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Review Article

Pathophysiology, Etiology and Complications of UTI during Pregnancy

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ABSTRACT

Urinary Tract Infections (UTI) include a wide range of symptoms, such as urethritis, cystitis, prostitis and pyelonephritis. The most frequent bacterial infections are UTIs. Lower and upper UTI's are used to categorise UTI's. While pyelonephritis is an upper tract infection, cystitis is a lower tract infection. Significant physiologic changes to the entire urinary system occur during pregnancy and drastically influence the prevalence of UTI's and pyelonephritis. Both symptomatic and asymptomatic forms are possible. Gram-negative bacteria are the most frequent causes of both symptomatic and acute UTI, including *Escherichia coli, Klebsiella pneumonia, Pseudomonas areuginosa, Enterobacter* and *Serratia*. The gold standard for the diagnosis of a urinary tract infection is quantitative culture methods. Untreated urinary tract infections have been linked to severe morbidity and mortality in pregnant women and their babies. According to Edward Kass's research, 6% of pregnant women reported asymptomatic bacteriuria, which was linked to higher preterm and perinatal death than those with sterile urine. According to the urine culture and sensitivity results, correct treatment is therefore of utmost importance. An agent with a seven-day dosage schedule that is safe for both the mother and the fetus should be used as the therapy. To prevent a recurrence of UTI, confirmation of the pathogenic organism's full eradication is required. Precautions and good cleanliness can also aid in preventing recurrence.

Keywords: Asymptomatic bacteriuria, Pyelonephritis, Acute cystitis, Pyuria, Urethritis

Abbreviations: ASB: Asymptomatic Bacteriuria; *E. coli*: *Escherichia coli*; GBS: Group B Streptococci; UTI: Urinary Tract Infection; CFU: Colony Forming Units

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INTRODUCTION

In all age groups, UTIs continue to be a major cause of morbidity and medical expenses. UTI is defined as the urothelium's inflammatory reaction to bacterial invasion, which is typically accompanied by bacteriuria and pyuria. Anywhere along the urinary tract can develop UTI, which comprises abscess, pyelonephritis, cystitis and urethritis. Due to anatomical problems including the proximity of the urethra to the anus, it is one of the most prevalent infectious diseases which seen in sexually active women, during pregnancy and after menopause (Macejko M, *et al.*, 2007). According to reports, 20% of the pregnant women are diagnosed with UTI due to physiological changes such an increase in the plasma volume that may induce reduction in urine concentration and enable bacterial growth that may or may not create symptoms. Additionally, 90% of the pregnant women have structural changes such as urethral dilatation and decreased bladder tone that cause urine stasis (due to pregnancy-related increases in progesterone and oestrogen levels) (Habak PJ and Griggs Jr RP, 2023). The risk of UTI may start in the 6th week and peak between 22 and 24 weeks later. Untreated UTIs or asymptomatic bacteriuria during pregnancy can have devastating effects on the mother and the fetus, increasing the risk of kidney failure, pyelonephritis, sepsis and other complications such intrauterine growth restriction, preeclampsia and premature delivery. In order to minimise UTI-related complaints, it is crucial to screen for this illness, raise suspicion and recognise it, which will allow to swiftly start the right therapy (Michelim L, *et al.*, 2016). All the pregnant women should undergo urine culture screening, the standard for detecting asymptomatic bacteriuria, at least once during early pregnancy (12-16 weeks), according to the Infectious Diseases Society of America (IDSA) and the United States of America (USA) preventive services task force (Nicolle LE, *et al.*, 2019). Romero RO, *et al.*, 1989, conducted a meta-analysis of 8 clinical studies and found that antibiotic treatment for asymptomatic bacteriuria reduced the incidence of low birthweight with relative risk of 0.56% (95% Confidence Interval (CI): 0.43-0.73). Obstetricians are concerned about it because of its link to high rates of maternal, neonatal illness and mortality (Widmer M, *et al.*, 2015).

