Asymptomatic bacteriuria and urinary tract infections in pregnancy – a review of the literature

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Abstract

The approach to the management of asymptomatic bacteriuria (AB) and urinary tract infections (UTIs) in pregnancy, including the choice of antibiotics, is not always straightforward. The aim of this article is to review the literature on AB and UTI in pregnancy and to discuss the findings. Various internet search engines were used to identify references regarding pregnancy-associated AB and UTI, which formed a framework for the literature review. Both conditions were found to be common in pregnancy. Pregnancy-associated UTI is defined as either a lower urinary tract infection (acute cystitis) or an upper urinary tract infection (acute pyelonephritis). The approach to the management of pregnancy-associated AB and UTI presents a complex issue, including the choice of antibiotics. UTIs occur when there are at least 100,000 organisms present per ml of urine in an asymptomatic patient, or more than 100 organisms per ml of urine with accompanying pyuria (more than seven white blood cells per ml in a symptomatic patient). A diagnosis of UTI requires a positive culture and identification of the pathogen, especially in patients with vague symptoms. UTIs are associated with risks to both the mother and the fetus, including pyelonephritis, preterm birth, low birthweight and increased risk of perinatal mortality. AB occurs when the bacterial count is greater than 100,000 organisms per ml in two consecutive samples of urine and in the absence of declared symptoms. If AB remains untreated during pregnancy, the risk of developing cystitis is 40% and the risk of developing pyelonephritis is 25–30%. The tendency for AB to progress to pyelonephritis is higher in pregnant women than in non-pregnant women and is associated with an increased risk of preterm birth, low birthweight and perinatal mortality. Appropriate antibiotics are recommended for both pregnant and non-pregnant women. Short-term courses have been recommended to minimize antimicrobial exposure to the fetus. The prognosis of the majority of pregnant women with UTI or AB during pregnancy is good. Most long-term sequelae are due to complications associated with septic shock, respiratory failure or hypotensive hypoxia with extreme gangrene. UTIs associated with pregnancy have few direct sequelae in view of the fact that fetal bloodstream infection is rare; nevertheless, uterine hypoperfusion due to maternal dehydration, maternal anaemia and direct bacterial endotoxin damage to the placental vasculature may result in fetal cerebral hypoperfusion. Untreated upper UTIs in pregnant women are associated with low birthweight, prematurity, premature labour, hypertension, pre-eclampsia, maternal anaemia and amnionitis. UTIs which occur during pregnancy are associated with intrauterine growth retardation, pre-eclampsia, preterm delivery and caesarean delivery. In order to avoid or minimize complications that may be associated with AB and UTI during pregnancy, both should be appropriately treated. Several antibiotic treatments are available and details of the antibiotic therapies are discussed below.

Introduction

Pregnancy causes a number of changes to a woman’s body, including mechanical and hormonal changes that may increase the risk of urinary stasis and vesicoureteric reflux. These changes, combined with a short female urethra (approximately 3–4 cm) and difficulty with hygiene as a result of distended abdomen during pregnancy, are responsible for the increase in frequency of urinary tract infections (UTIs) in pregnant women. UTIs are one of the most common bacterial infections occurring during pregnancy.

In view of the physiological changes associated with pregnancy, pregnant patients are regarded as immunocompromised hosts for UTIs. These physiological changes add to the risk of serious infectious complications that may be associated with asymptomatic and symptomatic UTIs, even in pregnant women who are considered to be healthy.

This article provides a review of the literature on asymptomatic bacteriuria (AB) and UTIs, including a summary of the salient points and recommendations.
regarding the management of AB and UTIs during pregnancy.

**Literature review**

**Definitions of key terms**

Conventionally, UTI has been categorised as upper urinary tract infection (acute pyelonephritis) or lower urinary tract infection (acute cystitis).

Asymptomatic bacteriuria can be diagnosed when a positive urine culture is identified in a patient who is asymptomatic.

**Urinary tract infection**

Urinary tract infection has been defined as the presence of at least 100,000 organisms per ml of urine in an asymptomatic patient, or more than 100 organisms per ml of urine when accompanied by pyuria (more than seven white blood cells per ml in a symptomatic patient). It has been stated that a diagnosis of UTI should be supported by a positive culture for a uropathogen, especially in patients with vague symptoms. It has also been reported that UTIs are associated with risks to both the mother and the fetus, including pyelonephritis, preterm delivery, low birthweight and perinatal mortality.1

**Asymptomatic bacteriuria**

Asymptomatic bacteriuria is usually defined as the presence of > 100,000 organisms per ml of urine in two consecutive samples of urine in an asymptomatic patient. It has been stated that the risk to pregnant women of developing cystitis following untreated AB is 40% and the risk of developing pyelonephritis is 25–30%, and that these cases account for 70% of all cases of symptomatic UTI in unscreened pregnant women.1

**Acute pyelonephritis**

It has been reported that pyelonephritis is the most common urinary tract complication in pregnant women and occurs in approximately 2% of all pregnancies.1 It has also been reported that acute pyelonephritis characteristically presents alongside nausea, vomiting, increased frequency of micturition, urinary urgency and dysuria. Additionally, women who have additional risk factors (for example, diabetes, immunosuppression, neurogenic bladder, sickle cell anaemia or recurrent persistent UTIs prior to pregnancy) are at increased risk for the development of a complicated UTI.1

