Review Urinary tract infection in pregnancy

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Key content:

- Urinary tract infection during pregnancy is common and is associated with significant maternal and perinatal morbidity and mortality.
- It can be asymptomatic.
- Screening of all women by urine culture should be performed in early pregnancy, despite the cost.
- Treatment should be guided by urine culture and sensitivity reports.
- Antibiotic treatment should continue for 7 days, as shorter courses are not as effective during pregnancy.

Learning objectives:

- To identify the clinical presentations.
- To understand the evidence base for effective investigation and treatment.

Ethical issues:

- The empirical use of antimicrobial treatments increases drug resistance and must be balanced against delay in treatment and the associated morbidities.

Keywords acute cystitis / asymptomatic bacteriuria / pyelonephritis

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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.

Definition

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[1] 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.

For diagnostic accuracy, it is essential that contamination is minimised. Sterile suprapubic bladder aspiration is the 'gold standard' for diagnosing UTI but the use of sterile catheter samples can also reduce the contamination rate. Both methods are, however, poorly tolerated by women and, therefore, impractical to consider in routine antenatal practice. Random voided cultures are effectively useless because of very high contamination rates. The only pragmatic solution is to collect midstream samples of urine (MSSUs) after careful decontamination of the urethral meatus.

Classification

Urinary tract infection in pregnancy has three principal presentations (**Box 1**).

Incidence

In pregnancy, the overall incidence of UTI is approximately 8%.[2,3] The incidence of asymptomatic bacteriuria in pregnant women as determined in UK studies is 2–5%.[4] The incidence of acute cystitis is more difficult to accurately determine, as many women are treated empirically and culture not performed. However, one study[5] over a 6-year period determined a 1.3% incidence rate. The incidence of pyelonephritis during pregnancy is 2%, with up to 23% of women experiencing a recurrence in the same pregnancy.[6]

Aetiology

Urine is bacteriostatic to most local commensal bacteria and this is thought to result from its relatively acidic pH, high osmolality and high urea concentration. In an anatomically normal urinary tract, sterility is maintained by free antegrade flow through the ureteral and urethral valves.

In pregnancy, significant physiological changes occur in the urogenital tract, increasing the potential for pathogenic colonisation. Bladder volume increases and detrusor tone decreases. Additionally, 90% of pregnant women develop ureteric dilatation as the result of a combination of progestogenic relaxation of ureteric smooth muscle and pressure from the expanding uterus. There is relative sparing of the left ureter because of protection from the sigmoid colon and upper rectum. The net effect, however, is increased urinary stasis, compromised ureteric valves and vesicoureteric reflux, which facilitates bacterial colonisation and ascending infection.[2]

Seventy percent of pregnant women develop glycosuria and this, in combination with physiological aminoaciduria of pregnancy and a fall in urine osmolality, favours bacterial proliferation.[7]

Sexual activity in women has been established as a significant risk factor for UTI.[8] Intercourse can traumatise the urothelium of the distal urethra, resulting in increased bacterial invasion. The vagina can act as a reservoir for gastrointestinal bacteria, facilitating inoculation. In contrast with most

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.

Box 1
Classification of urinary tract infection in pregnancy

vulval and perineal commensal bacteria, Gram-negative bacteria from the bowel thrive in urine. Consequently, most urinary infections are caused by aerobic Gram-negative bacilli from the gastrointestinal tract. Difficulty with hygiene because of a distended, gravid abdomen can exacerbate the problem.

The role of immune system status during pregnancy in organism pathogenicity remains controversial.[9] Maternal immunity undergoes modification, favouring the implantation and development of the embryo. Research[10] suggests that the immune response is modulated from a cell-mediated to a humoral response. This mechanism does not solely rely on the recognition of cell-surface major histocompatibility complex (MHC) proteins, resulting in less efficient responses to bacterial cell surface proteins and possibly facilitating pathogenicity. While it is a misconception to depict pregnancy as an immunodeficient state, theoretically, these changes allow uropathogens to infiltrate, proliferate and ascend proximally.

The prevalence of infection increases with age and lower socioeconomic grouping. Concomitant urinary tract anomalies and maternal disease (for example, diabetes or sickle cell disease) also significantly increase risk.

Finally, it must be remembered that medical interventions during pregnancy can result in nosocomial infection; for example, urethral instrumentation and catheterisation predispose to ascending bacteriuria.