LITERATURE REVIEW

UTI classification in pregnancy

Pregnancy urinary tract infections are divided as symptomatic and asymptomatic true bacteriuria (>1,00,000/ml). Cystitis and pyelonephritis are the two types, upper and lower tract infections that cause symptomatic bacteriuria.

Asymptomatic Bacteriuria (ASB): ASB is a type of UTI caused by bacteria which is identified by the presence of >10^5 Colony Forming Units (CFU)/ml of urine in a clinically asymptomatic individual. Approximately 10% of pregnancies have ASB (Glaser AP and Schaeffer AJ, 2015). Untreated ASB during pregnancy can result in symptomatic UTI in 20%-40% of women, putting both the mother and unborn child at risk (Matuszkiewicz-Rowińska J, *et al.*, 2015). It frequently happens in the 1st trimester of pregnancy and may be related to prior UTIs, diabetes mellitus, multiparity, low socioeconomic level and illiteracy (Fatima N and Ishrat S, 2006). Low birth weight babies and intrauterine growth retardation are both more likely as a result. Preeclampsia, anemia, chorioamnionitis and postpartum endometritis are also at higher risk. Fetal hazards include perinatal mortality, mental impairment, stillbirth, fetal growth restriction and developmental delay. So, it is advised to perform urinalysis and keep an eye on the quantity, colour, etc., of the urine during the course of the pregnancy (Getaneh T, *et al.*, 2021; Kalinderi K, *et al.*, 2018).

The most typical organism found in urine samples from women with ASB is *E. coli*. There are frequent correlations between *enterobacter*ial species such *Streptococcus, Klebsiella* sp. (Behzadi P, *et al.*, 2010).

Acute cystitis: It is an infection of the bladder that frequently spreads to the urethra. About 1% of all pregnant mothers are affected. The presence of symptoms like dysuria, urgency, frequency, nocturia, haematuria and suprapubic discomfort in afebrile women with no signs of systemic illness distinguishes it from asymptomatic bacteriuria, which is defined as significant bacteriuria without associated bladder mucosal invasion (McCormick T, *et al.*, 2008; Gilstrap III LC and Ramin SM, 2001). When a pregnant woman with symptoms has bacterial growth of a urine culture, the diagnosis is established by the presence of pyuria (>7 white blood cells/ml) and quantitative count of 10^5 CFU/ml or 10^3 CFU/ml (Macejko AM and Schaeffer AJ, 2007). In 15%-50% of patients, pyelonephritis, an upper urinary tract infection complicates acute cystitis (Guptha K, 2010).

Pyelonephritis: It is an infection of the kidneys and upper urinary system, which is a serious pregnancy complication that can cause serious morbidity for both the mother and fetus (Delzell Jr JE and Lefevre ML, 2000). It is a disease that is suspected when a Midstream Specimen of Urine (MSSU) culture identifies at least 1,00,000 bacteria/ml of single uropathogen with concomitant inflammation of the renal parenchyma, calices, and pelvis in the presence of systemic illness (Mittal P and Wing DA, 2005). Pyelonephritis is most common in the 2nd and 3rd trimesters (Patterson TF and Andriole VT, 1987). Pyuria is typically prevalent in pyelonephritis-affected women whose absence may indicate different diagnosis or total obstruction. Immunosuppression, already existing diabetes, history of sickle cell anaemia, neurogenic bladder, frequent or chronic UTIs before pregnancy, tobacco use, age<20 years and being late for prenatal care are additional risk factors for complex UTI in pregnancy (Lucas MJ and Cunningham FG, 1993).

