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Review Article

Urinary Tract Infections in Pregnancy

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ABSTRACT

Urinary tract infections are the most common bacterial infections during pregnancy. A history of previous urinary tract infections and low socioeconomic status are risk factor for bacteriuria in pregnancy. *Escherichia coli* is the most common etiologic agent in both symptomatic and asymptomatic infection. Treatment of asymptomatic bacteriuria has been shown to reduce the rate of pyelonephritis in pregnancy and decrease the incidence of low birth weight babies. Therefore, screening for and treatment of asymptomatic bacteriuria has become a standard of obstetrical care.

Keywords: Asymptomatic Bacteriuria, *Escherichia Coli,* Pregnancy, Risk Factor.

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INTRODUCTION

Urinary tract infection (UTI) is common in pregnancy. It can be asymptomatic, as well as symptomatic. Hormonal and mechanical changes associated with pregnancy increase the risk of urinary stasis and vesico-ureteral reflux which in conjunction with an already short urethra and difficulty with hygiene due to a distended belly increase the frequency of UTIs in pregnant women. The physiological increase in plasma volume during pregnancy decrease urine concentration and up to 70% pregnant women develop glycosuria, which encourages bacterial growth in the urine.[1] UTI has been reported among 20% of the pregnant women and it is the most common cause of admission in obstetrical wards.[2] The majority of the UTI occur due to ascending infection.[3,4] Three common clinical manifestations of UTIs (as shown in table 1 below) in pregnancy are: asymptomatic bacteriuria (ASB), acute cystitis and acute pyelonephritis.[5]

Traditionally, the criterion of 10^5 bacteria/ml has been used, as concentrations at this level represent a chance of contamination of <1%. At concentrations of 10^3-10^4 bacteria/ml there is a 50% chance that contamination is responsible. The only pragmatic solution is to collect midstream samples of urine (MSSUs) after careful decontamination of the urethral meatus.[6]

PATHOGENESIS

Pregnant women develop ureteral dilatation starting in week 6 and peaking during weeks 22 to 24, which persists until delivery (hydronephrosis of pregnancy). Increase in urinary progestogens and estrogens cause relaxation of the ureteric smooth muscle, leading onto dilatation of ureters, which is further aggravated by pressure from the enlarging uterus. This, along with increased bladder volume and decreased bladder tone, contributes to increased urinary stasis and ureterovesical reflux, facilitating bacterial colonization and ascending infection.

During pregnancy, the content of amino acids, vitamins and other nutrients is also increased in the urine, further favouring growth of bacteria[7].

Increasing age, low socioeconomic status and medical interventions, such as catheterization, diabetes mellitus, gestational diabetes and pre-pregnancy UTIs are other risk factors that predispose to UTI during pregnancy.

About 30-40 percent of the asymptomatic bacteriuria cases develop into acute symptomatic UTI. Hence, early detection and timely treatment is crucial to prevent acute pyelonephritis and chronic renal failure in the mother, and to reduce prematurity and fetal mortality in the fetus.

CLINICAL PRESENTATION

Onset in usually acute and presents in the second and third trimesters of the pregnancy.

COMPLICATIONS

Meta-analyses of studies evaluating asymptomatic bacteriuria in pregnancy conclude that there are true associations with preterm delivery and low birthweight. In addition, there are increased risk of pre-eclampsia, anaemia, chorioamnionitis and postpartum endometritis. Fetal risk include fetal growth restrication, stillbirth, perinatal mortality, mental retardation and developmental delay.

Table 1: Classification of urinary tract infection in pregnancy

Asymptomatic bacteriuria	Defined as persistent colonisation of the urinary tract by significant number of bacteria in women without urinary symptoms.
Acute cystitis	Distinguished from asymptomatic bacteriuria by the presence of symptoms such as dysuria, urgency, frequency, nocturia, hematuria and suprapubic discomfort in afebrile women with no evidence of systemic illness.
Pyelonephritis	Defined as significant bacteriuria in the presence of systemic illness and symptoms such as flank or renal angle pain, pyrexia, rigor, nausea and vomiting.

