Uncomplicated urinary tract infections in pregnancy

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Abstract

Urinary tract infections (UTIs) represent a common problem in pregnancy.

Asymptomatic bacteriuria (ASB) increases the risk of infection of the upper urinary tract as a consequence of physiological changes. The growing uterus results in urinary retention, in addition maternal hormonal changes (progesterone) relax the ureteral muscle and cause accumulation of urine in the bladder increasing the chance of developing a UTI.

Uropathogens responsible for UTIs in pregnancy are the same as those that cause ASB and UTIs in non-pregnant women, with more than 70% of cases supported by *E. coli*.

The two common clinical manifestations are: 1) acute cystitis, generally occurring in the first trimester of pregnancy or 2) pyelonephritis, occurring in the second and third trimesters.

The selection of an appropriate antimicrobial agent in pregnancy is limited by the safety not only for the woman, but particularly for the fetus. Acute cystitis should be treated for 3–7 days, but shorter courses of therapy are preferred because of less fetal exposure. The first-line antimicrobial drug is fosfomycin, also in the first trimester.

The management of pregnant women with pyelonephritis includes hospital admission for parental fluid and antibiotic therapy with broad-spectrum beta-lactams. After 48 hours, it is usually possible to switch to the oral beta-lactams or trimethoprim-sulfamethoxazole, in the second trimester (at least for 10–14 days). After the first episode of pyelonephritis an antimicrobial urinary suppression and an aggressive follow-up care for the remainder of the pregnancy, due to the high risk of recurrence, are recommended.

Summary of recommendations

Uncomplicated UTIs

- Acute uncomplicated UTIs are infections of the low urinary tract (acute cystitis) and high urinary tract (acute pyelonephritis) affecting immunocompetent women without underlying urologic abnormalities. The most common bacteria involved are the *E. coli* (70%).
- Acute cystitis should be suspected in case of new onset dysuria, frequency or urgency in pregnant women. The diagnosis requires a bacterial growth ≥10 ^{3}cfu/mL on urine culture.
- Acute pyelonephritis is suggested by the presence of fever (>38°C or 100.4°F), flank pain, nausea/vomiting and/or costovertebral angle tenderness and is confirmed by the finding of pyuria and bacteriuria.

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Acute cystitis in pregnancy

Treatment

- A single-dose of fosfomycin represents the first line therapy. Other potential options include beta-lactams and nitrofurantoin.
- Short courses of antimicrobial therapy (3 days) should be preferred.
- For women with persistent or recurrent infection, a prophylactic or suppressive antibiotic treatment with nitrofurantoin or cephalexin is indicated.

Follow-up

- A urine culture should be carried out 1–2 weeks after the end of the therapy and then once a month for the whole pregnancy.

Acute pyelonephritis in pregnancy

Treatment

- The management includes hospital admission for parental antibiotic therapy with broad-spectrum beta-lactams.
- Once afebrile for 48 hours patients can be switched to oral therapy with beta-lactams or trimethoprim-sulfamethoxazole in the second trimester.
- Given the high risk of recurrence of pyelonephritis, low dose suppressive therapy, with nitrofurantoin or cephalexin, is recommended.

Follow-up

It is recommended to perform at least one urine culture at the beginning of the third trimester to ensure that the therapy is working.

1 Introduction

Urinary tract infections (UTIs) are the most common type of infections during pregnancy, affecting up to 10% of pregnant women.

The term UTIs includes both asymptomatic bacteriuria (ASB) and lower tract (acute cystitis) or upper tract (acute pyelonephritis) infections. Pregnancy-related changes of the urinary tract are a predisposing factor for the progression from ASB to symptomatic UTI. Unlike the general population, all pregnant women should be screened for bacteriuria with urine culture and ASB must be treated for the high risk of pyelonephritis resulting. In this setting, pregnant women may be at risk for both medical and obstetrical complications, such as preterm labor, low birth weight, preeclampsia or maternal systemic infection.

Pregnancy-related acute cystitis and pyelonephritis will be reviewed in the present chapter with attention to the current international recommendations for diagnosis and treatment.