Epidemiology: In comparison to most data gathered in the 1980s and the end of the 1990s in diverse populations throughout the world, the incidences of asymptomatic bacteriuria and the related problems documented by Kass in 1962 are higher (Pastore LM, *et al.*, 1999). Up to 15% of women will experience one episode of UTI at some point in their lives, and UTI accounts for roughly 10% of the primary care consultations made by pregnant women. Pregnant women report getting UTIs about 8% of the time (Andriole VT and Patterson TF, 1991). Women are 14 times as likely than men to have a UTI. Pyelonephritis is the most common cause of shock in pregnant women and affects 2%-4% of pregnancies. It is more frequently right-sided but can be bilateral in up to 25% of cases, and it has 23% recurrence rate right after birth. Pyelonephritis is most common in the second trimester of pregnancy. Asymptomatic Bacteriuria (ASB), with a rate of up to 2%-7%, is the main risk factor for UTI in pregnant women. Contrarily, 1.3% of pregnancies are complicated with cystitis. ASB is more common in women with low socioeconomic status and sickle cell trait carriers. A postpartum UTI is likely to occur in about 25% of cases of ASB that are not treated during pregnancy. Between 2%-13% of studies from the USA, Europe, and Australia found asymptomatic bacteriuria. It has been asserted in the past that bacteriuria increases the risk of anemia and high blood pressure during pregnancy. It is advised that all pregnant women get an ASB screening at their first prenatal appointment due to the high prevalence and probable severity of pyelonephritis. Treatment for ASB reduces clinical infection rates to 3%-4% (Schnarr J and Smaill F, 2008).

Etiology: Numerous bacterial species, the majority of which are part of the normal perineal flora, are responsible for causing urinary infections in females. About 70%-80% of pregnancies are caused by *E.coli*, making it the most frequent cause of UTI. Other pathogens that cause UTI include *Proteus* sp. (2%) and *Klebsiella pneumonia* (5%) as well as *Enterobacter* sp. (3%) and *Staphylococcus saprophyticus* (3%) and GBS (2%-5%) (Balachandran L, *et al.*, 2022; Corrales M, *et al.*, 2022).

Infection with GBS

Penicillin *vs.* placebo treatment for GBS bacteriuria was compared in a randomized, controlled trial. Results showed that women who took antibiotics experienced significantly lower rates of premature membrane rupture and preterm delivery. Although it is unknown whether GBS bacteriuria is the same as GBS vaginal colonization, pregnant women who have the condition ought to be treated as GBS carriers and given a preventative antibiotic during childbirth (Schnarr J and Smaill F, 2008).

During childbirth, urinary catheterization is a common procedure that might introduce bacteria and cause UTI. Changes in bladder reactivity and bladder excessive expansion during the postpartum period may predispose to UTI (Easter SR, *et al.*, 2016).

The risk of UTI is significantly increased in women who engage in sexual activity. The distal urethra's urothelium can become traumatized during sexual contact, which increases bacterial invasion. Inoculation can be facilitated by the vagina acting as a repository for stomach germs. Gram negative bacteria from the bowel flourish in urine, in contrast to the majority of vulval and perineal commensal microorganisms. As a result, aerobic Gram-negative bacilli from the gastrointestinal system are the main source of urine infections. The issue might be made worse by a swollen, gravid abdomen that makes it difficult to maintain personal hygiene. The same bacteria that cause UTIs in non-pregnant patients also cause UTIs in pregnant women (Amiri M, *et al.*, 2015).

Pathophysiology

Same uropathogens that frequently cause UTI in non-pregnant patients also cause UTI in pregnant women. Ureteral dilatation occurs in 90% of pregnant women and lasts till birth (hydronephrosis of pregnancy). Increased urine stasis and ureterovesical reflux are caused by increased bladder volume, decreased bladder tone, and decreased ureteral tone. This decreased the kidneys' defences against bacterial reflux. Bacterial reservoirs may exist in urinary stasis. The glomerular filtration rate and urine output both rise in response to blood volume expansion. Urine stasis, which can arise from an increase in urine output volume and the lack of ureteral tone, can cause the ureters, renal pelvis, and calyces to enlarge. This dilatation seems to start at 10 week's gestation, increase throughout pregnancy and resolve between 6 and 12 weeks after delivery. Progesterone also causes urinary stasis by relaxing the ureteral smooth muscle (Loh KY and Sivalingam N, 2007).

