



Review Article

A Review on Urinary Tract Infection in Pregnancy

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ABSTRACT

Background: Infections of the urinary tract represent a wide variety of syndromes, including urethritis, cystitis, prostatitis, and pyelonephritis. Urinary tract infections (UTIs) are the most commonly occurring bacterial infections and account for 8 million patient visits annually. Approximately 1 in 3 females will have had a urinary tract infection by age 24 years. The incidence of bacteriuria in pregnant women is similar to that in non-pregnant women. Due to several anatomical and hormonal changes, pregnant women are more susceptible to develop urinary tract infections. Pregnant women are at increased risk for UTI's starting in week 6 through week 24. *Escherichia coli* accounts for 80 to 90 percent of infections. UTIs in pregnancy are classified as either asymptomatic or symptomatic. Symptomatic urinary tract infections are divided into lower tract (acute cystitis) or upper tract (acute pyelonephritis) infections. Urine culture remains the most reliable test. A follow-up urine culture 1 to 2 weeks after completing therapy and then monthly until gestation is complete is recommended, since as many as one-third of them experience a recurrent infection. Therapy should consist of an agent administered for 7 days that has a relatively low adverse effect potential and is safe for the mother and baby. The administration of a sulfonamide, amoxicillin, amoxicillin/clavulanate, cephalexin, or nitrofurantoin is effective in 70% to 80% of patients. Tetracyclines should be avoided because of teratogenic effects. Appropriate management of UTI in pregnant women can avoid or reduce associated complications such as preterm labour, sepsis and pyelonephritis.

Keywords: Acute cystitis, pregnant women, pyelonephritis, therapy, urinary tract infection

INTRODUCTION

Urinary Tract Infection (UTI) is defined as the presence of microorganisms in the urinary tract that cannot be accounted for by contamination. The organisms present have the potential to invade the tissues of the urinary tract and adjacent structures. Infection may be limited to the growth of bacteria in the urine, which frequently may not produce symptoms. UTIs are the most commonly occurring bacterial infections and account for 8 million patients visit annually. UTI is one of the most common bacterial infections in adults, affecting more women than men

[1]. Approximately half of women have at least one UTI in their lifetime, and 20-30% have two or more [2].

UTI can present as several syndromes associated with an inflammatory response to microbial invasion and can range from asymptomatic bacteriuria to pyelonephritis with bacteraemia or sepsis.

UTIs are classified by several methods

Based on anatomic site of involvement

- Lower tract infections include
- Cystitis (bladder)
- Urethritis (urethra)
- Prostatitis (prostate gland)
- Epididymitis
- Pyelonephritis is an infection involving the kidneys and represents upper tract infection

Urinary tract infections (UTIs) are classified as

- **Uncomplicated infection** refers to an infection that occur in females of childbearing age (15 to 45 years) who are otherwise healthy female who lacks structural or functional abnormalities of the urinary tract which interferes with the normal flow of urine or voiding mechanism. Infections in males generally are not classified as uncomplicated because these infections are rare and most often represent a structural or neurologic abnormality [3].
- **Complicated UTIs** are associated with predisposing lesion of the urinary tract, such as a distortion of the urinary tract, a stone, indwelling catheter, prostatic hypertrophy, obstruction or congenital abnormality or neurologic deficit which interferes with the normal flow of urine and urinary tract defences. Complicated infections occur in both genders and frequently involve the upper and lower urinary tract [3].

Recurrent UTIs in healthy non-pregnant women, three or more UTIs occurring within 1 year, are a common problem which is characterized by multiple symptomatic infections with asymptomatic periods occurring between each episode and may be either reinfections relapses or reinfections. Re-infections are caused by different organisms than originally isolated and account for the majority of recurrent UTIs. Relapses are the development of repeated infections with the same initial organism and usually indicate a persistent infectious source [3].