2 Methods

A systematic search in PubMed for literature of the last 30 years was performed with the following keywords: UTI, cystitis, pyelonephritis, treatment, management, outcome, pregnancy. A total of 585 publications were identified and screened by title and abstract. A manual search of references from some specific studies was also conducted. Search results were limited to studies written in English language. After removing duplicates, a total of 72 studies were included.

3 Incidence and risk factors

UTIs are frequently encountered medical complications of pregnancy and may result in significant morbidity for the pregnant woman and the fetus [1], [2], [3], [4], [5], [6].

Acute uncomplicated UTI affects women who are immunocompetent and without underlying urologic abnormalities (such as nephrolithiasis, strictures, stents, or urinary diversions) or poorly controlled diabetes mellitus [7].

Acute cystitis affects 1–2% of pregnant women while the incidence of pyelonephritis during pregnancy is approximately 0.5–2%, with 79% of cases occurring during the second and third trimesters of pregnancy [8], [9], [10].

While the incidence of bacteriuria does not change between pregnant and non-pregnant women, however pyelonephritis has a higher incidence than in the general population because of physiological changes of the urinary tract related to pregnant status [8], [9], [10], [11].

Although there is no agreement on the need to screen all pregnant women for ASB [12], failure to treat bacteriuria during pregnancy may result in as many as 25% of women experiencing acute pyelonephritis [8]. The risk of symptomatic UTI is reduced by 70–80% if bacteriuria in pregnacy is eradicated [13].

The most common risk factors for pyelonephritis are: a previous history of pyelonephritis and ASB. Other clinical characteristics associated with acute pyelonephritis during pregnancy include age <20 years, nulliparity, smoking, late presentation to care, sickle cell trait, and pre-existing diabetes mellitus. There is no association with maternal ethnicity [9], [10].

The management of these infections, generally treated empirically, is becoming complicated due to the emergence of resistance to several first-line antimicrobial agents. Infections caused by extended-spectrum beta-lactamase (ESBL)-producing strains are increasing in number [14], [15] .

This represents a particular problem even in pregnant women; up to 45% of *Escherichia Coli* isolated from the urine of both symptomatic and asymptomatic Indian pregnant women result with a ESBL phenotype [16], [17] .

4 Pathogenesis

In pregnant women some structural and functional changes in the urinary tract increase the risk of progression from ASB to pyelonephritis. The physiological hydronephrosis and hydroureteronephrosis are the result from hormonal effects, external compression from the growing uterus and intrinsic changes in the ureteral wall. The physiological high maternal circulating concentrations of progesterone increase the bladder smooth muscle relaxation (increasing bladder capacity) and decrease the detrusor tone and the ureteral peristalsis. These factors contribute to ureteral dilatation and urinary stasis and may serve as a reservoir for bacteria; moreover, the pressure of the bladder from the enlarging uterus may contribute to ascending infections from the urethra to the kidney and predispose to the progression to symptomatic UTI [18]. In addition, the increase of glomerular filtration leads to changes in the urine composition: glycosuria, alkalization of pH and decreased concentration capacity of the urine facilitate bacterial proliferation [19].

The presence of certain virulence factors may explain why some patients with ASB develop pyelonephritis and others do not; in particular the expression of P-fimbrie on the surface of the bacteria identify strains of *E. coli* that are particularly pathogenic, favoring the adhesion to uroepithelium and the ascent of the infection [20].

An additional role is played by the state of immunosuppression typical of pregnancy. The mucosal IL-6 and specific antibody responses to acute pyelonephritis caused by *E. coli* are lower in pregnant compared to non-pregnant women [21].

5 Microbiology

The organisms that cause asymptomatic bacteriuria and lower UTI in pregnancy are the same and have the same virulence factors as in nonpregnant women [22]. Intestinal bacteria colonize the urinary tract ascending from the urethra and *E. coli* is the most frequently identified pathogen in case of bacteriuria or UTI even during pregnancy, accounting for approximately 70% of cases. Other organisms responsible for infection include Klebsiella -Enterobacter (3%), Proteus (2%), and gram-positive organisms, including group B *Streptococcus* (10%) [1], [2], [3], [4], [5], [6], [7], [8], [9].