Because of urine pH, vesicoureteral valve, and other immunological and mucosal barriers, urine is devoid of germs, viruses, and fungus. The major defense against UTI is complete bladder emptying during urination. The pathophysiology of urinary tract infection may be influenced by a variety of bacteria that have the ability to infiltrate the urinary tract. When bacteria from the vaginal, perineal, and fecal flora spread to the entrance of the urethra and begin to grow, infection develops (Kaptilyy VA, 2015).

Significant physiologic changes to the entire urinary system occur during pregnancy and significantly alter the occurrence of UTIs and pyelonephritis. The presence of glucose in the urine and an increase in urinary amino acid levels during pregnancy are other causes of UTI. Glycosuria results from proximal collecting tubule and loop of Henle dysfunction in glucose reabsorption. Although it has been hypothesized that its presence will interfere with *E.coli*'s ability to adhere to the urothelium (Le J, *et al.*, 2004).

Due to the physiologic changes brought on by pregnancy, pregnant individuals are typically regarded as an immunocompromised potential UTI host. Additionally, there is a significant increase in wetness during pregnancy, which tends to boost the growth of bacteria (Millar LK and Cox SM, 1997).

Clinical signs and symptoms

Asymptomatic bacteriuria is characterized by a lack of symptoms. These patients can have a record of recurrent UTI or ASB from a previous pregnancy. Cystitis usually begins suddenly, often with urgency, burning, or

painful emptying of little amounts of urine. Nocturia with suprapubic discomfort. Hematuria can happen and urine is murky. A low-grade fever could appear. When an infection occurs from a vesicoenteric or vesicovaginal perforation or from emphysematous cystitis, pneumaturia may happen.

Pyelonephritis: Dysuria, fever, shivering, flank pain, constant abdomen unease, nausea, vomiting, and lethargy are symptoms of acute pyelonephritis (Santos JF, *et al.*, 2002).

Complications among mother and fetus

- Acute Respiratory Distress Syndrome (ARDS) or pulmonary edema may be present as a result of endotoxin-mediated alveolar injury. Monitoring of urine production and oxygen levels is recommended (MacLean AB, 2001)
- Anemia is caused by the release of endotoxins
- Endotoxin secretion may also trigger uterine contractions in preterm labor
- Preeclampsia
- Septic shock
- An ongoing infection
- Acute pyelonephritis
- Chorioamnionitis
- Acute cystitis with symptoms
- Hypertension
- Low birth weight
- Premature birth
- Embryonic death (Widmer M, *et al.*, 2015)
- Growth retardation within the womb

Differential diagnosis

Important differential diagnosis includes nephrolithiasis, placental abruption, intraamniotic infection, and bacterial infection in pregnant women who report with fever and flank or lower back pain. Significant flank or back discomfort and abnormal urine results are symptoms of nephrolithiasis.

The differential diagnosis includes pregnancy-related issues including preterm labor, chorioamnionitis, or placental abruption as well as acute intraabdominal disorders such appendicitis, pancreatitis, or cholecystitis (Ovalle A and Levancini M, 2001).

Diagnosis

Acute pyelonephritis, cystitis, and asymptomatic bacteriuria are diagnosed by examining the presence of bacteria in the urine. For the diagnosis of acute pyelonephritis and asymptomatic bacteriuria, a concentration of at least 10^5 cfu/ml of a single uropathogen is required, but only 10^3 CFU/ml are required for the diagnosis of cystitis. Urine culture is the standard for detecting bacteriuria in pregnancy. However, urine cultures are pricy, call extensive laboratory competence, and take 24-48 hours to provide findings (Wing DA, *et al.*, 2000). In 90% of cases of pyelonephritis, it is positive. Prior to beginning antibiotic therapy, cultures should be acquired as soon as feasible. For the diagnosis of UTI, urine microscopy has a poor sensitivity (between 40% and 70%) but a good specificity (between 85% and 95%). Pyuria is found in around 90% of instances of pyelonephritis. The diagnosis of acute pyelonephritis is more sensitive (95%) and specific (71%) when pyuria is present. White blood casts are a dead giveaway for an upper tract infection (Teppa RJ and Roberts JM, 2005).

