# URINARY TRACT INFECTIONS AND PREGNANCY

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## 1. PREVALENCE

The pregnancy itself is the most important risk factor in the urinary tract infections. From 5 to 10% of women will develop a low urinary tract infection (UTI) during pregnancy and the 10% of pregnancy hospitalisations are caused by urinary tract infections. Untreated asymptomatic bacteriuria is a risk factor for pyelonephritis, low weight at birth and preterm delivery.

There are some physiological changes that happen during pregnancy and increase the risk of presenting urinary tract infections:
- Ureteral dilatation secondary to the action of progesterone and uterine compression.
- Vesicoureteral reflux.
- Bladder stasis.
- Increased glomerular filtration rate with glycosuria and aminoaciduria with elevated urinary pH.

## 2. RISK FACTORS

These are different risk factors for developing a urinary tract infection during pregnancy:
1. Asymptomatic bacteriuria
2. History of recurrent UTIs
3. Renal lithiasis
4. Urogynaecological malformations
5. Vesicoureteral reflux
6. Kidney failure
7. Diabetes mellitus
8. Neurological disorders (incomplete emptying, neurogenic bladder, etc.)
9. Sickle cell disease
10. Chlamydia trachomatis infection
11. Multiparity
12. Low socioeconomic level

## 3. MICROBIOLOGY

1. Gram-negative bacilli: *Escherichia coli*, from enterobacterial flora, is the most common microorganism involved in the majority of these infections (in 80-90% of all the cases).

2. Gram-positive cocci: *Enterococcus spp*, *Staphylococcus saprophyticus* or *Group B Streptococcus agalactiae* (GBS). The higher the gestational age, the higher the likelihood that these infections could be caused by Gram-positive bacteria, mainly GBS.

## 4. TYPES OF URINARY TRACT INFECTIONS

### ASYMPTOMATIC BACTERIURIA

Asymptomatic bacteriuria (AB) is defined as the presence of more than 100,000 Colony Forming Units (CFUs) per ml of bacteria in a urine culture of a patient that has no clinical symptoms of urinary tract infection. Most AB occur in the first trimester of pregnancy.

**1. Prevalence**

It occurs in 2-10% of the cases. 25% of untreated AB will develop an acute pyelonephritis compared to 3% if they are treated.

Up to 30% of the treated AB will relapse despite correct antibiotic treatment, hence the importance of performing gestational screening. Although the frequency and timing of screening for AB during pregnancy is questionable, in Catalonia, gestational screening is recommended at around 16 weeks or at the first prenatal visit (only if it is after the 12$^{th}$ week) and it should only be repeated quarterly if the pregnant woman has other risk factors (e.g. maternal kidney disease, women with a solitary kidney, history of a kidney transplant, renal lithiasis, history of recurrent pyelonephritis or vesicoureteral reflux).

**2. Diagnosis**

The diagnosis is microbiological (urine culture with more than 100,000 CFU/mL). The urine sample must be obtained under certain aseptic conditions (such as prior cleansing of the external genitalia, separation of the vulvar labia and sample collection midstream of spontaneous urination). Bladder catheterisation is not necessary except in some clinical conditions that may interfere with the interpretation of results (e.g. blood loss in postpartum women).

The sample is deemed contaminated at 10,000 to 100,000 CFU/mL or when 3 or more germs are present. In those cases with a contaminated urine culture, it should be repeated, emphasising the aseptic measures mentioned above for a correct sampling. In the case of 3 contaminated cultures, consider it negative.

**3. Treatment:**

An antibiogram is usually available as the diagnosis is microbiological.

- Fosfomycin trometamol 3 g oral (single dose separate from meals) is the treatment of choice. It is not necessary to administer a second dose after 48-72 hours.
- If the bacteriuria is caused by *Enterococcus faecalis*, the treatment of choice will be Amoxicillin 500 mg/8 h for 4-7 days.
- In patients allergic or resistant to Fosfomycin, we should choose an antibiotic according to the antibiogram, giving priority to 1$^{st}$ and 2$^{nd}$ generation cephalosporins and avoiding the use of amoxicillin-clavulanic acid as far as possible. If cefixime is administered, the dosage is 400 mg/24 h for 3 days. Other antibiotics should be administered for 4 to 7 days.
- In case of beta-lactam allergy and allergy or resistance to Fosfomycin, Nitrofurantoin 50-100 mg/6 h oral could be used for 4 to 7 days. Another alternative (if no other sensible drugs) is Cotrimoxazole (Category C)160/800 mg every 12 hours for 3-5 days.