Bacteriology

The bacteria causing urinary infection in pregnancy essentially mirror those in nonpregnant patients. *Escherichia coli* accounts for 80–90% of infections[11] but other Gram-negative bacilli, such as *Proteus mirabilis* and *Klebsiella pneumoniae*, can be cultured. *Proteus, Klebsiella* and most *Enterobacteriaceae* species show urease activity and form urinary calculi, which can act as reservoirs of infection. The coagulase negative cocci, *Staphylococcus saprophyticus*, is the second most frequently cultured uropathogen,[12] while other Gram-positive cocci, such as group B haemolytic streptococci, are less frequently isolated but remain clinically important.[13] Other less common uropathogens include *Staphylococcus aureus* and *Mycobacterium tuberculosis*, which can arise via haematological inoculation rather than ascending infection. Nonbacterial causes include *Chlamydia* species and fungal infections, such as *Candida albicans*.

Group B streptococcal infection

Vaginal colonisation with group B streptococci is strongly associated with preterm rupture of membranes, labour and delivery and is a proven cause of neonatal sepsis. Evidence relating group B streptococcal bacteriuria with similar consequences is less well established.[14,15] However, treatment for urinary group B streptococcal infection is associated with a significant reduction in preterm, prelabour rupture of membranes and delivery rates.[16] Readers are referred to the Royal College of Obstetricians and Gynaecologists (RCOG) guideline[17] pertaining to prophylaxis of group B streptococcal infection.

Clinical manifestations

Asymptomatic bacteriuria

In 1962, Edward Kass[18] observed significant bacteriuria in 6% of asymptomatic pregnant women presenting for their first antenatal visit. He discovered that untreated asymptomatic bacteriuria was associated with adverse maternal outcomes, including symptomatic cystitis (up to 30%), pyelonephritis (up to 50%), preterm labour and delivery and adverse fetal outcomes, such as prematurity, low birthweight and increased perinatal mortality.[19,20] Other studies demonstrated subsequent pyelonephritis rates of up to 28% and preterm delivery rates of up to 12.8%.[21–23] While there have been undoubted changes in perinatal care since 1962 resulting in a reduction in overall morbidity and mortality, meta-analyses of studies evaluating asymptomatic bacteriuria in pregnancy conclude that there are true associations with preterm delivery and low birthweight.[24] In addition, there are increased risks of pre-eclampsia,[23] anaemia,[25] chorioamnionitis[26] and postpartum endometritis.[27] Fetal risks include fetal growth restriction,[28] stillbirth,[29] perinatal mortality,[29] mental retardation and developmental delay.[29] It is postulated that direct bacterial endotoxin damage, in combination with cerebral hypoperfusion, is responsible.[29] See **Table 1** and **Table 2**.

Screening and effective treatment significantly reduce the incidence of pyelonephritis, premature delivery and low birthweight[19,27,30] and with a bacteriuria prevalence of >2% is cost effective.[31] Urine culture has traditionally been the gold standard screening assessment but, despite excellent sensitivity, laboratory time and costs are considerable and it takes 24–48 hours to obtain results.

Archbald *et al.*[32] concluded that an ideal screening test should have high sensitivity, high specificity and should be simple, inexpensive and produce rapid results. Urine microscopy and reagent strip analysis have been postulated as alternatives to culture but concerns remain over the efficacy of these techniques. Most studies note a high false-negative rate for Gram staining and microscopy (up to 19.4%) and reagent strip testing

(up to 52.8%), precluding their use as screening tests for asymptomatic bacteriuria.[33–36] Other urine-based screening tests include the interleukin-8 test; rapid enzymatic test; chromogenic limulus amoebocyte lysate assay; semi-automated urine screen (Bac-T-screen®: Vitek Systems, Biomeriux Vitek Inc., Hazelwood, MO, USA); and the dip-slide quantitative kit (Uricult®: Orion Diagnostica Oy, Espoo, Finland). The RCOG have concluded that none of these approximate the sensitivity and specificity of urine culture and, therefore, cannot be advocated as screening tools for asymptomatic bacteriuria of pregnancy.[37]

In addition to providing a quantified assessment of the concentration of bacteriuria, culture also allows reliable identification of the organism involved and antibiotic sensitivity testing to guide effective therapy. With its high sensitivity and specificity, a single urine culture is sufficient for the reliable diagnosis of significant bacteriuria, provided there is rigorous attention to sample collection, storage and laboratory evaluation. Routine MSSU screening for asymptomatic bacteriuria in early pregnancy is a Grade A recommendation of the RCOG.[37] Follow-up cultures should be performed in women diagnosed with and treated for asymptomatic bacteriuria, as urine may not remain sterile for the entire pregnancy.[38]

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 non-gonococcal 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. Non-gonococcal 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.