As in other community-acquired infections, antimicrobial resistance has become a major global public health problem.

In an international survey on the antimicrobial resistance of pathogens involved in uncomplicated UTI more than 10% of *E. coli* were multiresistant. Resistance was most common to ampicillin (48.3%), trimethoprim/sulfamethoxazole (29.4%) and nalidixic acid (18.6%).

Extended-spectrum beta-lactamase (ESBL) enzymes were detected in *E. coli* and also in *K. pneumoniae* and *P. mirabilis* strains [14]. This phenomenon is increasingly emerging in pregnancy: prior urinary infections, hospitalization and antibiotic exposure in the last four weeks before UTI are significant risk factors for the isolation of ESBL-E pathogens from the urine of pregnant women [16]. However, this was not associated with worse obstetric outcomes compared with non-ESBL-E pathogens [23].

6 Pregnancy outcome

UTIs in pregnancy pose a great therapeutic challenge due to the high risk of serious complications in both the mother and her child. While ASB has been correlated with an increased risk of preterm delivery, low birth weight and perinatal mortality [1], [2], [3], [4], [5], this correlation has not been found with acute cystitis [1], perhaps because pregnant women with a symptomatology of low urinary tract infection receive timely treatment.

Pyelonephritis is associated with adverse maternal and fetal outcome. Serious medical complications and even mortality may occur [6].

In a large retrospective cohort study on singleton pregnancy (n= 546 092) the rate of preterm delivery and low birthweight is greater in women with pyelonephritis compared to controls (19.3% vs 7.9% and 5.5% vs 4.2% respectively). The highest risk of prematurity is between 33 and 36 weeks of gestation; acute pyelonephritis is also associated with an increased risk of chorioamniotitis and primary caesarean delivery. However, there is no increased risk of very low birthweight, neonatal mortality, stillbirth or preeclampsia (PE) among pregnant women (n= 2894) who have experienced pyelonephritis. Frequent medical complications in these patients are anemia, septicaemia, renal insufficiency and ARDS [10].

Several studies support the hypothesis that bacterial infections increase blood pressure values in pregnant women and predispose to PE with a 3-fold increased risk [24], [25], [26], [27]. The association was strongest for early cases of PE (that required delivery <34 weeks of gestation) and when the infection occurred late in the third trimester [28].

This association fits with the concept that infectious diseases, increasing maternal inflammatory response and endothelial injury may lead to an aberrant placentation and subsequent development of PE.

About 20% of cases requires hospitalization for over 4 days with significant maternal morbidities and an additional 20% requires a prolonged hospitalization for the emergence of complications also when pyelonephritis occurs early in pregnancy or in the post partum [29], [30], [31].

7 Acute cystitis

7.1 Clinical manifestations and diagnosis

The term acute simple cystitis refers to an acute urinary tract infection confined to the bladder without signs or symptoms of systemic infection. The typical manifestations include dysuria, urinary frequency, urgency, discomfort in the lower abdomen and hematuria in association with bacteriuria [32]. Some of these symptoms are also being experienced by healthy pregnants: frequency and urgency occur in up to 80% of patients from the beginning of pregnancy and worsen with pregnancy progression [33], [34], [35].

In case of new onset of dysuria, acute cystitis should be suspected and a urinalysis and urine culture should be performed. Pyuria is usually present and the diagnosis of symptomatic UTI is confirmed by findings of bacterial growth on urine culture [36]. No studies have been conducted to define the bacterial threshold for the diagnosis of cystitis in pregnancy. Based on data obtained in nonpregnant women a bacteriuria $\geq 10^2$–10^3 cfu/ml, in the presence of symptoms, is sufficient for the diagnosis.

As most clinical laboratories do not routinely quantify urine isolates to 10^2cfu/mL, it is reasonable to use a quantitative count $\geq 10^3$ cfu/mL in a symptomatic pregnant woman as an indicator of symptomatic UTI.