**Acute cystitis**

Acute cystitis affects the lower urinary tract only; inflammation of the urinary bladder may be a sequel of bacterial or non-bacterial causes, for example viral infection or radiation.1 It has been stated that about 1% of pregnant patients develop acute cystitis and 60% of these patients are found to have a negative result on initial screening.1 Their symptoms include dysuria, haematuria, suprapubic discomfort, increased frequency of micturition, urinary urgency and nocturia, which are symptoms that are often difficult to distinguish from the symptoms related to the pregnancy itself; in addition, upper urinary tract disease (for example, pyelonephritis) complicates acute cystitis in 15–50% of cases.1

**Pathophysiology**

**Epidemiology of asymptomatic bacteriuria**

Stenqvist et al.2 reported that bacteriuria occurs in 2–7% of pregnancies, and is more common in multiparous women. A similar prevalence of bacteriuria is seen in non-pregnant women and the causative species and their virulence factors are similar in both pregnant and non-pregnant women. In view of these facts, the basic mechanism of bacterial entry into the urinary tract is likely to be the same for both pregnant and non-pregnant women.2

Kaitz3 reported that bacteriuria often develops within the first months of pregnancy and is frequently associated with a reduction in the ability of the kidney to concentrate urine, which would suggest involvement of the kidney.3 A number of authors4–6 have suggested that the smooth muscle relaxation and subsequent ureteral dilatation that is associated with pregnancy facilitates the ascent of bacteria from the urinary bladder to the kidney. As a result, bacteriuria during pregnancy has a greater propensity to progress to the kidneys and the risk of developing pyelonephritis is 20- to 30-fold higher in pregnant women with AB than in non-pregnant women without AB.7

A number of authors8–11 have observed an association between bacteriuria and an increased
risk of preterm birth, low birthweight and increased risk of perinatal mortality. Naeye\textsuperscript{8} reviewed more than 50,000 pregnancies between 1959 and 1966, and found that the rate of perinatal mortality of any cause was higher among women who developed bacteriuria and/or pyuria (there was no comment regarding absence or presence of symptoms in this review paper) in the first 2 weeks of pregnancy than in those who did not. Reports of various studies\textsuperscript{5,12–16} have shown that treatment of bacteriuria during pregnancy reduces the incidence of these complications and lowers the long-term risk of sequelae following AB.\textsuperscript{17}

**Diagnosis of asymptomatic bacteriuria**

Nicolle et al.\textsuperscript{18} reported that the diagnosis of AB should be based on the result of a urine specimen culture that has been collected with minimal contamination and that, in the case of asymptomatic women, bacteriuria should be diagnosed based on two consecutive voided urine specimens with isolation of the same bacterial strain in quantitative counts of $\geq 10^5$ colony-forming units (cfu)/ml, or a single catheterized urine specimen with one bacterial species isolated with a quantitative count of $\geq 10^2$ cfu/ml. Hooton et al.\textsuperscript{19} stated that, despite the aforementioned, in clinical practice, only one voided urine specimen is usually obtained and treatment is usually commenced in women with asymptomatic bacterial counts of $\geq 10^5$ cfu/ml without a confirmatory repeat culture. Hooton et al.\textsuperscript{19} also reported that, in order to avoid the risk of infection, routine catheterization to screen for bacteriuria is not warranted.\textsuperscript{19}

Hooton et al.\textsuperscript{19} reported that in order to avoid false-positive results, proper handling and processing of the specimen is vital. Isolation of more than one species, or the presence of *Lactobacillus* or *Propionibacterium*, may suggest a contaminated specimen, and isolation of *Lactobacillus* necessitates treatment if it is the only organism that has been isolated in consecutive urine cultures with high colony counts, although the significance in pregnancy is unknown.

A number of studies that have examined rapid screening tests, for example reagent strip, enzymatic screen or interleukin 8, have found that the sensitivity, specificity and predictive value of these tests for the detection of AB in pregnant women are nowhere near those of urine culture and therefore should not be used.\textsuperscript{20–22} Furthermore, urine cultures are beneficial in guiding therapy and this can be pertinent in pregnancy, when there is reduction in the number of safe therapeutic alternatives.

Lin and Fajardo\textsuperscript{23} stipulated that screening for AB should be undertaken either during the first prenatal visit or between weeks 12 and 16 of pregnancy. Hooton et al.\textsuperscript{19} reported that rescreening for bacteriuria could be considered in women who are at high risk, for example women with haemoglobin S, women during preterm labour and women with urinary tract abnormalities.

Infectious Diseases Society of America (ISDA) 2005 guidelines for the diagnosis and treatment of AB in adults recommended screening urine during pregnancy and treatment of a positive urine culture.\textsuperscript{18} A number of studies have found that early screening and treatment for AB during pregnancy is associated with benefits for both the mother and the fetus.\textsuperscript{6,13–15}

It is widely accepted that penicillin and cephalosporins are reasonably safe antibiotics to prescribe to pregnant women. However, it may be inappropriate to prescribe antibiotics with high protein binding, for example ceftriaxone, within 24 hours of parturition because of the risk of displacement of bilirubin and subsequent development of kernicterus.\textsuperscript{19}

Some problems are reported to be associated with some drugs during pregnancy:

- **Nitrofurantoin and sulphonamides:** Crider et al.\textsuperscript{24} reported an association with birth defects. Hooton et al.\textsuperscript{19} suggested that if there is an alternative antibiotic which is safe and effective, then the safest course would be to avoid nitrofurantoin during the first trimester of pregnancy.