Table 1
Perinatal consequences of bacteriuria in pregnancy[26,29]

Outcome	Odds ratio	95% CI
Low birthweight (<2.5 kg)	1.4	1.2–1.6
Prematurity (<37 weeks of gestation)	1.3	1.1–1.4
Preterm low birthweight (<2.5 kg/<37 weeks of gestation)	1.5	1.2–1.7
Developmental delay/mental retardation	1.4	1.0–1.9
Perinatal mortality	2.2	1.4–3.5

CI = confidence interval

Table 2
Maternal consequences of bacteriuria in pregnancy[26]

Outcome	Odds ratio	95% CI
Preterm labour (<37 weeks of gestation)	1.6	1.4–1.8
Severe hypertension/pre-eclampsia	1.4	1.2–1.7
Anaemia	1.6	1.3–2.0
Chorioamionitis	1.4	1.1–1.9

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

Asymptomatic bacteriuria

A Cochrane review[40] established that treatment reduces the risk of pyelonephritis in pregnancy and, consequently, the risks of preterm delivery and low birthweight. This review recommends that treatment schedules are directed by urine culture and sensitivity testing and that appropriate antibiotics are continued for at least 7 days. Several studies have tested shorter treatment courses and even single-dose schedules.[41,42] The rationale is to improve patient compliance and reduce side-effects but a Cochrane systematic review of short courses[42] found insufficient evidence to confirm treatment efficacy.

Careful follow-up is necessary to establish urine sterility; some authors advocate repeating MSSUs regularly until delivery.[39]

Acute cystitis

Most women with acute cystitis in pregnancy rapidly seek medical advice. Increasing oral fluid intake is frequently advocated as a first-line treatment for pregnant women with features of symptomatic urinary infection. This may be advised pending results of culture or in the belief that uropathogen concentration will be diluted. There is little evidence in the literature to advocate this treatment and it can exacerbate urinary frequency and dysuria in symptomatic women.[44]

Generations of women have been advised to drink cranberry juice to treat urinary infection and inhibit the symptoms. A Cochrane systematic review[45] determined that there is no good-quality evidence in the literature to suggest that this is an effective treatment.

Urine alkalinising agents have also been popular for the treatment of women with urinary symptoms but, again, the benefits of such treatments have not been established and there are particular concerns with regard to hypernatraemia and the use of sodium citrate in pregnancy. The general advice is to avoid these preparations.[46]

The use of simple analgesia is appropriate to reduce the symptoms of suprapubic discomfort and, perhaps, dysuria but caution must be taken to ensure that the treatments used have no teratogenic potential, that they have minimal side-effects and that women do not inadvertently exceed the maximum dosages. There is little evidence to support the use of topical local anaesthetics to reduce dysuria symptoms.

In many cases, empirical antimicrobial treatment is initiated before results of urine culture and sensitivity testing become available. It is essential to re-evaluate empirical treatment once culture results are known and to adjust it accordingly. Again, a 7–10 day course of an appropriate antimicrobial is usually sufficient to eradicate infection. Shorter courses and single-dose strategies for uncomplicated infections have been tested but reported success rates vary and a consensus opinion on the suitability of these strategies is not available.[47–50] The concern is undertreatment, leading to persistent infection and progression to pyelonephritis.

Follow-up is essential and primary treatment failures or relapses should be treated with a full 7-day course of a different antimicrobial in accordance with sensitivity testing. The possibility of underlying pathology should also be considered.