The diagnosis of UTI is primarily based on signs and symptoms rather than isolated laboratory findings. Antimicrobial therapy should be tailored to each patient taking into consideration the severity of disease, individual and local patterns of antimicrobial resistance and the potential for collateral damage associated with antimicrobial use. Selection of correct drug, with right dose, and shortest clinically effective duration of therapy when possible, is key to optimal anti-microbial stewardship. Strategies to prevent recurrent UTIs and catheter-associated bacteriuria could greatly reduce the use of antimicrobials [4].

The incidence of bacteriuria in pregnant women is similar to that in non-pregnant women, the incidence of acute pyelonephritis in pregnant women with bacteriuria is significantly increased. Due to several anatomical and hormonal changes, pregnant women are more susceptible to develop urinary tract infections [5]. The uterus sits directly on top of the bladder. As the uterus grows, it increases in weight and block the drainage of urine from the bladder, causing an infection [6]. UTI is a major health problem, it has been reported among 20% of the pregnant women [7]. Pregnant women are at increased risk for UTI's starting in week 6 through week 24 [6].

Urinary tract infections in pregnancy are classified as either asymptomatic or symptomatic. Asymptomatic bacteriuria is defined as the presence of significant bacteriuria without the symptoms of an acute UTI. Asymptomatic bacteriuria is a common finding, particularly among those 65 years of age and older, when there is significant bacteriuria (>10⁵ bacteria/mL of urine) in the absence of symptoms. Symptomatic urinary tract infections or acute urethral syndrome consists of symptoms of frequency and dysuria in the absence of significant bacteriuria. Symptomatic urinary tract infections are divided into lower tract (acute cystitis) or upper tract (acute pyelonephritis) infections.

Symptomatic and asymptomatic bacteriuria have been reported among 17.9% and 13.0% pregnant women, respectively [8]. Cystitis is defined as the significant bacteriuria with associated bladder mucosal invasion, whereas pyelonephritis is the significant bacteriuria with associated inflammation of the renal parenchyma, calices and pelvis. Lower urinary tract infection occurs in approximately 1% of pregnancies, while upper tract infection (pyelonephritis) occurs in 3% of pregnant women [9].

1.1 BACTERIOLOGY

UTIs caused by organisms during pregnancy are same as those found in non-pregnant patients. *Escherichia coli* accounts for 80 to 90 percent of infections. Other gram-negative rods such as *Proteus mirabilis* and *Klebsiella pneumoniae* are also common. Gram-positive organisms such as group B streptococcus and *Staphylococcus saprophyticus* are less common causes of UTI. Group B streptococcus has important implications in the management of pregnancy. Less common organisms that may cause UTI include enterococci, *Gardnerella vaginalis* and *Ureaplasma ureolyticum* [10-12].

1.2 PATHOGENESIS

In general, organisms gain entry into the urinary tract via three routes: the ascending, hematogenous (descending), and lymphatic pathways. The female urethra usually is colonized by bacteria which is believed to originate from the faecal flora. The short length of the female urethra and its proximity to the perirectal area make colonization of the urethra likely. UTIs are more common in females than in males

because of the anatomic differences in location and length of the urethra tends to support the ascending route of infections as the primary acquisition route. Pregnant women are at increased risk for UTIs which begins in week 6 and peaks during weeks 22 to 24, approximately 90 percent of pregnant women develop ureteral dilatation, which will remain until delivery (hydronephrosis of pregnancy). Increased bladder volume and decreased bladder tone and decreased ureteral tone, contribute to increased urinary stasis and ureterovesical reflux [10]. Additionally, the physiologic increase in plasma volume during pregnancy decreases urine concentration. Up to 70% of pregnant women develop glycosuria, which encourages bacterial growth in the urine. Increase in urinary progesterone and estrogens may lead to a decreased ability of the lower urinary tract to resist invading bacteria, this decreased ability may be caused by decreased ureteral tone or possibly by allowing some strains of bacteria to selectively grow [10,13]. These factors may all contribute to the development of UTIs during pregnancy.

1.3 SIGN AND SYMPTOMS OF UTI DURING PREGNANCY [14]

Urethritis

- Dysuria
- Urethral discharge- Discharge can be purulent, whitish, or mucoid. Characteristics of the discharge, such as the amount of purulence, do not reliably differentiate gonococcal from non-gonococcal urethritis.

