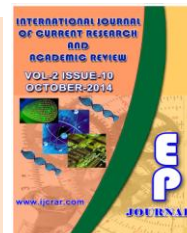




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Urinary Tract Infection in Pregnant women

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A B S T R A C T

Urinary tract infection (UTI) is common in pregnancy. It can be asymptomatic, as well as symptomatic, complicating the diagnostic process. It is of importance to obstetricians because of its association with significant maternal and perinatal morbidity and mortality. The main causative pathogen involved in recurrent UTI in women is *Escherchia coli*, which is responsible for approximately 80% of all episodes of infection. Other significant pathogens include *Staphylococcus saprophyticus*, *Klebsiella pneumoniae*, and *Proteus mirabilis*, which each cause approximately 4% of all episodes of acute cystitis. *Citrobacter* and *Enterococci* are less likely causes of UTI in women. Treatment and drugs involved in the urinary tract infection. Role of drugs in the recovery from UTI to prevent the infertility.

Introduction

Urinary tract infection (UTI) is common in pregnancy. It can be asymptomatic, as well as symptomatic, complicating the diagnostic process. It is of importance to obstetricians because of its association with significant maternal and perinatal morbidity and mortality. It is estimated that in young women there are 0.5 episodes of acute cystitis per person per year.(3) This incidence decreases with age. In postmenopausal women, it is estimated that there are 0.07 episodes of acute cystitis per person per year.4 Recurrent UTI is defined as 2 uncomplicated UTIs in 6 months or, more traditionally, as > 3 positive cultures

within the preceding 12 months.(5,6) This is estimated to affect 25% of women with a history of UTI. When there is recurrent infection with the same organism despite adequate therapy, it is considered a relapse. Reinfection is defined as recurrent UTI caused by a different bacterial isolate, or by the previously isolated bacteria after a negative intervening culture or an adequate time period (2 weeks) between infections.(7) Reinfection is more common than relapse.8 Most recurrences occur within the first 3 months after the primary infection, and there can often be clustering of infections.(9,10) When the initial infection is caused by E.

coli, there is a higher risk of reinfection within the first 6 months.(11)

Classic symptoms of acute lower UTI include dysuria, urinary frequency, and suprapubic pain plus or minus hematuria. Differential diagnoses include vaginitis, acute urethritis, interstitial cystitis, and pelvic inflammatory disease. Other organisms that may be involved and mimic acute cystitis include Chlamydia, *Neisseria gonorrhoea*, *Candida*, bacterial vaginosis, and herpes simplex virus.(12) Classic symptoms seem to be highly predictive of true disease. If dysuria, frequency, and hematuria are present in the absence of vaginal discharge, the probability of a positive culture is 81%.(12) Women with recurrent UTI can self-diagnose on the basis of symptoms very accurately, with an 84% positive culture rate.(13) Positive predictive factors for recurrent UTIs in women are symptoms after intercourse, a prior history of pyelonephritis, absence of nocturia, and prompt resolution of symptoms (48 hours) after initiation of treatment. The main negative predictors are the presence of nocturia and persistence of symptoms between episodes of treated infection. (5)

Normal urine is sterile: therefore infection could, theoretically, be diagnosed if a single bacterium was isolated from the urinary tract. In practice, voided urine becomes contaminated in the nonsterile distal urethra. Consequently, with logarithmic bacterial proliferation rates, most individuals diagnosed with urinary infection have bacterial counts of 10^4 – 10^5 /ml. Quantitative urine culture is, therefore, a necessity for diagnosis. Even among bacteriologists there is little consensus on the urinary bacterial concentration that is truly diagnostic of infection. Traditionally, the criterion of 10^5 bacteria/ml has been used, as concentrations at this level

represent a chance of contamination of 1%. Use of the lower concentration of 10^4 bacteria/ml is also appropriate but, because of the higher risk that it represents only bacterial contamination rather than true infection, purity of culture becomes the major determinant of an accurate diagnosis. Consequently, a diagnosis is only made if a single strain of uropathogen (or predominantly one with only very minor contamination) is isolated. At concentrations of 10^3 – 10^4 bacteria/ml there is a 50% chance that contamination is responsible; most laboratories request a repeat sample and culture. Isolation of the same organism in a second culture is more indicative of significant bacteriuria.

