

Review Article

Urinary Tract Infection in Pregnancy: Review of Clinical Management

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Abstract

Urinary tract infection (UTI) is an important health problem all over the world. Pregnant women are in higher risk for UTI because of physiological adaptations, and several studies have described a relationship between adverse outcomes and maternal UTI. Acute cystitis should be suspected in pregnant women who complain about dysuria, while most cases of pyelonephritis occur during the second and third trimesters, and complications include septic shock syndrome, anemia, bacteremia, respiratory insufficiency, and renal dysfunction. Pregnancy is a period that asymptomatic bacteriuria has a different meaning: indication for treatment is required as well as prevents recurrence of UTI during pregnancy is essential given the severity of possible complications. This review summarizes epidemiology, clinical features and clinical management of this important infection in pregnancy.

Keywords

- Urinary tract infection
- Pregnancy
- Asymptomatic bacteriuria
- Dysuria
- Pyelonephritis
- Recurrent urinary infection

ABBREVIATIONS

UTI: Urinary Tract Infection; ESBL: Extended-Spectrum Beta-Lactamase (ESBL)-Producing Bacteria.

INTRODUCTION

Urinary tract infections (UTI) are common during pregnancy [1]. Women are significantly more likely to be affected by UTI due to anatomical issues, such as proximity of the urethra to the anus [2]. Pregnant women are in higher risk for UTI because of physiological adaptations, like increase in plasma volume, could result in decreased urine concentration, facilitating bacterial growth. Additionally, 90% of pregnant women develop anatomical changes such as dilatation of urethra and decreased bladder tone leading to urinary stasis [3–5].

Risk of UTI begins in the 6th week and has its peak during the 22–24th weeks [3,4]. Currently, it is one of the most frequent causes of admission in obstetrical wards resulting in an hospitalization period of approximately three days [6]. Untreated UTI or asymptomatic bacteriuria during pregnancy may lead to serious consequences for maternal life and fetus, like higher risk of pyelonephritis, sepsis and transient renal failure; and complicated outcomes such as intrauterine growth restriction, preeclampsia and premature delivery [7,8].

Therefore, it is important to screen, raise suspicion and know how to recognize this condition, intending to promptly initiate appropriate treatment in order to minimize complications associated with UTI. This article aims to review and compile the

current evidence about this issue, since it can be considered a public health problem all over the world.

Epidemiology

Incidence of bacteriuria in pregnant women is roughly the same as in non-pregnant women; however, recurrent bacteriuria is more frequent during pregnancy. Additionally, the incidence of pyelonephritis is higher than in the general population, likely as a result of physiologic changes in the urinary tract during pregnancy [7]. Factors that have been associated with a higher risk of bacteriuria include history of prior urinary tract infection, pre-existing diabetes mellitus, increased parity, and low socioeconomic status. The estimated incidence of asymptomatic bacteriuria is 2 to 7 percent of pregnant women, acute cystitis occurs in approximately 1 to 2 percent and acute pyelonephritis in 0.5 to 2 percent [9,10].

Several studies have described a relationship between adverse outcomes and maternal urinary tract infection, particularly asymptomatic bacteriuria and acute pyelonephritis. Untreated bacteriuria has been associated with an increased risk of preterm birth, low birth weight, and perinatal mortality. Pyelonephritis, however, has been associated with anemia, sepsis, maternal and perinatal mortality. Development of preeclampsia is associated with maternal UTI (asymptomatic bacteriuria or symptomatic infection) during pregnancy [11]. Minassian *et al* demonstrated increased odds (1.22-fold) of preeclampsia in women with any UTI during pregnancy versus those without UTI [12].