Cystitis onset is usually sudden, typically with frequency, urgency, and burning or painful voiding of small volumes of urine.

- Nocturia along with suprapubic pain and often low back pain, is common.
- The urine is often turbid, and microscopic haematuria can occur.
- Low-grade fever may develop.

- Pneumaturia occurs when infection results from a vesicoenteric or vesicovaginal fistula or from emphysematous cystitis.

Frequent urge to urinate is common during pregnancy which makes it hard to tell the presence of cystitis, especially if symptoms are mild.

Untreated cystitis puts the patient at high risk for getting a kidney infection, especially while pregnancy. **Acute pyelonephritis**, symptoms are similar as those of cystitis.

- One third of patients have frequency and dysuria
- Chills
- Fever
- Flank pain
- Colicky abdominal pain
- Nausea
- Vomiting
- Abdominal rigidity is absent or slight, a tender, enlarged kidney is sometimes palpable. Costovertebral angle percussion tenderness is generally present on the infected side.

1.4 COMPLICATIONS OF UTI

Women with asymptomatic bacteriuria in early pregnancy have a 20–30-fold increased risk of developing pyelonephritis, compared with women without bacteriuria [15].

The prevalence of asymptomatic bacteriuria in pregnancy is about 10%. Lower serum interleukin-6 levels and serum antibody responses to *E. coli* antigens which occurs in pregnancy has been associated with increased incidence of asymptomatic bacteriuria in pregnancy [16].

Non-treated asymptomatic bacteriuria in fact represents a considerable risk factor since it may lead to the onset of acute pyelonephritis in approximately 5% of pregnant women and may increase the risk of foetal mortality. (**Table 1**)

Without treatment, this condition leads to symptomatic cystitis in about 30% of pregnant mothers of whom about 50% will eventually develop acute pyelonephritis [16, 19, 20].

Table 1: Maternal and foetal complications of asymptomatic bacteriuria in pregnancy [17,18]

Maternal complications	Foetal complications
Hypertension	Intrauterine growth retardation
Pre-eclampsia	Retardation
Anaemia	Intrauterine death
Chorioamnionitis	Low birth weight
Symptomatic acute cystitis Acute pyelonephritis	Prematurity

1.5 DIAGNOSIS IN DIFFERENT CLINICAL FORMS OF URINARY TRACT INFECTIONS

The criteria for diagnosis and treatment of UTI are more restrictive compared with the general population, since the potential risks concern not only an expectant mother but also her unborn child.

➤ Asymptomatic bacteriuria (ASB)

Effective antimicrobial therapy of ASB in

pregnancy significantly reduces the risk of pyelonephritis and possibly also adverse foetal outcomes, routine screening for the presence of clinically significant bacteriuria in all pregnant women has become necessary. Urine culture remains the most reliable test allowing the diagnosis of ASB. Based on the recommendations developed by the IDSA (Infectious Diseases Society

of America), significant bacteriuria in asymptomatic women is defined as bacterial monoculture in the quantity of $\geq 10^5$ colony-forming units (CFU) per ml in two consecutive mid-stream clean-catch urine specimens or $\geq 10^2$ CFU/ml in urine collected from single urinary bladder catheterization [21]. However, for practical and economic reasons the guidelines for routine screening in pregnancy accept a single urine culture taken between weeks 12 and 16, or at first prenatal visit (if later), although there is only an 80% probability that the woman has true bacteriuria (vs. 95% with the original criteria) [22, 23]. Due to this high rate of false positive results, in some women with a positive urine culture are asked to return within 1 week for the second testing, to avoid unnecessary treatment [24].