- **Nitrofurantoin:** Ben David et al.\textsuperscript{25} reported nitrofurantoin to be a cause of haemolytic anaemia in both the mother and the fetus with glucose-6-phosphate dehydrogenase deficiency. Some studies\textsuperscript{26,27} estimated the risk of haemolytic anaemia, in association with the use of nitrofurantoin, to be 0.0004% of cases but authors\textsuperscript{26,27} recommend that nitrofurantoin should be avoided near term in order to avoid haemolytic anaemia in both the mother and the fetus.

- **Sulphonamides:** In view of the fact that sulphonamides have the ability to increase the level of unbound bilirubin in the neonate
Despite the fact that kernicterus related to in utero sulphonamide exposure has so far not been reported, Hooton et al.\(^1^9\) advised that the use of sulphonamides during pregnancy should be avoided.

- **Trimethoprim**: Crider et al.\(^2^4\) advised that trimethoprim should be avoided during the first trimester of pregnancy as it is a folic acid antagonist and has caused abnormal embryo development in experimental animals. Although it is not a proven teratogen in human beings, some studies\(^2^8,2^9\) have reported a possible association between the use of trimethoprim and birth defects. Hooton et al.\(^1^9\) suggested that as pregnant women are routinely prescribed folic acid supplements, the use of trimethoprim should be avoided.

- **Fluoroquinolones and tetracyclines**: Hooton et al.\(^1^9\) stated that fluoroquinolones and tetracyclines are inadvisable during pregnancy.

- **Fosfomycin**: Stein\(^3^0\) reported that the use of fosfomycin is safe during pregnancy.

Some authors have stipulated that the use of short-course antibiotic therapy is most often effective in eradicating AB during pregnancy.\(^3^1,3^3\)

Hooton et al.\(^1^9\) recommended a short course of the following therapeutic treatments to eradicate AB if the bacteria are susceptible:

- **amoxicillin**: 500 mg orally every 12 hours for 3–7 days;
- **Augmentin**: amoxicillin (500 mg) and clavulanate (125 mg) orally every 12 hours for 3–7 days;
- **nitrofurantoin**: 100 mg orally every 12 hours for 5 days;
- **cephalexin**: 500 mg orally every 12 hours for 3–7 days;
- **fosfomycin**: 3 g orally as a single dose.

- **Sulphonamides**: Hooton et al.\(^1^9\) advised that sulphonamides should not be given in the final days preceding parturition because they easily traverse the placenta and can displace bilirubin from bilirubin binding sites in the newborn and, therefore, there is a theoretical risk of kernicterus in the newborn. Hooton et al.\(^1^9\) also stated that sulphonamides may be used in pregnancy; however, it should be kept in mind that resistance among uropathogens is high and sulphonamides offer no advantage over the aforementioned antibiotics.

With regard to patient follow-up, Patterson and Andriole\(^1^0\) stated that a follow-up urine culture should be performed 1 week after the completion of treatment but a short course of treatment fails to eliminate AB in up to 30% of women. Hooton et al.\(^1^9\) recommend repeating the urine cultures at monthly intervals until parturition in order to identify persistent or recurrent bacteriuria.

Hooton et al.\(^1^9\) reported that suppressive or prophylactic antibiotics may be prescribed in women with persistent bacteriuria after two or more courses of therapy. They suggested that 50–100 mg of nitrofurantoin should be taken orally every day (if the bacterium is susceptible to nitrofurantoin) throughout the pregnancy and that monthly urine cultures are not necessary if suppressive therapy is being given. As breakthrough bacteriuria can occur during suppressive therapy, Hooton et al.\(^1^9\) suggested that a urine culture should be performed at the beginning of the third trimester to ensure the suppression is effective.

### Acute Cystitis

Acute cystitis is defined as a symptomatic infection of the urinary bladder that can occur alone or it may be complicated by ascending infection and pyelonephritis. When acute cystitis occurs during pregnancy, it is considered complicated as it is often associated with ascending infection or pyelonephritis.\(^1^9\) Some authors\(^3^4,3^5\) report that acute cystitis occurs in about 1–2% of pregnant women.

Stamm et al.\(^3^6\) stated that:

- A urine culture should be performed in pregnant women with symptoms suggestive of acute cystitis.
- Low colony counts in the urine culture specimens have been noted to be significant in symptomatic non-pregnant women, despite the fact that studies to define thresholds representing significant bacteriuria in pregnant women have not been performed.
- In women who have had uncomplicated cystitis, coliform colony counts in voided urine specimens as low as 10\(^2\) cfu/ml were adjudged to reflect infection.

Nevertheless, Hooton et al.\(^1^9\) reported that the majority of clinical laboratories do not routinely...
quantify urine isolates to the level of $10^2$ cfu/ml and thus they recommend that it would be reasonable to adopt a quantitative count of $\geq 10^3$ cfu/ml in a symptomatic pregnant woman as an indicator of symptomatic UTI.