Escherichia coli is the predominant uropathogen found

in both asymptomatic bacteriuria and UTI (cystitis and pyelonephritis) in approximately 70 to 90% of cases. Other organisms responsible for UTI included *B Streptococcus* (10%), *Klebsiella* and *Enterobacter* species (3% each), and *Proteus* and *Staphylococcus saprophyticus* (2% each). Some urea-splitting bacteria, including *Proteus*, Coagulase-negative *Staphylococcus*, *Klebsiella*, *Pseudomonas*, alkalize the urine and may be associated with struvite stones. Chlamydial infections are associated with sterile pyuria and account for more than 30% of atypical pathogens. Isolation of more than one species or the presence of *Lactobacillus* or *Propionibacterium* may indicate a specimen contaminated by vaginal or skin flora. However, repeated isolation of *Lactobacillus* with high colony counts ($\geq 10^5$ cfu/mL) can be eligible for treatment. Infections caused by extended-spectrum beta-lactamase (ESBL)-producing strains are increasing in number, even in uncomplicated UTI, and becoming a world health problem even in community settings [7,13,14].

Cystitis

Symptomatic infection of the bladder is called cystitis and clinical symptoms are the same in pregnant and non-pregnant women: dysuria, hematuria, pyuria, urinary urgency and frequency. Acute cystitis should be suspected in pregnant women who complain about dysuria, and urinalysis and urine culture should be performed in order to guide the best antibiotic treatment. Dysuria in pregnant women can also be a result of vaginitis or urethritis and can be distinguished by the presence of bacteriuria. The diagnosis is confirmed by finding of bacterial growth on urine culture in a symptomatic pregnant woman: quantitative count $\geq 10^5$ colony forming units (cfu)/mL, or $\geq 10^3$ cfu/mL and pyuria (> 7 white blood cells/mL). [7,13]

Treatment of acute cystitis in pregnant women includes empiric antibiotic therapy initiated at the time of complaints of dysuria, subsequently tailored to culture results to the susceptibility pattern of the isolated organism and follow-up cultures must be done to confirm sterilization of the urine (Figure1). Empirical treatment agents should also take into account any prior microbiological data and drug safety, including the particular stage of pregnancy. [14] Table 1 shows the potential antimicrobial agents and the choice between them should be individualized on the basis of several factors, including patient allergy history, local practice patterns, local community resistance prevalence, availability, and cost. A meta-analysis suggested that there are no large differences in outcomes between different antibiotic regimens in terms of cure rates, recurrent infection, incidence of preterm delivery, and the need for a change of antibiotics [15,16].

Optimal duration of treatment of cystitis is uncertain, but usually three to seven days are enough. There appear to be no differences between short and longer antibiotic courses and single-dose therapy is limited to fosfomycin. Patients who are at risk for or have documented infection with ESBL-producing Enterobacteriaceae can be treated with nitrofurantoin and fosfomycin and subsequently tailored to culture results. For those women with persistent or recurrent bacteriuria, prophylactic or suppressive antibiotics may be warranted in addition to retreatment [14–16].

Pyelonephritis

Infection of the upper urinary tract and kidneys is called pyelonephritis, and typical symptoms in the pregnant and non-pregnant women are the same. Typical symptoms include fever ($>38^\circ\text{C}$ or 100.4°F), flank pain, nausea, vomiting, pyuria, costovertebral angle tenderness, and is confirmed by the finding of bacteriuria in the setting of these symptoms. Flank pain is a common symptom due to pregnancy-induced hydronephrosis and most commonly unilateral over the involved kidney, although bilateral discomfort may be present. Calyceal and ureteral dilatation are more common on the right side in 86% of cases and this dilatation appears to begin by the 10th week and worsens throughout pregnancy [7]. Most cases of pyelonephritis occur during the second and third trimesters (2% during the first, 52% during the second, and 46% in the third trimester) and complications include septic shock syndrome, anemia, bacteremia, respiratory insufficiency, and renal dysfunction. Mechanism of anemia is not well understood, but hemolysis, perhaps mediated by endotoxin, may be important. Acute renal failure associated with microabscesses and suppurative pyelonephritis has been described in isolated cases, independent of sepsis. [13,15]

Urinalysis and urine culture are important for diagnosis of pyelonephritis in pregnant women who present with typical symptoms. Pyuria is present in majority of women with pyelonephritis, and its absence suggests an alternative diagnosis or complete obstruction. Pregnant women who have back or flank pain should be evaluated for bacteriuria and a diagnosis of pyelonephritis, given the risk of complications [13,15]. Blood cultures are important for patients with signs of sepsis or serious underlying medical conditions such as diabetes [16].

