer LG, Roberts SW, Sheffield JS, et al. Ampicillin resistance and outcome differences in acute antepartum pyelonephritis. *Infect Dis Obstet Gynecol* 2008; 2008: 891426. DOI:10.1155/2008/891426.
58. Sanchez-Ramos L, McAlpine JK, Adair CD, et al. Pyelonephritis in pregnancy: once-a-day ceftriaxone versus multiple doses of cefazolin. A randomized, double-blind trial. *Am J Obstet Gynecol* 1995; 172: 129–33.
59. Wing DA, Hendershott CA, Debuque L, Millar LK. A randomized trial of three antibiotic regimens for the treatment of pyelonephritis in pregnancy. *Obstet Gynecol* 1998; 92: 249–53.
60. Safrin S, Siegel D, Black D. Pyelonephritis in adult women: in-patient versus outpatient therapy. *Am J Med* 1988; 85: 793–8.
61. Angel JL, O'Brien WF, Finan MA, et al. Acute pyelonephritis in pregnancy: a prospective study of oral versus intravenous antibiotic therapy. *Obstet Gynecol* 1990; 76: 28–32.
62. Millar LK, Wing DA, Paul RH, Grimes DA. Outpatient treatment of pyelonephritis in pregnancy: a randomized controlled trial. *Obstet Gynecol* 1995; 86: 560–4.
63. Wing DA, Hendershott CA, Debuque L, Millar LK. Outpatient treatment of acute pyelonephritis in pregnancy after 24 weeks. *Obstet Gynecol* 1999; 94: 683–8.
64. Vazquez JC, Villar J. Treatments for symptomatic urinary tract infections during pregnancy. *Cochrane Database Syst Rev* 2003; (4): CD002256. DOI:10.1002/14651858.CD002256.
65. Lenke RR, VanDorsten JP, Schiffrin BS. Pyelonephritis in pregnancy: a prospective randomized trial to prevent recurrent disease evaluating suppressive therapy with nitrofurantoin and close surveillance. *Am J Obstet Gynecol* 1983; 146: 953–7.
66. Sandberg T, Brorson J-E. Efficacy of long-term antimicrobial prophylaxis after acute pyelonephritis in pregnancy. *Scand J Infect Dis* 1991; 23: 221–3.
67. Cunningham FG, Morris GB, Mickal A. Acute pyelonephritis of pregnancy: a clinical review. *Obstet Gynecol* 1973; 42: 112–17.
68. Fowler KA, Locken JA, Duchesne JH, Williamson MR. US for detecting renal calculi with non-enhanced CT as a reference standard. *Radiology* 2002; 110: 109–13.
69. Whalley PJ, Cunningham FG, Martin FG. Transient renal dysfunction associated with acute pyelonephritis of pregnancy. *Obstet Gynecol* 1975; 46: 174–7.
70. Cunningham FG, Lucas MJ, Hankins GDV. Pulmonary injury complicating antepartum pyelonephritis. *Am J Obstet Gynecol* 1987; 156: 797–804.
71. Gilstrap LC, Leveno KJ, Cunningham FG, et al. Renal infection and pregnancy outcome. *Am J Obstet Gynecol* 1981; 141: 709–16.