If bacteria that are not typical uropathogens (such as *lactobacillus*) are isolated, the diagnosis of cystitis is typically made only if they are isolated in high bacterial counts (≥10^5cfu/mL) and >10^4 cfu/mL for group B *streptococcus* [37].

7.2 Antimicrobial treatment

In most cases an empirical antibiotic treatment is started and then modified on the result of the antimicrobial susceptibility testing. The optimal duration of treatment of acute cystitis in pregnancy is uncertain. Studies conducted in non-pregnant population do not report a different outcome between short (1–3 days) and long (5–7 days) regimens [7], [38], [39]. It is recommended to reduce the drug exposure time to minimize fetal risks.

The therapeutic options for the treatment of acute cystitis, as empirical or direct treatment, are beta-lactams, nitrofurantoin and fosfomycin (table 1). However, a Cochrane review concludes that there are insufficient data to recommend any specific drug regimen for treatment of symptomatic UTIs during pregnancy. No significant difference was found between the different treatments with regard to cure rates, recurrent infection, need for change of antibiotic, incidence of preterm delivery or admission to neonatal intensive care unit [40]. For empiric therapy it is indicated to choose cefpodoxime, amoxicillin-clavulanate or fosfomycin considering their safety and their broad spectrum of action [37]. Amoxicillin or ampicillin should not be used given the relatively poor efficacy and the very high prevalence of antimicrobial resistance [7], [37].

Table 1: Antimicrobial agents for cystitis in pregnancy (modified from Hooton and Gupta [37])

Drug	**Dose**
Nitrofurantoin	100 mg orally every 12 hours
Amoxicillin	500 mg orally every 8 hours or 875 mg orally every 12 hours
Amoxicillin-clavulanate	500 mg orally every 8 hours or 875 mg orally every 12 hours
Cephalexin	500 mg orally every 6 hours
Cefpodoxime	100 mg orally every 12 hours
Fosfomycin	3 g orally as single dose
Trimethoprim-sulfamethoxazole	800/160 mg every 12 hours

Nitrofurantoin is often used even if there are potential risks of birth defects [41], [42]. In a population-based study, the first trimester nitrofurantoin exposure showed no association with risk of major malformations, but this drug should be avoided during the first trimester and at term of gestation, if other options are available [7], [43]. Nitrofurantoin has also been reported to cause hemolytic anemia in the mother and fetus with G-6PD deficiency [44], [45] . Use of trimethoprim-sulfamethoxazole is typically limited to mid-pregnancy. Even if a teratogenic effect has not been proven in humans, it behaves like a folic acid antagonist and in some case-control studies, an association with birth defects has been reported [41], [42].

The committee opinion n. 717 (2017) from the American College of Obstetricians and Gynecologists recommended that sulfonamides and nitrofurantoins may continue to be used as first-line agents for the treatment and prevention of UTIs in pregnancy only during the second and third trimester [46].

Fosfomycin is considered safe in pregnancy and represents a reasonable first-line choice, also in the first trimester [47]. A single-dose fosfomycin trometamol has been shown to have similar clinical and bacteriological efficacy to a 5-day course of cefuroxime axetil or amoxicillin/clavulanic acid or a 3-day course of ceftibuten in pregnant women [48], [49]. Fosfomycin and nitrofurantoin have also in-vitro activity against extended-spectrum beta-lactamase (ESBL)-producing *Enterobacteriaceae* and they can be used to treat women with documented infection from these strains[15], [50], [51].

7.3 Follow-up and management of recurrent cystitis

Follow-up urine cultures are recommended 1–2 weeks after the treatment and then once a month for the duration of pregnancy [37].

In women with recurrent acute cystitis, antimicrobial urinary suppression based on daily use of a small dose of antibacterial drug during the symptom-free period is recommended or, in the case of an evident relationship of the disease with sexual activity, only after intercourse (nitrofurantoin 50–100 mg or cephalexin 250–500 mg) [52].