With regard to treatment of cystitis during pregnancy, some authors\textsuperscript{10,37} have suggested a 3–7-day course of antibiotics, provided there are no symptoms suggestive of pyelonephritis. Other studies\textsuperscript{38–40} stated that short-term therapy is associated with decreased costs and side-effects, with improved compliance, and less fetal exposure to drugs.\textsuperscript{37}

Hooton \textit{et al.}\textsuperscript{19} suggested the use of one of the following treatment options while awaiting the results of urine culture and sensitivity:

- Augmentin: amoxicillin (500 mg) and clavulanic acid (125 mg) orally every 12 hours for 3–7 days;
- nitrofurantoin: 100 mg orally every 12 hours for 5 days;
- cefpodoxime: 100 mg twice daily for 3–7 days;
- fosfomycin: 3 g orally as a single dose;
- trimethoprim–sulphamethoxaxole: one double-strength dose twice daily for 3 days in the second trimester, but this should be avoided both in the first trimester and near term;
- amoxicillin: 500 mg twice daily every 12 hours for 7 days for the treatment of Enterococcus infection.

Hooton \textit{et al.}\textsuperscript{19} additionally warned that fluoroquinolones should be avoided in pregnancy.

With regard to follow-up, it has been recommended that a urine specimen should be collected and sent for culture and sensitivity 1 week after completion of treatment to confirm the absence of bacterial growth and resolution of cystitis.\textsuperscript{19} It has also been recommended that the urine culture should be repeated at monthly intervals until the end of pregnancy to assess for persistent or recurrent bacteriuria.\textsuperscript{19}

It has been suggested that if bacteriuria persists after two or three courses of antibiotic treatment, suppressive therapy could be initiated and a daily oral dose of 50 mg nitrofurantoin at bedtime for the duration of the pregnancy could be prescribed, if the organism is susceptible.\textsuperscript{19} Monthly urine culture may not be necessary if suppressive therapy is used; however, in order to detect a breakthrough infection, another urine culture should be conducted at the beginning of the third trimester and, if a subsequent urine culture is positive, then a different antibiotic therapy should be used, based on the sensitivity pattern of the bacteria and an assessment of the suppressive therapy.\textsuperscript{19}

With regard to recurrent UTIs (recurrent cystitis), the use of prophylactic antibiotics has been recommended for the duration of the pregnancy in the following forms depending on the sensitivity profile of the cystitis-causing strains.\textsuperscript{19}

- Postcoital prophylaxis: if the UTI or cystitis is presumed to be coitus related, treat with 50–100 mg nitrofurantoin orally and postcoitally, or 250–500 mg cephalexin orally and postcoitally.
- Daily prophylaxis: to be prescribed in situations of increased risk of urinary complications during episodes of UTI or cystitis (for example, if the patient suffers from diabetes mellitus or sickle cell trait). In such situations, prophylaxis must be considered following the first UTI (50–100 mg of nitrofurantoin orally every evening or 250–500 mg of cephalexin orally every evening).

With regard to recurrent cystitis or UTIs preceding pregnancy, which is usually related to sexual intercourse and treated with postcoital prophylaxis, Pfau and Sacks\textsuperscript{41} carried out a prospective study on 33 women with a history of recurrent UTIs and who had a total of 39 pregnancies with a single postcoital dose of either 250 mg cephalexin or 50 mg nitrofurantoin. Only one UTI occurred during pregnancy in comparison with the 130 UTIs that had occurred during a mean observation period of 7 months prior to the use of prophylaxis. Based upon the experience of Pfau and Sacks,\textsuperscript{41} Hooton \textit{et al.}\textsuperscript{19} made the following recommendations:

- In pregnant women who have had recurrent UTIs that are considered to be temporally related to sexual intercourse, postcoital prophylaxis should be used.
- The preferred prophylactic treatment should be a single postcoital dose of either 250 mg cephalexin or 50 mg nitrofurantoin.

**Acute pyelonephritis**

Acute pyelonephritis is an infection of the kidney that tends to present with flank pain, nausea and
vomiting, pyrexia > 38°C and/or costovertebral angle tenderness, which may occur in the absence or presence of cystitis symptoms.

Some authors\textsuperscript{10,18} have reported that, although the prevalence of AB in pregnant women is similar to that in non-pregnant women, as many as 30–40% of pregnant women with untreated AB may develop a symptomatic UTI, including pyelonephritis, during pregnancy. Other authors\textsuperscript{6,18} have reported that the risk of pregnant women developing acute pyelonephritis is reduced by 70–80% if bacteria are eradicated.

The pregnancy-related anatomical changes in the urinary tract that predispose pregnant women to pyelonephritis include:

- pressure on the urinary bladder from the enlarging uterus;
- an increase in the size of the ureters due to smooth muscle relaxation;
- the immune suppression of pregnancy; for example, mucosal interleukin-6 levels and serum antibody responses to \textit{Escherichia coli} antigens are reported to be lower in pregnant women.\textsuperscript{42}

Organisms reported to be cultured in the general obstetric population include:

- \textit{E. coli}, in 70% of cases;\textsuperscript{43}
- \textit{Klebsiella} or \textit{Enterobacter}, in 3% of cases;
- \textit{Proteus}, in 2% of cases;
- Gram-negative organisms including group B \textit{Streptococcus}, in 10% of cases.

With regard to the clinical manifestations of acute pyelonephritis in pregnancy, Hooton \textit{et al.}\textsuperscript{19} reported that the presentation is similar in pregnant and non-pregnant women and that pregnant women may become ill and are at risk of developing both medical and obstetric complications from pyelonephritis.