Due to its dependable rates and quick results, the dipstick method (for nitrites and leukocyte esterase) has emerged as the most used test. With dipstick analysis and clinical judgement, accuracy in patients with vague symptoms is significantly increased. Protein, white blood cells, and red blood cells are examined during a urine test. False negative test findings are frequent, and these tests have relatively low predictive values.

A complete blood count, electrolytes, and serum creatinine test are among the laboratory tests that are typically used to diagnose pyelonephritis. Pyelonephritis can be diagnosed routinely in patients who are critically ill, have symptoms of renal colic or a history of renal stones, have diabetes mellitus, a history of prior urologic surgery, immunosuppression, repeated episodes of pyelonephritis, or have urosepsis using Computed Tomography (CT), renal ultrasound (to avoid contrast or radiation exposure) or Magnetic Resonance Imaging (MRI).

When comparing inpatient treatment for pyelonephritis to screening for bacteriuria in pregnant women, studies found that screening resulted in a significant reduction in overall costs. One patient's test for bacteriuria to detect the onset of pyelonephritis cost $1,605, but one patient's pyelonephritis treatment cost $2,485. In a family practice obstetric population, Wadland and Plante carried out a comparable analysis and discovered that screening for asymptomatic bacteriuria was cost-effective (Szweda H and Jóźwik M, 2016).

Pharmacological treatment

Antibiotic therapy was observed to be successful in eradicating asymptomatic bacteriuria and lowering the frequency of pyelonephritis, premature delivery, and low birthweight when compared to placebo or no therapy (Smaill FM and Vazquez JC, 2019). The effect of administering antibiotics for asymptomatic urinary tract infections on recurring bacteria in the urine during pregnancy, the possibility of premature delivery, and the occurrence of pyelonephritis after pregnancy were all assessed in a Cochrane review of 13 studies. The antibiotic sensitivity of Gram-negative urinary pathogens acquired from pregnant women with asymptomatic bacterial infections or cystitis was examined in a study (*Table 1*).

The infectious agent(s) can typically be eliminated with a 7-10 day antibiotic course. Shorter treatment durations, including one-day therapy, have been recommended by some experts. There is still debate over when pregnant patients should receive shorter antibiotic regimens of treatment. In ampicillin-sensitive isolates, Masterton achieved an 88 percent cure rate with a single 3 g dosage of ampicillin. According to several other trials, cure rates for bacteriuria ranged from 50%-78% when a single administration of amoxicillin, cephalexin (Keflex), or nitrofurantoin was administered.

When taken as directed, a single 3 g sachet of fosfomycin is effective. Analgesia is required because significant renal angle discomfort affects many women. Simple analgesics are usually sufficient, but opiates may be required in extreme circumstances or if there is concurrent renal colic. Nonsteroidal Anti-Inflammatory Drugs (NSAIDs) should be avoided since they raise the risk of stomach mucosal ulcers and impaired renal perfusion in mothers and the fetal condition oligohydramnios and early ductus arteriosus closure.

If the lady has restricted mobility or needs to be bedridden for a while, thromboprophylaxis should be utilized. Low molecular weight heparin and progressive compression stockings are advised.

Acute pyelonephritis episodes dramatically enhance the risks of premature labor. Often, tocolysis is required. If there is evidence of suspected preterm labor, antenatal steroids for fetal lung development should be taken into consideration. Regarding tocolysis and the administration of prenatal steroids, we point readers to the Royal College of Obstetricians and Gynaecologist (RCOG) recommendations (Johnson EK, 2016).