Table 2: Clinical signs and symptoms of UTI

Symptoms	Signs
1. Fever with rigor and chills	1. Patient is dehydrated and febrile (fever 101^0F)
2. Malaise	2. Costovertebral tenderness
3. Back pain usually located in the upper lumber area radiating to the groin.	3. Urine is turbid or bloody
4. Anorexia, nausea and vomiting	4. Tachycardia
5. Dysuria and frequency of micturition	
6. Uterine contractions	

Table 3: Screening for asymptomatic bacteriuria in pregnant women-clinical summary of a US Preventive Service Task Force recommendation statement. [11]

Recommendation	Screen with urine culture
Detection and screening test	ASB can be reliably detected through urine culture. The presence of at least 10^5 colony forming units per ml of urine, of single uropathogen, and in a midstream clean-catch specimen is considered a positive test result.
Screening intervals	A clean-catch urine specimen should be collected for screening culture at 12-16 weeks' gestation or at the first prenatal visit, if later. The optimal frequency of subsequent urine testing during pregnancy is uncertain.
Benefits of detection and early treatment.	The detection and treatment of asymptomatic bacteriuria with antibiotics significantly reduces the incidence of symptomatic maternal urinary tract infections and low birthweight.
Harms of detection and early treatment	Potential harms associated with treatment of asymptomatic bacterial includes: • Adverse effects from antibiotics • Development of bacterial resistance

SCREENING AND DIAGNOSIS

A urine culture at the first antenatal visit.[8,9] A repeat urine culture should be obtained during the third trimester, because the urine of treated patients may not remain sterile throughout the pregnancy.

Infectious Diseases Society of America (IDSA)[7] and the US Preventive Services Task Force[10,11], also recommend that all pregnant women should undergo screening with urine culture at least once during early pregnancy (12-16 weeks), which is the gold standard for screening of asymptomatic bacteriuria. Routine urinalysis is not adequate as it may give false negative results in bacteriuria without pyuria and false positive results with contamination from vaginal secretions.

Diagnosis of asymptomatic bacteriuria is confirmed if two consecutive urine specimens are positive.

Infectious Diseases Society of America guidelines for the diagnosis and treatment of asymptomatic bacteriuria in adults.[9]

Summary Of Recommendations

1. The diagnosis of asymptomatic bacteriuria should be based on results of culture of a urine specimen collected in a manner that minimizes contamination.
   - For asymptomatic women, bacteriuria is defined as 2 consecutive voided urine specimens with isolation of the same bacterial strain in quantitative counts $\geq 10^5$ cfu/ml.
   - A single, clean-catch voided urine specimen with 1 bacterial species isolated in a quantitative count $\geq 10^5$ cfu/ml identifies bacteriuria in men.

- A single catheterized urine specimen with 1 bacterial species isolated in a quantitative count $\geq 10^2$ cfu/ml identifies bacteriuria in women or men.

2. Pyuria accompanying asymptomatic bacteriuria is not an indication for antimicrobial treatment.
3. Pregnant women should be screened for bacteriuria by urine culture at least once in early pregnancy, and they should be treated if the results are positive.
    - The duration of antimicrobial therapy should be 3-7 days.
    - Periodic screening for recurrent bacteriuria should be undertaken following therapy.
    - No recommendation can be made for or against repeated screening of culture-negative women in later pregnancy.
4. Screening for and treatment of asymptomatic bacteriuria is recommended before other urologic procedures for which mucosal bleeding is anticipated.
5. Screening for or treatment of asymptomatic bacteriuria is not recommended for the following persons:
    - Premenopausal, non-pregnant women
    - Diabetic women
    - Older persons living in the community
    - Elderly, institutionalized subjects
    - Persons with spinal cord injury
    - Catheterized patients while the catheter remains *in situ.*
6. Antimicrobial treatment of asymptomatic women with catheter-acquired bacteriuria that persists 48 h after indwelling catheter removal may be considered

Lumbiganon et al[12] observed that a positive dip slide test is very likely to indicate a definitive diagnosis of ASB, whereas a negative result effectively rules out ASB. As for the urine dipstick test, it is currently not appropriate to recommend it for screening ASB in pregnancy due to conflicting results.

Choice of antibiotics should be guided by antimicrobial susceptibility testing whenever possible. The investigators found nitrofurantoin to be the antibiotic of choice for ASB in pregnancy. They recommended that pregnant women with ASB should be treated with a 7-day regimen of antibiotics, although a 1-day regimen might be appropriate in some settings.

TREATMENT

Asymptomatic Bacteriuria

The treatment schedules are directed by urine culture and sensitivity testing and appropriate antibiotics are continued for at least 7 days. Careful follow-up is necessary to establish urine sterility; some authors advocate repeating MSSUs regularly until delivery.[13,14] There has been no systematic review of which antibiotic is best for the treatment of asymptomatic bacteriuria. The antibiotic chosen should have a good maternal and fetal safety profile, excellent efficacy and low resistance rates in a given population. Fluoroquinolones have been shown to impair cartilage development in animal studies. Although this adverse effect has not been described in humans, quinolones should be avoided in pregnancy. Tetracycline is not an appropriate agent to use in pregnancy because it leads to discoloration of deciduous teeth if given after 5 months gestation.[15] Table 4 reviews common antibiotics for asymptomatic and symptomatic lower urinary tract infections.