Table 1: Antibiotics for AB and Acute Cystitis.

| | TREATMENT OF CHOICE | ALLERGY TO BETA-LACTAMS |
|---|---|---|
| **EMPIRICAL** | - **Fosfomycin trometamol** 3 g oral single dose<br>- **Cefuroxime** 250 mg/12 h oral x 4-7 days | - **Fosfomycin trometamol** 3 g oral single dose |
| **IF AVAILABLE ANTIBIOGRAM** (choose the lower-spectrum antibiotic) | - **Fosfomycin trometamol** 3 g oral single dose<br>- **Amoxicillin** 500 mg/8 h oral x 4- 7 days<br>- **Cefuroxime** 250 mg/12 h oral x 4-7 days or<br>- **Amoxicillin-clavulanic acid** 500-125 mg/8 h oral x 4-7 days (if possible, choose another option because of flora alteration associated with clavulanic acid) | - **Fosfomycin trometamol** 3 g oral single dose<br>- **Nitrofurantoin** 50-100 mg/6 h oral x 4-7 days.<br>**Cotrimoxazole: in selected conditions if no other possible options (Category C).** |

When an antibiotic treatment is prescribed, it is crucial to explain different hygienic measures to the patient aimed at reducing bacterial contamination of the urinary meatus in order to prevent reinfection:
1. Avoid immersion baths.
2. Clean hands before using the toilet.
3. Use liquid soap to prevent colonisation that can occur on the bar of soap.
4. Wipe from front to back after urinating or defecating.
5. Initiate genital and perineal hygiene through the urinary meatus.

**4. Follow-up:**
- Check for cure with a urine culture 7 to 15 days after the end of treatment.
- In case of recurrence, act according to antibiogram and, if it is not available, broaden the spectrum of the antibiotics.
- It is recommended to repeat a urine culture quarterly. If it is not possible, a single urine culture should be performed in the third trimester.
- Prophylactic antibiotic treatment is indicated in cases of recurrent AB after three or more positive urine cultures despite an effective complete treatment. After the third correct treatment (4 to 7 days of treatment) prophylaxis should be initiated (view Recurrent UTI prophylaxis).

**ASYMPTOMATIC BACTERIURIA FROM *Streptococcus agalactiae* (GBS)**
The presence of GBS in urine indicates high colonisation of the genital tract and is associated with an increased risk of pyelonephritis, chorioamnionitis and early neonatal sepsis.
- If more than 100,000 CFU of GBS are found in urine: antibiotic treatment of asymptomatic bacteriuria and intrapartum prophylaxis for GBS should be performed. It is not necessary to perform a vagino-rectal culture for GBS at 35-37$^{th}$ week of gestation.
- If 10,000 to 100,000 CFU of GBS are found in urine: treatment of asymptomatic bacteriuria is not recommended since most women recolonise rapidly and in those cases it does not seem to reduce the incidence of pyelonephritis, chorioamnionitis or preterm delivery. In case of contamination, a repeat urine culture should be performed. Intrapartum prophylaxis for GBS is recommended however, so vagino-rectal culture for GBS is not necessary at 35-37$^{th}$ week.

**ACUTE CYSTITIS**
Acute cystitis is a syndrome characterised by urinary frequency and urgency, dysuria and suprapubic pain in the absence of involvement of systemic symptoms (fever) or low back pain.

**1. Prevalence**
It occurs in 1.3% of pregnancies. Most cases of acute cystitis appear in the second trimester of pregnancy.

**2. Diagnosis**
The diagnosis is made with suggestive symptoms and a positive urine culture (more than 100,000 CFU/mL). Either macroscopic or microscopic haematuria may appear. It is important to remember the measures for the urine sample collection for urine cultures. A bladder catheterisation is not necessarily required, but it must be collected under certain aseptic conditions: prior cleansing of the external genitalia, separation of vulvar labia and sample collection midstream of urination.

Diagnostic suspicion is obtained by performing a urine dipstick test. The presence of leucocytes, nitrites, proteins or red blood cells in a pregnant woman with symptoms suggests infection. Pyuria (positive leucocytes) is present in almost all cystitis. The presence of bacteria in the urine sediment can help in the diagnosis, although contamination has to be considered if bacteriuria is not accompanied by pyuria. When findings are pathological in urine dipstick or urine sediment examination in a patient with suggesting symptoms, antibiotic treatment should be initiated. Nevertheless, a urine culture must be performed to confirm the diagnosis and detect possible resistances in the antibiogram.