Table 1: Pharmacological treatment of UTIs in pregnancy

Antibiotic	Indication	Dose	Pregnancy category	Lactation	Observation
Nitrofurantoin	Asymtomatic bacteriuria, recurrent cystitis	100 mg BD for 5 to 7 days	Contraindicated term (38-42 weeks)	Enters breast milk	Renal function, liver function
Cephalexin	Asymtomatic bacteriuria, recurrent cystitis	500 mg orally every 6 hours, for 5-7 days	Safe	Safe	Use with caution among renal hepatic disease patients
Amoxicillin clavulanate	Asymtomatic bacteriurea	500/125 mg orally for 8 hours, for 5-7 days	-	Enters into breast milk	Hepatic impairment
Amoxicillin	Asymtomatic bacteriuria	500 mg orally 8 hours for 5-7 days	Safe	Safe	Use with caution among renal and hepatic diseases
Cefuroxime	Asymtomatic bacteriuria	250 mg orally BD for 3-7 days	-	-	Hepatic and kidney injury
Fosfomycin	Asymtomatic bacteriuria	3 g orally as single dose in 3-4 of water	Caution by manufacturer	Excreted in breast milk	Hepatic injury
Ceftriaxone	Pyelonephritis	1-2 g IV once daily	-	Use with caution	Immune meadiated hemolytic anemia
Ertapenam	Pyelonephritis	1 g/day IV/IM	-	Present in breast milk	CNS disorders
					Renal impairments
Trimethoprim	Asymptomatic bacteriuria, cystitis	200/300 mg BD	Avoid in 1st trimester	Safe in short term	Renal function

Note: IV: Intravenous; IM: Intramuscular; BD: Twice a day; CNS: Central Nervous System

Because of how some antibiotics affect the developing fetus, some should not be used during pregnancy (Schneeberger C, *et al.*, 2012), they consist of the following-

- Tetracyclines can harm fetus teeth and bones.
- Avoid fluroquinolones during pregnancy and nursing as they are harmful to growing cartilage.
- During the first and third trimesters, avoid taking trimethoprim-sulphamethoxazole.
- If at all possible, avoid using aminoglycosides because they have been linked to ototoxicity after extended exposure during fetal development.

Preventive actions

You can prevent UTI from developing and saving yourself. The trouble of subsequently treating it by taking the following precautions (Rahiman F, *et al.*, 2015)

- Practicing good hygiene, such as cleaning the genital region and urinating after sexual activity, had a protective impact. After using the bathroom, wipe your genital area from front to back to keep it clean.
- The chemical in cranberry juice may help prevent bacteria from adhering to the lining of the urinary tract. This action aids in infection control and prevention.
- Vaccination.
- Eat foods and supplements high in vitamin C or ascorbic acid, which can raise urine acidity. The acidity prevents infection and aids in the death of germs.
- Urinating whenever the desire strikes, which promotes faster removal of microorganisms from the urinary system.
- Taking specific supplements, such as a vitamin C, cranberry and probiotic combination, may help treat recurring UTIs in females.
- Drinking enough fluids, especially water, can assist the urinary tract's bacteria be flushed out.
- Consuming yogurt, which includes live lactobacilli.
- Remember not to wear tighter or wet clothing, and wear cotton underwear.
- Avoid clear of soap or cleansing products that might harm your genitalia.

CONCLUSION

Urinary tract infections, whether symptomatic or asymptomatic, present a major risk to expectant mothers. This article has reviewed the pathophysiology, etiology, complications, diagnosis, preventative strategies, and therapy of UTI in pregnancy. urine cultures should be used to check for asymptomatic bacteriuria in pregnant women, and the right antimicrobials should be used to treat it. On the basis of cost, safety during pregnancy, and availability, broad-spectrum antibiotics with activity against *E.coli* should be selected as the initial course of treatment for symptomatic UTI. While pyelonephritis necessitates hospitalization and intravenous antibiotics, asymptomatic bacteriuria and cystitis are best treated with oral antibiotics, 7 day course of treatment is preferable to a one-dose course.

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