Imaging is routinely used to diagnose pyelonephritis in patients who are severely ill, have symptoms of renal colic or history of renal stones, diabetes, history of prior urologic surgery, immunosuppression, repeated episodes of pyelonephritis, or urosepsis. In pregnant women, renal ultrasound is the preferred imaging modality in order to avoid contrast or radiation exposure. If symptoms and fever persist beyond the first 24 to 48 hours of treatment, a repeat urine culture and renal ultrasound should be performed to rule out persistent infection and urinary tract pathology. [10,13,15]

Differential diagnosis in pregnant women presenting with fever and/or flank or back pain are important, such as nephrolithiasis, placental abruption, intraamniotic and bacterial infections [17]. Nephrolithiasis is characterized as significant flank or back pain and abnormal findings on the urinalysis, but fever is uncommon and it can also be distinguished by visualization of the stones on renal ultrasound. Kidney stones should initially be treated conservatively because 50-67% of stones diagnosed during pregnancy pass spontaneously. Conservative therapy includes appropriate antibiotic coverage, adequate hydration, and systemic analgesics (usually narcotics, which are class C agents in pregnancy). Surgical treatments are required in 20-30% and used to provide temporizing drainage of an obstructed system with placement of a ureteral stent or percutaneous nephrostomy, to delay treatment until completion of the pregnancy, or to definitively diagnose and treat the stone

with ureteroscopic methods. Placental abruption is another cause of acute back or abdominal pain during pregnancy. Fever is absent, but vaginal bleeding and a rigid and tender uterus are classically present with abruption, and a retroplacental hematoma on magnetic resonance or ultrasound supports the diagnosis of abruption [18]. Other potential causes of fever and back or flank pain in the absence of bacteriuria include other bacterial infections, such as pneumonia and appendicitis. Intraamniotic infection is also an important diagnostic in pregnant women who should be evaluated for premature rupture of membranes, uterine tenderness and/or foul odor of the amniotic fluid, and the absence of bacteriuria [17–19].

Pyelonephritis should be treated with hospitalization and intravenous antibiotics until the woman is afebrile for 24 to 48 hours and symptomatically improved. Initial empiric therapy of pyelonephritis should be done with parenteral, broad spectrum beta-lactams (Figure1). The choice between them should be guided by local microbiology and susceptibility data as well as expected patient tolerance (Table 1). Fluoroquinolones and aminoglycosides, which are often used for pyelonephritis in non-pregnant individuals, should be avoided during pregnancy. Once afebrile for 48 hours, pregnant patients can be switched to oral therapy guided by culture susceptibility results and discharged to complete 10 to 14 days of treatment. Agents of choice for initial intravenous therapy are: ceftriaxone, amoxicillin-clavulonate or ampicillin plus gentamicin. Oral options for hospital discharge are mainly limited to beta-lactams, such as oral cephalexin or amoxicillin-clavulonate, and if in the second trimester, trimethoprim-sulfamethoxazole can be an option. Nitrofurantoin and fosfomycin are not appropriate for treatment of pyelonephritis due to inadequate tissue levels [20–24].

Efficacy of beta-lactams was demonstrated in a randomized trial of 179 pregnant women with acute pyelonephritis before the 24th week of gestation: intravenous cefazolin or intramuscular ceftriaxone had equivalent efficacy to intravenous ampicillin plus gentamicin. For women with a history of infections with ESBL-producing Enterobacteriaceae (or other risk factors), a carbapenem is an appropriate choice for empiric therapy. Of note, some animal studies have shown adverse fetal effects with imipenem-cilastatin, so ertapenem, meropenem or doripenem are the preferred carbapenems for use during pregnancy [24–27].

Asymptomatic Bacteriuria

Asymptomatic bacteriuria means the isolation of a specified semi-quantitative count of bacteria in an adequate sample of urine collected from a person without symptoms related to UTI [28]. However, the optimal method for collecting urine is not yet established. Routinely, recommendation is to clean urethral meatus and collecting urine midstream, intending to minimize contamination of the sample [29]. Although, it is not clear that these measures reduce contamination rates and several authors have questioned the validity of the clean-catch midstream technique. [30–32]. Overall rates of contamination are high in various methods of collecting even in people well informed about the technique [32,33].