Classification

Asymptomatic bacteriuria: Defined as persistent colonisation of the urinary tract by significant numbers of bacteria in women without urinary symptoms.

Acute cystitis: Distinguished from asymptomatic bacteriuria by the presence of symptoms such as dysuria, urgency, frequency, nocturia, haematuria 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.

Pathophysiology: The main causative pathogen involved in recurrent UTI in women is *E. coli*, which is responsible for approximately 80% of all episodes of infection. Other significant pathogens include *Staphylococcus saprophyticus*, *Klebsiella pneumoniae*, and *Proteus mirabilis*, which each cause approximately

4% of all episodes of acute cystitis. Citrobacter and Enterococci are less likely causes of UTI in women.(14) Infection with organisms that do not usually cause UTIs may be an indicator of underlying structural abnormalities or renal calculi.(7) Uropathogenic E. coli have virulence factors, such as the type of fimbria, that promote binding to the epithelium of the vagina and urethra and enhance their ability to cause cystitis. Other factors increase resistance to serum bactericidal activity and host defence mechanisms. Animal models suggest that E. coli can remain dormant in large bacterial reservoirs within the host and be reactivated to cause infection in the future.(15) In a 2007 study,(16) midstream urine samples from women with acute uncomplicated cystitis also showed evidence of intracellular bacterial communities of uropathogenic E. coli. These communities are relatively protected from host immune response mechanisms and antibiotic therapy and may reactivate, causing recurrent UTI.(16) In the classic theory for development of UTI, the uropathogen is part of the fecal flora. It colonizes the vagina and distal urethra. Subsequently, it ascends into the bladder and causes infection. This model is the same for sporadic and for recurrent UTI in women.(8,17) Reservoirs of uropathogenic bacteria can remain in the gastrointestinal tract and vagina of the susceptible individual. The results of one study suggest that household members, including pets, could act as reservoirs for the recolonization of a person with UTI.(18) Lactobacilli in the vagina are protective, because they prevent initial colonization with uropathogens.(19)

Clinical manifestations

Acute cystitis: Acute cystitis affects approximately 1% of all pregnant women. This condition is distinguished from

asymptomatic bacteriuria by the presence of symptoms such as dysuria, frequency, urgency and suprapubic pain in the absence of systemic illness. Thirty percent of women with asymptomatic bacteriuria will develop acute cystitis during their pregnancy. Whereas reagent strip analysis lacks the sensitivity to be used for asymptomatic bacteriuria screening, studies (39) have shown that the presence of nitrites in the urine of symptomatic women is strongly suggestive of significant bacteriuria. Positive detection of nitrite using a dipstick may be sufficient to prompt commencement of empirical antimicrobial treatment. As with asymptomatic bacteriuria, the final diagnosis rests on quantitative urine culture. Any empirical treatment should be reviewed and changed if necessary following antimicrobial sensitivity testing. A differential diagnosis of gonococcal and nongonococcal urethritis must be considered. These acute urethral syndromes can present with dysuria, frequency, pyuria and sometimes haematuria but without significant bacteriuria upon culture. The only distinguishing clinical finding is the presence of urethral discharge. Nongonococcal urethritis can be caused by Chlamydia, Mycoplasma and, rarely, Gram-negative bacteria. In one-third of cases, the cause remains unidentified. Nonurethral, non-urinary tract infections and chemical cystitis must also be excluded. Women can also present with symptoms of acute cystitis but have vulvitis, vaginitis or cervicitis secondary to conditions such as herpes simplex. It is, therefore, essential that an accurate physical examination is performed to complement a detailed clinical history