Role of Nitrofurantoin in UTIs

Nitrofurantoin has been in clinical use for many decades now for the treatment of UTIs due to its long record of safety in pregnancy and its bioavailability in urine, making it a good choice.[22] Moreover, there is no associated R-factor resistance with nitrofurantoin compared to recently introduced antimicrobials.[23]

Also, no significant correlation between nitrofurantoin treatment and fetal malformations has been reported.[24] All these characteristics make nitrofurantoin a suitable agent for treating bacteriuria in pregnancy.

In a descriptive, cross sectional study in Ibaden, Africa by Awonuga et al, Nitrofurantoin was one of the antibiotics demonstrating high efficacy against uropathogens with antibiotic sensitivity rates between 72.7% and 81.8%.

Table 4: Common antibiotics for asymptomatic and symptomatic lower urinary tract infections

Ampicillin	**Advantages:** No β-lactam antibiotic is known to be teratogenic[15] **Disadvantages:** High resistance rates limit its use as a single agent. Resistance to ampicillin in E. coli in European countries and Canada averaged 29.8%, but was high as 53.9% in Spain.[16] Malaysia and Tanzania reported rates of resistance of E. coli to ampicillin of 48% and 17%, respectively.[17,18] Pharmacokinetic changes of pregnancy decrease plasma concentrations of β-lactams by up to 50%.
Cephalexin	**Advantages:** No evidence of teratogenicity[19] **Disadvantages:** Penicillins and cephalosporins are sometimes associated with allergic and at times anaphylactic reactions. Cephalexin is not active against Enterococcus spp.[19]
Trimethoporim-Sulfamethoxazole	**Disadvantages:** Based on observational and case-control data there have been concern raised over the use of Trimethoporim-Sulfamethoxazole in the first trimester due to an association with neural tube and other birth defects. The evidence in the literature is however, mixed. In theory, sulfonamides should also be avoided after 32 weeks gestation because of their associated toxicity in newborns. Sulfonamides could displace bilirubin from albumin-binding sites and could cause severe jaundice leading to kernicterus. Practical evidence of the risk, however, is sparse. Actual haemolytic anaemia is another complication that could occur in newborn with glucose-6-phosphate dehydrogenase deficiency.[20] Overall rates of resistance of E. coli to trimethoprim sulfamethoxazole among urinary tract isolates across the US was 16.8% but was as high as 33.3% in some states.[21]

Table 5: Treatment regimens for urinary tract infections in pregnancy.

Oral antibiotics	1. Nitrofurantoin 100 mg QID (4 times a day) or Nitrofurantoin MR (modified release twice daily) is the treatment of choice. 2. Ampicillin 500 mg (MD (6 hourly). 3. Amoxiciilin 500 mg TDS (3 times a day 8 hourly). 4. Cephalexin 250 mg TDS. 5. Fosfomycin one 3g satchet
Intravenous antibiotics (For pyelonephritis).	1. Cefuroxime 750 mg TDS. 2. Amoxicillin and clavulanic acid 1.2 g TDS. 3. Gentamicin 2-5 mg/ kg/ day in 8 hourly divided does (for organisms resistant to penicillins and cephalosporins and in women allergic to penicillins and cephalosporin).
Duration of Treatment	1. Asymptomatic bacteriuria: 3-5 day. 2. Acute cystitis: 7 day. 3. Acute Pyelonephritis: 14 day (IV X 2 days; oral X 12 days).
For Treatment Failure	1. Nitrofurantoin 100 mg four times daily for 21 days. 2. Nitrofurantoin 100 mg OD (once a day) at bed time. 3. Cephalexin 250 mg OD. 4. Amoxicillin 250 mg OD.

A multicenter, double-blind randomized, placebo controlled noninferiority trial[25] was conducted in Thailand, Philippines, Vietnam, and Argentina to evaluate whether a 1-day nitrofurantoin regimen is as effective as a 7-day regimen in eradicating asymptomatic bacteriuria during pregnancy.

Escherichia coli was the most common potentially pathogenic organism detected, with prevalence approaching 50%. Bacteriologic cure rates at treatment day 14 were 75.7% and 86. 2% for 1 day and 7-day regimens, respectively.

Since the 7-day regimen of nitrofurantoin was found to be significantly more effective than the 1-day regimen, the authors recommended that women with asymptomatic bacteriuria in pregnancy should receive the standard 7-day regimen.

CONCLUSION

Symptomatic and asymptomatic bacteriuria is commonly encountered in pregnant women. Untreated asymptomatic bacteriuria is a risk factor for pyelonephritis in pregnancy. E. Coli is the most common etiologic agent in asymptomatic and symptomatic bacteriuria of pregnancy. The condition can be detected by urine culture, which should be performed at least once during early pregnancy (12-16 weeks). For treatment, nitrofurantoin has been found to be the antibiotic of choice because it achieves therapeutic levels only in the urine and is safe during pregnancy.

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