For women, bacteriuria is defined as two consecutive urine specimens with isolation of the same bacterial strain in quantitative counts $\geq 10^5$ cfu/mL or a single catheterized urine specimen with one bacterial species isolated in a quantitative count $\geq 10^2$ cfu/mL. [7]

Pregnancy is a period that asymptomatic bacteriuria has

Table 1: Antibiotics for urinary tract infection in pregnant women.

Antibiotic	Dose	Duration	Indication	Notes
Nitrofurantoin monohydrate/ macrocrystals	100 mg orally every 12 hours	5-7 days	AS,C	Avoid during the first trimester.
Amoxicillin	500 mg orally every 8 hours	3-7 days	AS, C	Bactericidal against uropathogens.
Amoxicillin-clavulanate	500 mg orally/IV every 8 hours	7-10 days	C, P	Choice for beta-lactam resistant pathogens.
Ampicillin-sulbactam	3g IV every 6 hours	10-14 days	C, P	Choice for beta-lactam resistant pathogens.
Ampicillin + Gentamicina	1-2g every 6 hours IV 1.5mg/kg IV every 8 hours	10-14 days	P	First choice for inpatients with pyelonephritis
Cephalexin	500 mg orally every 6 hours	3-7 days	AS,C	Bactericidal against uropathogens.
Cefpodoxime	100 mg orally every 12 hours	3-7 days	AS,C	Bactericidal against uropathogens.
Ceftriaxone	1 g IV or IM every 24 hours	10-14 days	P	Choice for outpatient
Cefepime	1 g IV every 12 hours	10-14 days	P	Choice for HAI.
Piperacillin-tazobactam	3.375 g IV every 6 hours	10-14 days	P	Choice for HAI
Trimethoprim-sulfamethoxazole	800/160 mg (one double strength tablet) every 12 hours	3-7 days	AS,C	Avoid during the first trimester and at term
Ertapenem	1 g every IV or IM 24 hours	10-14 days	P	ESBL treatment
Meropenem	1g IV every 8 hours	10-14 days	P	ESBL treatment
Doripenem	500 mg IV every 8 hours	10-14 days	P	ESBL treatment
Fosfomycin	3 g orally as single dose	Single dose	AS,C	Bactericidal against uropathogens.

Abbreviations: AS: Asymptomatic Bacteriuria; C: Cystitis; P: Pyelonephritis; IV: Intravenous; IM: Intramuscular; HAI: Healthcare-Associated Infection; ESBL: Extended-Spectrum Beta-Lactamase (ESBL)-Producing Bacteria

a different meaning since treatment is required according to international guidelines [7]. Reasons for this indication stem from the fact that asymptomatic bacteriuria in pregnancy increases the risk of adverse outcomes, progression to pyelonephritis [34,35] and without treatment nearly 40% of pregnant woman will develop symptomatic UTI [11]. It commonly occurs during the early pregnancy, period in which screening is indicated [7]. Prevalence of bacteriuria during pregnancy varies between 2-10% [36], remaining constant even in the developing countries [37,38]. and it could be associated with a previous story of UTI, diabetes mellitus, multiparity, low socioeconomic status and illiteracy [9,39].

E. coli is the most common microorganism isolated in urine samples in women with asymptomatic bacteriuria [40]. Group B Streptococcus, *Klebsiella sp* and other Enterobacteriaceae species are frequently associated [7]. Adequate antimicrobial therapy, directed accordingly to the susceptibility panel of the isolated bacteria, while also taking into account safety during pregnancy is strongly recommended, as can be seen in Figure 1 [7,11]. The rationale of treatment is to minimize the negative outcomes, such as pyelonephritis and low birth weight and preterm birth [11]. However, optimal duration of antimicrobial therapy is still controversial. Seemingly, single dose regimen is less effective

than seven-day regimen. So, pregnant women should be treated with short-course therapy, consisting in three to seven days of treatment. Since 30% of women fail to clear asymptomatic bacteriuria following a short course of therapy, a follow-up culture should be obtained as a test of cure after completion of the treatment [7,41,42].