Complications associated with pyelonephritis in pregnancy which were reported by Hill \textit{et al.}\textsuperscript{43} include:

- anaemia: 23%;
- bacteraemia: 17% in the minority of the pregnant patients who were tested;
- respiratory insufficiency: 7%;
- renal dysfunction: 2%.

Cox \textit{et al.}\textsuperscript{44} reported that the mechanism of anaemia associated with pyelonephritis in pregnancy is not well understood; nevertheless, haemolysis mediated by endotoxin may be of importance.

Some authors\textsuperscript{45,46} estimated that 20% of women with severe pyelonephritis will develop complications that include septic shock syndrome or its variants, including acute respiratory distress syndrome. Thompson \textit{et al.}\textsuperscript{47} described acute renal failure with microabscesses and suppurative pyelonephritis in isolated cases, independent of sepsis.

A number of authors have reported a relationship between maternal UTI, especially AB, and adverse pregnancy outcomes including preterm birth and low birthweight.\textsuperscript{6,10,48,49} They have suggested that acute pyelonephritis has a similar association with adverse pregnancy outcomes but the association is not definitely known, in view of confounding variables such as economic status and previous preterm birth. It is worth noting that Hill \textit{et al.}\textsuperscript{43} reported that preterm birth occurred in 5% of women with pyelonephritis, which is similar to the rate of preterm birth in the general obstetric population.

Hooton \textit{et al.}\textsuperscript{19} stated that pyelonephritis should not be an indication for induction of labour or caesarean section. If induction of labour or caesarean section is planned for standard obstetric reasons in patient receiving treatment for pyelonephritis, the authors recommended delaying induction until the patient is afebrile, as long as the delay in delivery is relatively safe for both the mother and the fetus.

It has been stated that pregnant women with pyelonephritis are traditionally admitted to hospital and given intravenous antibiotics until the mother has been afebrile for 24 hours and her symptoms have improved.\textsuperscript{50}

With regard to treatment of acute pyelonephritis in pregnancy, Hooton \textit{et al.}\textsuperscript{19} recommend that the initial choice of antibiotics should be guided by the local microbiology and sensitivity data; however, generally, parenteral beta-lactams (\beta-lactams) are the preferred antibiotics which include:

1. \textit{In mild to moderate pyelonephritis}
   - ceftriaxone: 1 g every 24 hours;
   - cefepime: 1 g every 12 hours;
aztreonam: 1 g every 8–12 hours (with a warning of the possibility of ototoxicity which occurs with aminoglycosides and that this treatment should be used only if intolerance precludes the use of less toxic agents);
ampicillin: 1–2 g every 6 hours;
gentamicin: 1.5 mg/kg every 8 hours (with a warning of the possibility of ototoxicity which occurs with aminoglycosides and that this treatment should be used only if intolerance precludes the use of less toxic agents).

2 In severe pyelonephritis with immune compromise and/or incomplete urinary drainage

ticarcillin–clavulanate: 3.1 g every 6 hours;
piperacillin–tazobactam: 3.375 g every 6 hours;
meropenem: 500 mg every 8 hours;
etrapenem: 1 g every 24 hours;
doripenem: 500 mg every 8 hours.

According to Hooton et al.,19 fluoroquinolones should be avoided in pregnancy.

With regard to duration of therapy, it has been stated that both pregnant and non-pregnant patients with complicated pyelonephritis should show definite improvement within 24–48 hours of therapy. Once the patient has been afebrile for 48 hours, oral antibiotic therapy, guided by culture susceptibility results, can be initiated and the patient can be discharged with a 10- to 14-day course of treatment.50 It has also been advised that if the symptoms and fever persist beyond 24–48 hours of treatment, a repeat urine culture and ultrasonography should be performed to rule out persistent infection and urinary tract pathology.19

Some studies38,51,52 found recurrent pyelonephritis during pregnancy in 6–8% of women and one treatment plan for this is the use of low-dose antimicrobial prophylaxis with an antibiotic to which the bacteria are sensitive, taken by the patient for the duration of the pregnancy.27,50 Some of the recommended antibiotics include:

- nitrofurantoin: 50–100 mg orally every day;
- cephalexin: 250–500 mg orally every day.27,50

Hooton et al.19 stated that if preventative therapy is given, then monthly urine cultures are not necessary; nevertheless, in view of the fact that breakthrough bacteriuria can occur during preventative therapy, the authors recommend one later urine culture being conducted at the beginning of the third trimester in order to confirm that the preventative therapy is working. Hooton et al.19 recommended that if a follow-up urine culture is positive (≥ 10^5 cfu/ml), then a course of antibiotics based upon the sensitivity data should be given and, additionally, the preventative treatment plan should be reassessed and adjusted if required.

Discussion

Awonuga et al.51 conducted a cross-sectional study to determine prevalence of AB in Ibadan, Nigeria, and to evaluate the diagnostic accuracy and relative cost-effectiveness of dipstick tests for nitrite and leucocyte esterase in comparison with laboratory culture. Urine samples obtained from 205 participants in the study were subjected to two tests: reagent dipstick test for nitrite and leucocyte esterase, and a routine laboratory culture. The main outcome measures in the study included sensitivity, specificity, positive and negative predictive values of the reagent dipstick tests as well as likelihood ratios. Awonuga et al.51 reported the following results:

- The prevalence of AB in pregnancy with routine laboratory culture and using combined leucocyte esterase and nitrite strip tests was 10.7% and 11.7%, respectively.
- In comparison with laboratory culture of urine specimens, combined strip tests had sensitivity, specificity and negative predictive values of 50%, 92.9%, and 93.9%, respectively, which indicated a statistically significant lower level of accuracy (P < 0.05).
- The corresponding likelihood ratios for positive and negative strip tests (LR+ and LR−) were 7 and 0.5, respectively.