Pyelonephritis

The majority of women with clinical features of pyelonephritis require hospital admission. Outpatient management and oral antimicrobial treatment can be considered for some women with minimal symptoms.[51,52]

A full maternal clinical history and examination is mandatory, along with an assessment of fetal wellbeing. Blood culture (aerobic and anaerobic) should be performed and vaginal swabs and an MSSU taken for culture before starting treatment. In general, antimicrobial therapy is initiated empirically, usually parenterally, particularly where the woman is pyrexial or has nausea and vomiting. Initial therapy is usually broad spectrum, with subsequent narrowing of the treatment spectrum when culture and sensitivity reports are available. Parenteral treatment should be continued until the woman is afebrile for a minimum of 24 hours. While most maternity units have their own antibiotic protocols and regimens, it is important to re-evaluate treatment if the woman is not responding within 24–48 hours and once culture and sensitivity results become available.

Many women experience severe renal angle pain and analgesia is necessary. Simple analgesics usually suffice but opiates can be necessary in severe cases, or for concomitant renal colic. Nonsteroidal anti-inflammatory drugs (NSAIDs) should be avoided, as they are associated with fetal risks of oligohydramnios and premature ductus arteriosus closure and maternal risks of gastric mucosal ulceration and reduced renal perfusion.

Thromboprophylaxis should be used if the woman has reduced mobility or a period of bedrest. The use of graduated compression stockings and low molecular weight heparin is advocated.[53]

The risks of preterm labour increase significantly during an episode of acute pyelonephritis. Tocolysis is frequently necessary. Antenatal steroids for fetal

lung maturity should be considered if there is evidence of threatened preterm labour. We refer readers to the RCOG guidelines with respect to tocolysis[54] and antenatal steroid administration.[55]

Antimicrobial treatment for pyelonephritis should be continued for a minimum of 10 days, as relapses can occur after only 7 days of treatment. Some advocate treatment for a longer, 14–21 day, period. Urine sterility must be confirmed after treatment and assessed throughout the remainder of the pregnancy.

If the woman deteriorates or is unresponsive to conventional treatment, appropriate specialists should become involved, for example, urologists, nephrologists, intensivists and microbiologists. Initial investigation and resuscitation should be instituted as soon as severe sepsis or septic shock is diagnosed and not delayed pending specialist assessment or admission to an intensive care unit.[53]

The most common reason for initial treatment failure and deterioration is uropathogen resistance to antimicrobial treatment. This should be re-evaluated in the light of culture results and the advice of the microbiology department should be sought and antibiotics changed as appropriate. If there is treatment failure when appropriate antimicrobials have been used, it is important to exclude underlying pathology or renal tract anomaly. Renal calculi (incidence: 1/1500 pregnancies)[56] can cause persistent infection. Radiological advice regarding appropriate imaging modalities should be sought.

Recurrent infection

Urinary infection recurs in 4–5% of pregnancies. The risks of developing pyelonephritis and its potential consequences are the same as for the primary infection. The exact aetiology is uncertain but re-infection by coliform bacteria from the vaginal reservoir can occur as a result of sexual activity. Urinary tract anomalies must be excluded and postpartum evaluation is advisable after several episodes of antenatal infection.[56] Long-term, low-dose antimicrobial cover, or single postcoital doses, have been advocated for the remainder of the pregnancy.[27]

Antimicrobials in pregnancy

Pregnancy increases glomerular filtration rates, with a resultant increase in the elimination rate of renally-excreted medications. This, combined with increased maternal plasma volume, effectively reduces serum drug concentrations and can adversely affect the amount of therapeutic activity at the target tissue (bio-availability). This is especially a problem with ß-Lactam antibiotics, including penicillins and cephalosporins.[57] In addition, polyuria and frequency reduce urinary drug concentration and the therapeutic window within the urinary tract.[48] Consequently, it may be necessary to increase administration dosages or prescribe hydrophilic drugs to ensure efficacy.[58]

It is essential to remember potential maternal side-effects, drug interactions and the possibility of teratogenicity when any medication is prescribed in the antenatal period, especially in early pregnancy.[59] Even when organogenesis is complete, the potential fetal effects of medications must be considered.[60]

When instituting empirical treatments, it is vital to consider the profile of putative causative organisms and antimicrobial resistance trends within the local antenatal population.[61] As this varies between areas, audit and liaison with local microbiologists is essential to guide efficacious treatment strategies.

Within the context of this review, it is impractical to cover the spectrum, pharmacokinetics, interactions and risks of specific antimicrobials in pregnancy. We refer readers to authoritative texts such as the *British National Formulary*, which should be consulted prior to treatment commencement.

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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