Recurrent urinary tract infections

Recurrent UTI is a common health-care problem in women, especially during pregnancy. There are several possible definitions for recurrent UTI in pregnancy, but one of the most accepted is: pregnant women with a new episode of UTI and previous history of one or more UTI before or during pregnancy [43]. It occurs in 4-30% of pregnancies, [44,45] and tends to recur in the 3 subsequent months after the initial infection [46].

Pathogenesis of recurrent UTI is similar than initial episode. Uropathogens, usually originated from rectal flora, ascend to the bladder after colonizing the urethra. Probably, recolonization occurs because the bacteria had not been eliminated with the prior treatment [43,47,48]. *E. coli* is the most causative pathogen involved in recurrent UTI, which is responsible for about 80% of all episodes [48]. Main risk factors for recurrent UTI are the age of first UTI (less than 15 years indicates higher risk), frequency

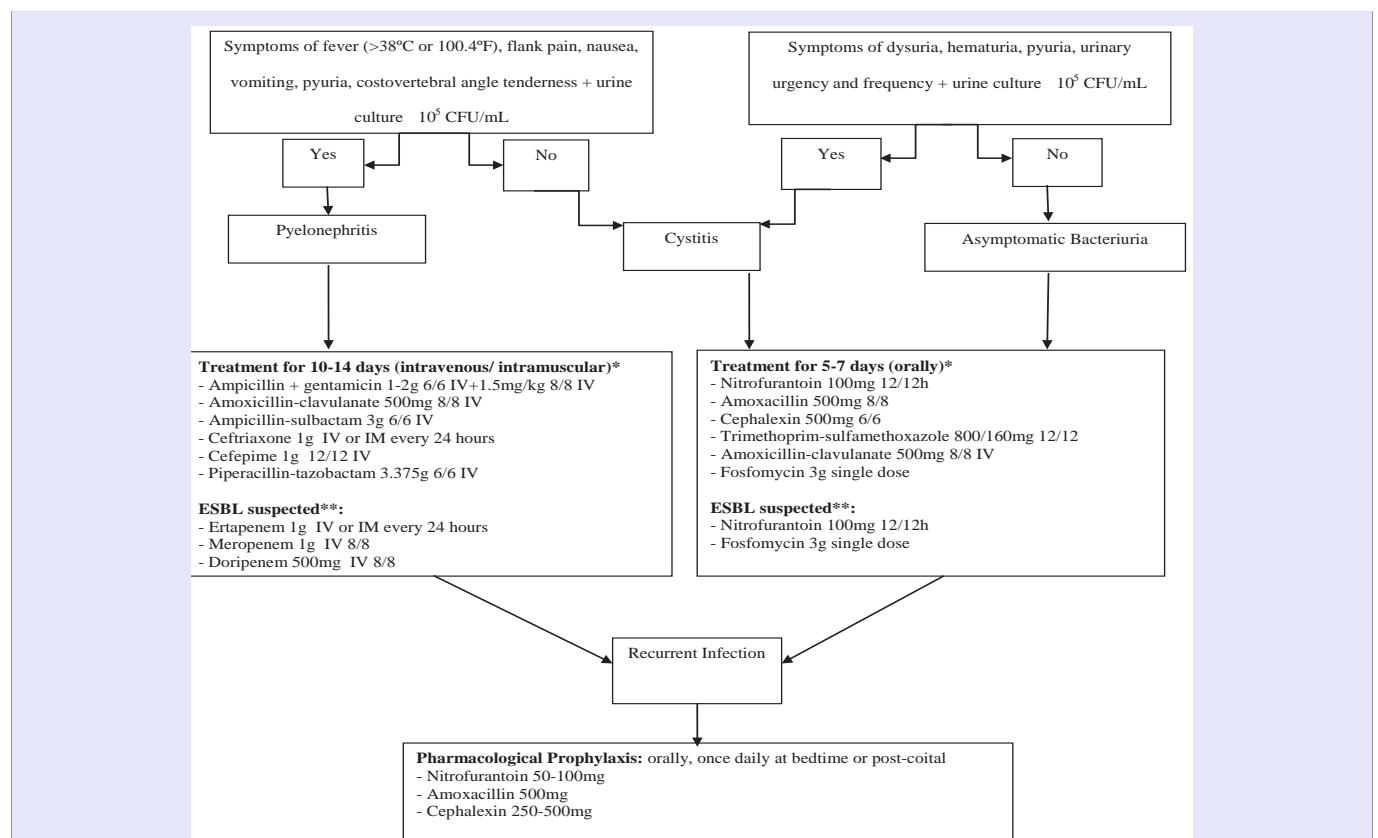


Figure 1 Empiric treatment for urinary tract infections in pregnant women.