Pyelonephritis: Pyelonephritis is the most serious type of urinary infection in pregnancy, with an incidence of approximately 2%. It is responsible for most of the perinatal complications associated

with the presence of bacteriuria. Ninety percent of antepartum cases occur in the last two trimesters. It represents infection of a renal papilla, which if untreated can spread to multiple papillae and occasionally to the renal cortex. Pyonephrosis occurs when there is infection of the whole kidney; if the capsule ruptures, a perinephric abscess can develop. Gram-negative septicaemia and septic shock, leading to multiple organ failure, are serious sequelae. As women with pyelonephritis have acute cystitis in the early stages, lower urinary tract symptoms can initially predominate. It is, therefore, essential to evaluate all women for systemic symptoms such as pyrexia, rigor, nausea, vomiting and renal angle pain in order to establish an accurate diagnosis and initiate treatment. Fetal tachycardia can also be indicative of systemic infection and the fetus should be assessed as part of any clinical evaluation. The diagnostic gold standard in pyelonephritis is renal biopsy but this is impractical in clinical practice. A combination of symptoms, full blood count, inflammatory markers, renal function tests, blood culture, urine culture and sensitivity testing are used.

Treatment: Ampicillin and sulfonamides generally should not be used for empiric therapy because more than one third of isolates demonstrate in vitro resistance.(26,27) More than 15% to 20% of *E. coli* strains causing uncomplicated cystitis are now resistant to these agents in several areas of the United States and other countries.(28) The prevalence of resistance to nitrofurantoin among *E. coli* is < 5%, although non-*E. coli* uropathogens are often resistant. Resistance to the fluoroquinolones remains < 5% in most studies of uropathogenic strains. Three-day regimens are recommended because they are associated with better compliance, lower cost, and lower frequency of adverse

reactions than 7- to 10-day regimens.(29) Several studies and clinical experience have confirmed the effectiveness of 3-day regimens of trimethoprim, trimethoprim-sulfamethoxazole, or a fluoroquinolone for treatment of acute uncomplicated cystitis, and these agents are generally recommended for empiric therapy.(29) In comparison, 3-day regimens with beta-lactams are less effective than 5 days of therapy.(29) Nitrofurantoin is a safe and generally effective agent, but it should be administered for a minimum of 7 days. Single-dose regimens are somewhat less effective than 3- to 7-day regimens, even with fluoroquinolones.(27,29) First-line treatment suggested by the Infectious Disease Society of America in 1999 was TMP-SMX in a 3-day regimen.(29) Given the increasing prevalence of TMP-SMX resistance among uropathogens, it is important to examine risk factors predicting in vitro resistance. These are diabetes, recent hospitalization, antibiotic use in the past 3 to 6 months (for any reason), and recent TMP-SMX use.(30) Fluoroquinolones (norfloxacin, ciprofloxacin, ofloxacin, fleroxacin) are generally not recommended as first-line treatment because of their greater expense and concerns regarding the promotion of quinolone resistance. However, fluoroquinolones can become a reasonable first-line treatment for women who have or are suspected of having antimicrobial resistance or of being allergic to or not tolerating more conventional therapy, and for women in areas where resistance to TMP-SMX is > 15% to 20%.²⁹ Other reasonable empiric choices for mild cystitis include a 7-day course of nitrofurantoin or a single-dose of fosfomycin.²⁹ In 2007, Gupta et al. demonstrated the equivalent efficacy of a 5-day course of nitrofurantoin and a 3-day course of TMP-SMX.³¹ Recurrent cystitis that occurs during or within the first week

following treatment suggests possible relapse and should be managed with a pre-treatment urine culture, antimicrobial susceptibility testing, and treatment with a fluoroquinolone for 7 days.(8)

Conclusion

Significant bacteriuria in pregnancy is common and a serious cause of maternal and perinatal morbidity and mortality. Clinical presentations include asymptomatic bacteriuria, acute cystitis and pyelonephritis. All are amenable to investigation and treatment, substantially improving outcome. Pregnant women should be screened for asymptomatic bacteriuria by urine culture and treated with appropriate antimicrobials. Acute cystitis and pyelonephritis demand full assessment and treatment, with early involvement of other specialists in severe or systemic infection. All women should be reviewed to confirm post-treatment urine sterility. Empirical antimicrobial treatments will occasionally be required but any decision to treat should be re-evaluated once culture and sensitivity reports are available. When choosing an antimicrobial, the pharmacokinetics and bioavailability of the individual drug in pregnancy must be considered along with the resistance profiles of microorganisms in the local antenatal population. It is also vital to use treatments with an established safety profile and, most importantly, without teratogenetic risks.

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