The efficacy and safety of non-antibiotic measures to prevent UTIs in pregnancy have not been largely studied. In a systematic review of alternate measures for the prevention of UTIs in pregnants only hygiene measures (washing the genital area and voiding the bladder after intercourse) were supported by evidence to be recommended in practice [53]. In addition, to drink an additional 1.5 liter of water daily to reduce the incidence of cystitis by about 50% should be recommended [54].

8 Acute Pyelonephritis

8.1 Clinical manifestations and diagnosis

The term acute pyelonephritis refers to an acute infection extended to the upper urinary tract and kidneys. It is usually a consequence of undiagnosed or inappropriately treated lower UTI, or a complication of 30–40% of cases of untreated ASB [55].

The typical symptoms are fever (>38° C or 100.4°F), back or flank pain, nausea and vomiting, costovertebral angle tenderness; symptoms of acute cystitis are not always present. The diagnosis is confirmed with a urinalysis and urine culture by the finding of bacteriuria and pyuria in association with this symptomatology. Nearly one in five pregnant women with pyelonephritis has septicemia at diagnosis [9], [56].

Urine and blood cultures are often obtained in the course of clinical management and microbiology tests are repeated 1–2 weeks after therapy to verify eradication of the infection [57], [58], [59].

Urine and blood cultures have limited utility in the clinical management of pyelonephritis in pregnancy [59], [60]. It is recommended to obtain cultures only in cases of lack of response to therapy, as demonstrated by persistent fever or costovertebral angle tenderness beyond 48–72 hours, and to institute changes in antibiotic therapy as clinically necessary [60]. The elimination of blood and urine cultures might simplify management and result in significant cost savings without compromising patient care.

8.2 Antimicrobial treatment

The safety of outpatient treatment of pyelonephritis in pregnancy is related only to two randomized trials. Although the authors conclude that the outpatient and inpatient treatments have the same outcome, the studies have many limitations [61], [62].

According to the 2005 IDSA guidelines, all suspected cases of pyelonephritis should be hospitalized at least for the initial 48 hours [63]. Broad-spectrum beta-lactamics are to be preferred for the empiric parenteral treatment [34], [63], [64].

Table 2 and table 3 show the antibiotics to choose on the basis of local microbiology and susceptibility data.

Table 2: Antimicrobial agents for acute pyelonephritis in pregnancy (modified from Hooton and Gupta [37]

Drug	Dose
Ceftriaxone	1 g every 24 hours
Cefepime	1 g every 12 hours
Aztreonam (in case of beta lactam allergy)	1 g every 8 hours
Ampicillin + Gentamicin	1-2 g every 6 hours + 1.5 mg/kg every 8 hours

Table 3: Antimicrobial agents for severe pyelonephritis with an impaired immune system and/or incomplete urinary drainage (modified from Hooton and Gupta [37])

Drug	Dose
Piperacillin-tazobactam	3.375 g every 6 hours
Meropenem	1 g every 8 hours
Ertapenem	1 g every 24 hours
Doripenem	500 mg every 8 hours

The efficacy of beta-lactam has been demonstrated in a randomized trial comparing three antibiotic regimens for the treatment of pyelonephritis before the 24th week of pregnancy [65].

The clinical response and the birth outcome among subjects treated with intravenous cefazolin or intramuscular ceftriaxone were similar to those treated with intravenous ampicillin and gentamicin. Most recent data show that ampicillin and first-generation cephalosporins are associated with a higher bacterial resistance while ceftriaxone have a high efficacy due to low bacterial resistance [66].

Aminoglycosides carry the risk of fetal ototoxicity and nephrotoxicity; their use should be limited when the patient's intolerance precludes the use of safer drugs [67]. In case of ESBL infection-producing *Enterobacteriaceaea carbapenem* may represent a viable alternative for the initial empirical treatment [37].

Once the patient has been afebrile for 48 hours, it is possible to switch to an oral antibiotic treatment based on the susceptibility results of the cultures; discharge is possible and oral therapy must be continued for 10–14 days, although its optimum duration has never been established [33], [68]. As oral therapy betalactams or, in the second trimester of pregnancy, trimethoprim-sulfamethoxazole are generally employed [37].