Repeated tests have been recommended only in high-risk women (with diabetes, sickle cell anaemia, immunological defects, urinary tract abnormalities or a history of recurring infections before pregnancy) [25, 26]. The more recent reports suggest that repeating the urine culture in each trimester improves the detection rate of ASB. ASB prevalence distribution in the first, second, and third trimesters was 0.9%, 1.83%, and 5.6%, respectively. [27, 28]

All pregnant women with ASB should have periodic screening after therapy, since as many as one-third of them experience a recurrent infection. Follow-up cultures should be obtained 1–2 weeks after treatment and then repeated once a month [28, 29]. In case of persistent or recurrent bacteriuria, longer antibiotic therapy using the same agent (e.g. 7 instead of 3 days of treatment) or another first line drug is recommended. Subsequent treatment courses are administered until the bacterial counts drop to non-significant levels [30]. If bacteriuria persists despite repeated courses of therapy, as well as in women with additional risk factors (e.g. immunosuppression, diabetes, sickle cell anaemia, neurogenic bladder) or recurrent/persistent UTIs before pregnancy, one should consider antimicrobial prophylaxis [30, 31].

➤ **Symptomatic Urinary Tract Infection** **Cystitis/urethritis**

The diagnosis is made on the basis of symptoms (cloudy urine, dysuria, frequency, urgency, abdominal or suprapubic pain) and the presence of even small bacterial colony counts ($\geq 10^2$ – 10^3 CFU/ml). [30]

Acute pyelonephritis

The clinical presentation is typical and includes lumbar pain, fever of $> 38^\circ\text{C}$, chills, nausea, vomiting and costo-vertebral angle tenderness, dysuria, polyuria $\geq 10^5$ CFU/ml in mid-stream urine specimen. Nearly one in five of pregnant women with pyelonephritis has septicaemia at

diagnosis. Complications included: anemia (23%), septicaemia (17%), transient renal dysfunction (2%), and pulmonary insufficiency (7%) [32-35].

1.6 Management of Urinary Tract Infections

Management of UTI in pregnant women is based on selecting a suitable agent and which should be based on the reports of antimicrobial susceptibility testing. The exact duration of treatment is unpredictable. Right dose and appropriate treatment duration are important factors in the management of UTI. Therapy should be such that the selected antimicrobial agent has low adverse effect and is safer for both mother and the baby. Appropriate treatment can reduce the risk of maternal sepsis, pyelonephritis, preterm labour and also adverse outcomes for the foetus [3]. Management of UTI in pregnant women mostly includes patients with asymptomatic bacteriuria and symptomatic bacteriuria, upper and lower UTI. In 70-80% of patients the administration of a sulfonamide, amoxicillin, amoxicillin clavulanate, cephalexin, or nitrofurantoin is found to be effective. Quinolones, Chloramphenicol, Trimethoprim/Sulfamethoxazoles and tetracyclines should be avoided because of teratogenic effects. and sulfonamides should not be administered during the third trimester because of the possible development of kernicterus and hyperbilirubinemia [4]. In addition, the available fluoroquinolones should not be given because of their potential to inhibit cartilage and bone development in the new born. Periodic screening should be done after completing the therapy until gestation is complete, since many develop recurrent infection. [3,36,37]

Asymptomatic Bacteriuria

Asymptomatic bacteriuria is the finding of two consecutive urine cultures with $>100,000/\text{ml}$ of the same organism in the absence of urinary symptoms. Asymptomatic bacteriuria occurs without any symptoms, this untreated condition may lead to develop symptomatic bacteriuria, and this can cause severe risk to both mother and baby. It occurs usually during the early pregnancy period [38].

Adequate antimicrobial therapy based on the susceptible microorganism, and also considering the safety of mother and foetus during the pregnancy is strongly recommended step. The main objective of the treatment is reducing the negative outcomes such as low birth weight and pre-term birth. Single dose regimen is less effective than seven-day regimen. Oral antibiotics treatment for 3-7 days along with follow up culture should be obtained as a confirmation of cure after completion treatment [14, 36, 37].