Awonuga et al.51 concluded that combined leucocyte esterase and nitrite dipstick test is not sufficiently sensitive or specific to be used for routine screening of bacteriuria in pregnancy in place of laboratory culture, although it may be cost-effective in low-resource settings.

In order to determine the epidemiological profile of women who were admitted to a university hospital in Brazil with a UTI, and to verify the most prevalent agents and response to antibiotic therapy, Calegari et al.54 undertook a retrospective study of 106 pregnant women who were admitted for the treatment of a UTI between
January 2007 and December 2010. Calegari et al.\textsuperscript{54} based their evaluation on the analysis of medical records of the pregnant women, observations during the hospitalization period, pregnancy data and the overall outcome. The authors\textsuperscript{54} performed statistical analysis using Statistical Package for the Social Sciences, version 15.0, and also used the bilateral Fisher exact test and Student’s $t$-test for data analysis, as well as descriptive statistical methods. Calegari et al.\textsuperscript{54} reported the following results:

- Positive urine cultures were obtained in 60.5% of the pregnant women who were admitted suffering from a UTI.
- The most frequent infectious agent that was cultured was \textit{E. coli} and there was no observed difference in resistance, recurrence or complications between the most frequent aetiological agents.
- Pregnant women who had suffered from previous UTIs had a higher recurrence risk [odds ratio (OR) = 10.8; $P < 0.05$].
- The antibiotics that were most frequently used were ampicillin and cefazolin.
- A necessary change of therapeutic agent as a result of bacterial resistance occurred in 11.9% of patients who took cefazolin and 20% of patients who took ampicillin (OR = 5.5; $P < 0.05$).
- The rate of gestational complications was the same for both treatments.
- There was no difference in mean hospitalization duration between the treatments.

Calegari \textit{et al.}\textsuperscript{54} concluded that, in their study population, ampicillin showed a higher rate of bacterial resistance than cefazolin, requiring a larger number of treatment alterations; however, this did not result in differences in clinical outcome or duration of hospitalization.

Versi \textit{et al.}\textsuperscript{55} reported a higher prevalence of bacteriuria among pregnant white women (6.3%) than in pregnant Bangladeshi women (2%). They also reported that pregnancies that resulted in preterm deliveries were strongly associated with bacteriuria in white women but this association was not observed in the Bangladeshi women. Versi \textit{et al.}\textsuperscript{55} postulated that the difference between the white and Bangladeshi pregnant women could be due to variation in hygiene practices and clothing.

A large population-based study of nearly 200 000 pregnant Israeli women\textsuperscript{56} found a 2.5% rate of AB and 2.3% rate of symptomatic UTI.\textsuperscript{56} It was observed in this study population that AB had an association with multiple pregnancy complications which included hypertension, diabetes, intrauterine growth retardation, prolonged hospitalization and preterm labour.\textsuperscript{56}

Mazor-Dray \textit{et al.}\textsuperscript{56} reported that their findings may be a marker for the intensity of prenatal care received, rather than a specific causal effect of the UTI. Furthermore, their follow-up study, which examined women with symptomatic UTIs, demonstrated a clear association between UTI and low birthweight and preterm delivery, a finding similar to those of multiple previous investigations.\textsuperscript{57–59}

Whitehead \textit{et al.}\textsuperscript{60} reported on a retrospective study of 24 000 births and found the prevalence of UTI during pregnancy to be 28.7% in whites and Asians combined, 30.1% in blacks, and 41.1% in Hispanics. Whitehead \textit{et al.}\textsuperscript{60} also reported that:

- When socioeconomic status was controlled for, no significant inter-racial differences existed.
- A survey-based analysis of self-reported UTI found similar trends.\textsuperscript{60}
- Their study also looked at Native American women and found the highest prevalence of UTIs in this population (24.2%) in comparison with Asian (10.3%), white (16.6%), Hispanic (18.3%) and black (20.3%) women.\textsuperscript{60}

Johnson and Kim\textsuperscript{61} reported that UTIs are associated with preterm delivery in patients of all races and that the adjusted OR in infants with very low birthweight is 2.8 for blacks and 5.6 for whites, when adjusted for parity, body mass index, maternal age, marital status, cigarette smoking, education and prenatal care. Johnson and Kim\textsuperscript{61} also reported that the overall relative risk of bacteriuria in blacks or whites was estimated at 1.5–2.3.