**3. Treatment**
Treatment should be started empirically because antibiograms are generally not available, following the same guidelines as for AB in terms of the type and duration of antibiotics (Table 1).

If an antibiogram is available, the same therapeutic strategy should be followed as in the case of AB, starting with the lowest-spectrum antibiotic, prioritising 1$^{st}$ and 2$^{nd}$ generation cephalosporins and avoiding amoxicillin-clavulanic acid as much as possible.

**4. Follow-up**
- Test for cure with a urine culture 7-15 days after the end of treatment.
- In case of recurrence, act according to antibiogram and, if it is not available, broaden the spectrum of the antibiotics.
- It is recommended to repeat a urine culture quarterly. If not possible, prioritise one at the third trimester.
- Prophylactic antibiotic treatment is indicated in cases of recurrent cystitis after 3 or more positive urine cultures, despite an effective complete treatment. After the third correct treatment (4 to 7 days of treatment) prophylaxis should be started (view Recurrent UTI prophylaxis).

**ACUTE PYELONEPHRITIS**
**1. Introduction**
A renal parenchymal infection appears in 1-2% of pregnancies, and its prevalence increases to 6% in pregnant women who have not been screened for asymptomatic bacteriuria during pregnancy. 80-90% of acute pyelonephritis (APN) occurs in the 2$^{nd}$ and 3$^{rd}$ trimester of pregnancy and during the puerperium.

The most frequent route of entry is an ascending infection through the urinary tract, although in immunocompromised patients the route of dissemination may be hematogenous (mainly in diabetics, patients undergoing treatment with corticosteroids, systemic diseases, etc.).

The most frequent location is the right kidney (50% of cases); 25% of cases occur in the left kidney and the remaining 25% occur bilaterally.

It is important to revise previous urinary tests because, if they had an asymptomatic bacteriuria, it is possible that the current APN will be caused by the same microorganism.

**2. Clinical features**
- Costovertebral pain with positive kidney percussion test.
- Fever/low-grade fever.
- Nausea and vomiting.
- In general, it does NOT present concurrently with acute cystitis.

**3. Complementary examinations**
- Clinical history and physical examination: evaluate the results of previous urine culture, if there was an AB, the germ identified and if it was correctly treated.
- General analysis (blood count, electrolytes, creatinine and CRP) and urinary sediment.
- Urine culture. It is important to remember the rules for urine culture sample collection. It does NOT necessarily require bladder catheterisation (except in the puerperium to avoid contamination of the sample by blood, lochia, etc.), but it should be collected under certain conditions: prior cleansing of external genitalia, separation of the vulvar labia and sample collection midstream of urination.
- Blood culture (bacteraemia is present in up to 20% of patients with pyelonephritis).
- Renal ultrasound: It is NOT necessary to perform it routinely. This examination is indicated in the following risk situations: absence of adequate response to antibiotic treatment in 48 to 72 hours, recurrent episodes of AB, cystitis or APN, affectation of general condition, in case of sepsis (infection with organ failure) or haematuria.

**4. Treatment**

4.1 Hospital treatment
The following situations are criteria for hospital admission:
- Gestational age above 24 weeks.
- Fever above 38ºC.
- Sepsis.
- Dehydration.
- Clinical picture of threatened preterm labour.
- Recurrent pyelonephritis.
- Comorbidity.
- Oral intolerance.
- Failure of outpatient treatment after 72 h (3 days).
- No possibility of outpatient treatment or expectancy of non-adherence.
- Allergy to beta-lactams.

Hydration should be ensured according to the hydroelectrolytic status of the patient (taking into account different aspects such as renal function or the presence of vomiting). In the case of a normohydrated patient, hydration can be simply oral.