8.3 Follow-up

A recurrence of pyelonephritis occurs in 6–8% of pregnant women, therefore a suppressive therapy for the whole gestation with nitrofurantoin (50–100 mg orally at bedtime) or cephalexin (250–500 mg orally at bedtime) is necessary [68], [69], [70]. However, this therapeutic regimen is not supported by evidence obtained in randomized trials [71].

At least one urine culture during the preventive treatment should be done, generally at the beginning of the third trimester. In case of positive culture ($\geq 10^5$ cfu/mL) a course of antimicrobial therapy tailored on susceptibility data is indicated [37], [72].

9 Further strategies

Antibiotic prophylaxis and treatment of UTI is essential for the prevention of adverse obstetric outcomes. Increasing antimicrobial resistance reduces the possibility of using antimicrobial agents safely for the fetus. Further research in adequately constructed clinical trials is needed in this field.

10 Conclusions

Pregnancy involves structural and functional changes of low and upper urinary tract promoting the progression from ASB to acute cystitis or pyelonephritis.

Most cases of symptomatic UTIs occur during the late pregnancy or in puerperium and are supported by *E. coli*.

Single-dose fosfomycin is the first-line empirical treatment of uncomplicated lower UTI also in the early pregnancy while sulfonamides and nitrofurantoins should be used as a first line in the second/third trimester.

Since acute cystitis is readily diagnosed and treated, it is not usually associated with severe maternal or fetal complications. Patients should be followed with serial cultures throughout pregnancy and prophylactic antimicrobial therapy should be considered.

Patients affected by pyelonephritis should initially be admitted for parental antimicrobial therapy with broad-spectrum beta-lactamics due to important maternal and fetal complications. After the first 48 hours it is possible a switch to oral antibiotic therapy with betalactams or, in the second trimester of pregnancy, trimethoprim-sulfamethoxazole. Prophylactic or adjusted, according to local resistance patterns, antimicrobial therapy should be strongly considered for the rest of pregnancy.

In conclusion, UTIs are a common, but preventable cause of pregnancy complications. Pyelonephritis, although not very frequent, can be much more severe than acute cystitis.

Screening for and treatment of UTIs should be part of routine antenatal care to prevent both maternal and fetal adverse outcome.

The most common pathogens demonstrate sensitivity to many drugs that can be safely administered during pregnancy (table 4) but the management of these infections is becoming complicated due to the emergence of drug resistance to several first-line antimicrobial agents. Factors associated with community-acquired infection, such as hospitalization or prior antibiotic use, make ESBL-E colonisation an important public health issue also in pregnant women. These considerations may help physicians who face the need to choose an empirical therapy for pregnant women with a UTI select an appropriate regimen, especially in areas with a high prevalence of ESBL-E pathogens.

Table 4: Antibiotic use during pregnancy according to Food and Drug Administration

Antibiotic	**Pregnancy Risk Category According to FDA**
Amoxicillin	B
Amoxicillin + clavulanic acid	B
Ampicillin	B
Cephalosporins	B
Chloramphenicol	C
Ciprofloxacin	C
Clindamycin	B
Doxycycline	D
Erythromycin	B
Gentamicin	C
Levofloxacin	C
Penicillin G	B
Penicillin V potassium	B
Rifampin	B
Sulfonamides	C, D in peripartum period
Vancomycin	C

Category B: Animal studies have failed to demonstrate a risk to the fetus and there are no adequate and well-controlled studies in pregnant women. Studies on animals demonstrated no adverse effects on the fetus. Studies on a group of pregnant women did not confirm any fetal risk.
Category C: Animal studies have shown teratogenic or lethal effects on the fetus. No controlled studies in pregnant women have been carried out or neither animal nor human studies have been carried out.
Category D: There is positive evidence of human fetal risks based on adverse reaction data, but potential benefits may warrant use of the drug in pregnant women despite potential risks.

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12 Conflict of interest

All Authors declare no conflict of interest.

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