Giraldo \textit{et al.}\textsuperscript{62} reported that urogenital infections are extremely prevalent during pregnancy and they are an important cause of premature labour in Brazil. Nevertheless, the prevalence of urogenital infections during childbirth is not well known. Giraldo \textit{et al.}\textsuperscript{62} conducted a study to identify urogenital infections which were present at the beginning of labour in both full-term and preterm pregnancies. Giraldo \textit{et al.}\textsuperscript{62} reported that, out of 94 women who were admitted to their inpatient maternity clinic, 49 women were
in preterm labour and 45 were in full-term labour. Samples of urinary, vaginal and perianal material were collected for microbiological analysis. They reported that:

- The prevalence of general infections in the preterm labour group and the full-term labour group was 49.0% and 53.3%, respectively ($P = 0.8300$).
- The rates of urogenital infections in the preterm and full-term labour groups were as follows: UTIs, 36.7% and 22.2% respectively; vaginal candidiasis, 20.4% and 28.9% respectively; bacterial vaginosis, 34.7% and 28.9% respectively; and group B Streptococcus, 6.1% and 15.6% respectively. Giraldo et al. concluded that urogenital infections were prevalent in women in preterm labour and full-term labour but significant differences between the groups were not observed.

Kladensky reported that UTIs in pregnant women are a relatively frequent occurrence and the spectrum of these infections ranges from lower urinary tract infection (AB, acute cystitis) to upper urinary tract infection (acute pyelonephritis). Kladensky reported that anatomical and functional changes in the urinary tract in pregnancy result in a significantly higher susceptibility to progression of the infection from AB tract in pregnancy result in a significantly higher number of newborns with low birthweight and low gestational age and is associated with a higher neonatal mortality rate than in pregnancy without bacteriuria.

- Untreated AB in pregnancy may lead to the development of acute pyelonephritis in as many as 40% of cases, which includes all the subsequent negative effects not only for the pregnant woman herself, but also, and particularly, for the fetus.
- Bacteriuria in pregnancy accounts for a significantly higher number of newborns with low birthweight and low gestational age and is associated with a higher neonatal mortality rate than in pregnancy without bacteriuria.
- In view of the points raised above, it is necessary to perform screening for bacteriuria in pregnant women and, when the finding is positive, treat the bacteriuria.
- The selection of an appropriate antimicrobial agent for the treatment of a UTI during pregnancy is limited by the safety of a given drug not only for the pregnant woman, but also for the fetus.
- The selection of an appropriate antibiotic should always be determined by the result of urine culture.

The efficacy of β-lactams in the treatment of pyelonephritis was demonstrated in a randomized trial of 179 pregnant women with acute pyelonephritis before the 24th week of gestation. Wing et al. reported that intravenous cefazolin, or intramuscular ceftriaxone, had the equivalent efficacy to the use of intravenous ampicillin in combination with gentamicin. Although a number of authors reported that the rates of resistance to first-generation cephalosporins had generally been < 10% in their surveillance studies, Warren et al. stated that β-lactams, including first-generation cephalosporins, have been generally less effective than trimethoprim–sulphamethoxazole, or fluoroquinolones, for the treatment of cystitis. Warren et al. reported that given the aforementioned data and the paucity of data evaluating the narrow spectrum of cephalosporins in the treatment of pyelonephritis, they favour the third-generation cephalosporins over the first and second generations, such as cefazolin, for the empirical treatment of acute pyelonephritis.

Le et al. reported an association of fetal exposure to aminoglycosides with ototoxicity and therefore, in view of this, Hooton et al. recommended that aminoglycosides should be avoided in pregnancy associated with pyelonephritis unless intolerance or resistance prohibits the use of less toxic agents.

Garau reported that carbapenems are usually effective in the treatment of serious extended-spectrum β-lactamase (ESBL)-producing strains that cause infections. However, Hooton et al. reported that some animal studies have exhibited adverse fetal effects when exposed to imipenem–cilastatin, and, in view of this, they recommended that meropenem, ertapenem or doripenem should be the preferred carbapenems for use during pregnancy.

Millar randomly assigned 120 pregnant women (less than 24 weeks’ gestation) with pyelonephritis to an outpatient regimen consisting of ceftriaxone (1 g intramuscularly daily for 2 days) followed by 500 mg cephalaxin orally four times per day for 10 days, or an inpatient treatment consisting of intravenous cefazolin, followed at discharge by 500 mg cephalaxin orally four times per day for 10 days. Millar et al. reported that the clinical responses to therapy and birth outcomes were similar in both the outpatient and the inpatient groups. They also reported that six patients who were initially treated with ceftriaxone were eventually admitted...
to the hospital for intravenous therapy and that one woman developed septic shock during observation in the emergency department.

Wing et al. undertook a study in pregnant women (more than 24 weeks' gestation) with pyelonephritis to establish whether or not early discharge and outpatient management with cephalexin after initial hospitalization and treatment with ceftriaxone is as effective and safe as conventional inpatient management. They reported that 51% of patients either did not qualify for outpatient management based upon their study criteria or developed complications which precluded early discharge from hospital. The studies of Millar et al. and Wing et al. suggest that outpatient therapy is less safe and less effective than inpatient treatment for pregnant women with pyelonephritis.

It has been stated that for the majority of UTIs and AB during pregnancy, the prognosis is good. Most of the long-term sequelae are due to complications associated with septic shock, respiratory failure and hypotensive hypoxia with extreme gangrene.

Urinary tract infections in pregnant women have few direct sequelae as fetal bloodstream infection is rare; nevertheless, uterine hypoperfusion as a result of maternal dehydration, maternal anaemia and direct bacterial endotoxin damage to the placental vasculature may result in fetal cerebral hypoperfusion.