The choices of antibiotic for the treatment of asymptomatic bacteriuria are the following:

- Amoxicillin (if susceptible): 250 mg three times a day
- Nitrofurantoin: 50 mg four times a day (avoid at 36+ weeks)
- Trimethoprim: 300 mg once a day (avoid in the first trimester)

- Cephalexin: 500 mg twice a day (least preferred option)

Cystitis

Cystitis is the infection of bladder and is differentiated from the asymptomatic bacteriuria by the presence of symptoms such as dysuria, urgency, frequency, nocturia and discomfort. The appropriate treatment is selected after conducting the urine culture. The diagnosis is confirmed by finding of bacterial growth on urine culture in a symptomatic pregnant woman: quantitative count ≥ 100000 colony forming units /ml [38].

The treatment for cystitis is similar to that used in asymptomatic bacteriuria. The goal of therapy is to eradicate the microorganism and to reduce the risk of relapse or reinfection. The duration of treatment is uncertain, short or longer courses except in the cases where Fosfomycin is used. A repeat urine culture should be done 1-2 times after the antimicrobial treatment is finished to ensure that the bacteriuria eradication [14,36,37].

The choices of antibiotic for the treatment of cystitis are the following:

- Nitrofurantoin: 50 mg four times a day (avoid at 36+ weeks)
- Trimethoprim: 300 mg once a day (avoid in the first trimester)
- Fosfomycin trometamol: 3 g sachet in a single dose (useful for patients with multi-drug resistant microorganisms)
- Cephalexin: 500 mg twice a day (7 days)
- Amoxicillin: 500mg thrice a day 7 days)
- Amoxicillin-Clavulanate: 625mg thrice a day(7days)

Pyelonephritis

Patients with high grade fever, flank pain, nausea or vomiting should be treated as pyelonephritis. Those patients with severe symptoms should be hospitalized and treated with intravenous antibiotics. Pyelonephritis in pregnancy can result in serious negative outcomes such as maternal sepsis, pre-term labour and premature delivery and requires appropriate and aggressive treatment. Intravenous antibiotics are usually used until the patient has been afebrile for 48 hours. Oral antibiotics are then used for 10–14 days [14, 36,37].

After the initial empirical therapy treatment should be guided based on the urine culture reports. Empiric therapy should be of broad spectrum activity and be started immediately. The main goal of the treatment is to eradicate the microorganisms or the residual infection from the tissues in the urinary tract. The choice of treatment in pregnant women with pyelonephritis is based on the severity of symptoms [4].

Mild to moderate symptoms:

- Ceftriaxone 1 g IV every 24 hours
- Cefepime 1 g IV every 24 hours

- Amoxicillin with clavulanic acid 1.2 g IV every 12 hours
- Aztreonam 1 g IV every 8–12 hours

Severe acute pyelonephritis

- Ticarcillin with clavulanic acid 3.1 g every 6 hours
- Piperacillin with tazobactam 3.375 g every 6 hours
- Meropenem 0.5 g every 8 hours
- Ertapenem 1 g every 24 hours
- Doripenem 1 g every 8 hours

β -Lactam antibiotics are mostly used because of the safety for both foetus and mother. Nitrofurantoin and Fosfomycin are not appropriate for treatment due to inadequate tissue levels 20-24. Patients with pyelonephritis can become dehydrated because of nausea and vomiting and may need IV hydration. Fever should be managed with antipyretics like Acetaminophen and nausea and vomiting with Antiemetic's.

CONCLUSION

Urinary tract infections are one of the most frequent complications during pregnancy which can cause fatal results in both mother and baby. Urinary tract infections in pregnancy are classified as either asymptomatic or symptomatic. E. coli was the most frequently found organism which accounts for UTI in pregnant women. Appropriate management of UTI in pregnant women can avoid or reduce associated complications such as preterm labour, sepsis and pyelonephritis. Selection of drug with the right dose and duration in the management of disease should be based on the reports of antimicrobial susceptibility testing. Asymptomatic bacteriuria and cystitis can be treated with oral antibiotics. Hospital admission and intravenous antibiotics are usually required in pyelonephritis treatment. A follow up urine culture is generally done for two weeks after the antibiotic course has been completed to ensure the complete elimination of microorganism.

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