* The choice between these agents should be individualized and based on patient allergy and compliance history, local practice patterns, local community resistance prevalence, availability, cost, and patient and provider threshold for failure.

** Antibiotic treatment should be tailored to culture results.

Abbreviations: IV: Intravenous; IM: Intramuscular; CFU: Colony- Forming Units; ESBL: Extended-Spectrum Beta-Lactamase (ESBL)-Producing Bacteria.

of sexual intercourse, use of spermicides, parity and lower socioeconomic status [43,47].

Occurrence of infections by multidrug-resistant bacteria should be actually considered as a public health problem as a result of the inadvertent use of antibiotics. ESBL-producing species are often found in hospital and community acquired UTI [49]. ESBL are found predominantly in *E. coli* and *Klebsiella* spp, but also have been described in other genera of Enterobacteriaceae. [50] Data collected in one study in Latin America shows rates of ESBL of 1.7% and 16.3% of *Klebsiella* spp and *E. coli*, respectively [51].

Prevention of UTI recurrence during pregnancy is essential given the severity of possible complications. Interventions can be pharmacological or not. Pharmacological measures consist of antibiotics given in different ways besides continuous or post-coital prophylaxis [43,52-54]. Canadian guidelines suggest that pregnant women at risk of recurrent UTI should be offered continuous or post-coital prophylaxis with nitrofurantoin or cephalexin, except during the last 4 weeks of pregnancy. Choice of antimicrobial prophylaxis should be based on the susceptibility profile of the cystitis strains. Daily or post-coital prophylaxis with low dose nitrofurantoin (50 to 100 mg) or cephalexin (250 to 500 mg) can be used [53]. Nearly 6% of pregnant women who were affected by pyelonephritis have relapses [23]. In such cases, low dose antimicrobial suppressive therapy with an agent to which the original organism is susceptible should be used for the remainder of the pregnancy. Cephalexin (250 to 500 mg) or amoxicillin (250 mg) given orally at bedtime are acceptable options (Table 2) [55].

Possibility of alternative approach by using vaccines produced from inactivated bacteria or structural components of these microorganisms is a tangible reality. Apparently, they are capable to reduce the incidence of UTI recurrence in non-pregnant women without major side effects. However, there is no evidence for pregnant women [56].

Non-pharmacological interventions include probiotics, consumption of cranberries, acupuncture and behavioral modifications. Behavioral methods may be used to ensure good hygiene and reduce bacterial contamination of the urethral meatus and include frequent and complete voiding (mainly after sexual intercourse), use of washcloths to clean the perineum or liquid soap to prevent colonization from bar soap, and clean the urethral meatus first when bathing [43,53]. Maybe the use of *Lactobacillus* species given orally or vaginally could prevent vaginal uropathogen colonization therefore preventing recurrent UTI [57,58].

CONCLUSION

Pregnant woman are at risk of serious infectious complications

Table 2: Prophylaxis for recurrent UTI during pregnancy.		
Drug	Dose (mg)	Frequency
Nitrofurantoin	50-100	QD (bedtime or post-coital)
Cephalexin	250-500	QD (bedtime or post-coital)
Amoxicillin	250	QD (bedtime or post-coital)
Abbreviations: QD: Once Daily		

from symptomatic and asymptomatic urinary tract infections. Oral antibiotics are the treatment of choice for asymptomatic bacteriuria and cystitis, while pyelonephritis requires hospital admission and intravenous antibiotics. Antibiotic prophylaxis is indicated in recurrent infection and daily prophylactic antibiotics should be continued for the duration of the pregnancy. Goals for future research include targeting screening and early treatment based on local epidemiology, as well as best preventive measures for recurrent infections.

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