Untreated upper UTIs in pregnant women are associated with low birthweight, prematurity, premature labour, hypertension, pre-eclampsia, maternal anaemia and amnionitis. UTIs during pregnancy are associated with intrauterine growth retardation, pre-eclampsia, preterm delivery and caesarean delivery.

Summary

Asymptomatic bacteriuria

Asymptomatic bacteriuria refers to the presence of a positive urine culture in an asymptomatic person. The risk of developing pyelonephritis is 20- to 30-fold higher in pregnant women with AB than in non-pregnant women without AB and the progression of AB to pyelonephritis is associated with an increased risk of preterm birth, low birthweight and perinatal mortality.

Asymptomatic bacteriuria is diagnosed following the culture of a urine specimen that has been collected with minimal contamination. Treatment of AB usually commences if a colony urine culture has a count of $\geq 10^5$ cfu/ml.

The 2005 Infectious Diseases Society of America guidelines for the diagnosis and treatment of AB in adults recommended screening all pregnant women for AB and the instituting treatment in the event of a positive culture.

Hooton et al. recommended short courses of any of the following therapeutic treatments to minimize antimicrobial exposure to the fetus:

- amoxicillin: 500 mg orally every 12 hours for 3–7 days;
- Augmentin: amoxicillin (500 mg) and clavulanate (125 mg)] every 12 hours for 3–7 days;
- nitrofurantoin: 100 mg orally every 12 hours for 5 days;
- cephalexin: 500 mg orally every 12 hours for 3–7 days.

In view of the fact that up to 30% of women are not cleared of AB following a short course of therapy, Hooton et al. recommend a repeat urine culture 1 week after completion of antibiotic therapy, as well as repeat urine cultures on a monthly basis until parturition to assess for persistent or recurrent bacteriuria.

Acute cystitis

Cystitis refers to a symptomatic infection of the urinary bladder which can occur either alone or complicated by ascending infection and pyelonephritis. Acute cystitis in pregnant women is generally considered to be complicated as it is often associated with an ascending infection or pyelonephritis.

A urine culture must be performed for pregnant women with symptoms of acute cystitis and a resulting quantitative count of $\geq 10^4$ cfu/ml in a symptomatic pregnant woman should be taken as an indicator of symptomatic UTI. Pregnant women with acute cystitis should be treated with a 3- to 7-day
course of antibiotics as long as they do not have symptoms suggestive of pyelonephritis.

Hooton et al. suggested one of the following empirical treatments should be prescribed while awaiting urine culture and sensitivity results.

- nitrofurantoin: 100 mg orally every 12 hours for 5 days;
- cefpodoxime: 100 mg twice daily for 3–7 days;
- amoxicillin–clavulanate: 500 mg orally every 12 hours for 3–7 days;
- fosfomycin: 3 g orally as a single dose;
- trimethoprim–sulphamethoxazole: one double-strength dose twice daily for 3 days in the second trimester (this should be avoided in the first trimester or near term);
- amoxicillin (for treatment of Enterococcus): 500 mg twice daily every 12 hours for 7 days;
- fluoroquinolones: should be avoided during pregnancy.

A repeat urine culture should be conducted 1 week after completion of treatment and monthly thereafter until parturition.

**Pyelonephritis**

Acute pyelonephritis tends to manifest with flank pain, nausea and vomiting, pyrexia > 38°C and costovertebral angle tenderness, which may occur in the presence or absence of symptoms of cystitis.

Organisms responsible for acute pyelonephritis in pregnancy include *E. coli* (approximately 70%), *Klebsiella*, *Enterobacter*, *Proteus* and Gram-positive organisms inclusive of group B *Streptococcus*.

In view of the high risk of complications associated with pyelonephritis in pregnancy, pregnant women with pyelonephritis are usually admitted to hospital for intravenous antibiotics until they are afebrile for 24 hours and their symptoms have improved. Taking blood samples for a culture is recommended in pregnant women with signs of sepsis or serious underlying medical conditions such as diabetes mellitus.

When the patient has been afebrile for 48 hours on intravenous antibiotics, oral antibiotic therapy, based upon the culture and sensitivity pattern of the causative organism, can be initiated and the patient discharged to complete 10–14 days of antibiotic treatment.

Recurrent pyelonephritis occurs during pregnancy in 6–8% of women; therefore, low-dose antibiotic prophylaxis with an agent to which the bacteria is sensitive is recommended for the duration of the pregnancy. Some of the treatment options to choose from include 50–100 mg nitrofurantoin orally every evening, or 250–500 mg cephalaxin orally every evening.

**Conclusions**

For the majority of UTI and AB cases diagnosed during in pregnancy, the prognosis is good. Most of the long-term sequelae are due to complications associated with septic shock, respiratory failure and hypotensive hypoxia with extreme gangrene.

Urinary tract infections which develop in pregnant women have few direct sequelae as fetal bloodstream infection is rare; nevertheless, uterine hypoperfusion as a result of maternal dehydration, maternal anaemia and direct bacterial endotoxin damage to the placental vasculature may result in fetal cerebral hypoperfusion.

Untreated upper UTIs in pregnant women are associated with low birthweight, prematurity, premature labour, hypertension, pre-eclampsia, maternal anaemia and amnionitis. UTIs that develop during pregnancy are also associated with intrauterine growth retardation, pre-eclampsia, preterm delivery and caesarean delivery.

In order to avoid, or minimize, complications that may be associated with AB and UTI, both should be appropriately treated during pregnancy.

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