Parenteral antibiotic treatment should not be started until the patient has been afebrile for 48-72 hours. When prescribing empirical antibiotic therapy, it is important to assess whether the patient has risk factors for colonisation by extended-spectrum beta-lactamase (ESBL)-producing GNB:
- Patients with comorbidity such as chronic kidney disease, diabetes mellitus, liver cirrhosis or COPD.
- Immunosuppression: neutropenic patients, prior solid organ or haematopoietic stem cell transplantation, corticotherapy with more than 20 mg/d of prednisone or equivalent for more than two weeks, immunosuppressants or cytostatic drugs, HIV with less than 200 CD4+, primary immunodeficiencies, etc.
- Bladder catheterisation.
- History of hospital admissions for more than 48 hours in the previous 3 months (higher risk if admission in ICU and/or prior surgery).
- Use of systemic antibiotics in the previous 3 months (which is frequent in patients with repeated UTIs).
- Patients from endemic areas (Latin America, Caribbean, Asia, Mediterranean region outside the EU).

In pregnant women without ESBL risk factors, Ceftriaxone 1 g every 24 h IV should be the treatment of choice, and in cases of allergy to beta-lactams, we should administer Aztreonam 1 g every 8 h IV. In pregnant women with ESBL risk factors, Ertapenem 1 g every 24 h IV should be the treatment of choice, and in patients with allergy to beta-lactams we should start Fosfomycin 4 g every 8 h IV.

In the puerperium, *Enterococcus faecalis* should be also covered. Hence, in women without ESBL risk factors, the treatment of choice should be either Ceftriaxone 1 g/24 h IV + Ampicillin 2 g/6 h IV or Piperacillin/Tazobactam 2 g/8 h IV in monotherapy. In women allergic to beta-lactams, the treatment of choice is Aztreonam 1 g/8 h IV + Teicoplanin 600 mg/24 h IV. On the other hand, in women with ESBL risk factors, the treatment of choice will be Ertapenem 1 g/24 h IV + Ampicillin 2 g/6 h IV, and in women allergic to beta-lactam and with ESBL risk factors, we should administer Fosfomycin 4 g/8 h + three doses of Teicoplanin 400 mg/12 h followed by 400 mg/24 h IV.

In all cases, the results of urine cultures and previous antibiograms should be reviewed, considering the causative germ and its sensitivity spectrum in order to de-escalate according to the antibiogram results. If we rule out ESBL germs, we will substitute the antibiotic treatment with the antibiotic of choice for germs without ESBL risk factors. If there is no response, we should act according to the antibiogram with the possibility of more complex guidelines in consensus with the Infection Specialists.

4.2 Outpatient treatment

Outpatient antibiotic treatment is possible when hospitalisation criteria are not met. In these cases, we should administer a single dose of ceftriaxone 1 g IV when the diagnosis is made and follow the treatment at home with cefixime 200 mg/12 h oral for up to 7 days. It is important to ensure good oral hydration and be able to perform a follow-up in 48-72 h to assess evolution and check the results from the urine culture.

Treatment of uncomplicated APN is 7 days and empirical treatment should be adjusted to the antibiogram result. In case of persistent febrile syndrome and no clinical response after 72 h (3 days) of outpatient medical treatment, hospital admission should be indicated.

**5. Clinical follow-up**

After 48-72 hours in afebrile condition, we will change to an oral antibiotic treatment (according to the antibiogram results) until completion of 7 days of treatment. If complications (abscesses or nephritis foci) are identified, treatment will be extended and its duration will depend on the imaging evolution (in consensus with the Infectious Disease Specialists).

- Consider ultrasound according to the indications of point 3 (complementary scans) and even pyelography if ultrasound is inconclusive and there is no response to treatment.
- A urine culture should be performed 7-15 days after completion of antibiotic treatment. A urine culture should be repeated monthly, since up to 20% of pyelonephritis recur.
- Prophylactic antibiotic treatment should be considered in case of recurrent pyelonephritis during pregnancy, if a urine culture results positive after a properly treated episode of APN, or after a single episode of APN in patients with renal or excretory tract pathology (solitary kidney, renal transplant, vesicoureteral reflux, etc.), in immunocompromised patients or other severe maternal medical conditions.

## 5. RECURRENT UTI PROPHYLAXIS

This consists of the administration of antibiotic treatment to prevent the recurrence of urinary tract infections. It is performed once the treatment regimen is completed and during the rest of gestation up to 4-6 weeks postpartum.

These are the indications for recurrent UTI prophylaxis:

- In cases of recurrent AB or acute cystitis, after 3 or more positive urine cultures, despite effective complete treatment. After the 3rd treatment (4-7 days) we would initiate the prophylaxis.
- Recurrent pyelonephritis during pregnancy or a positive urine culture after an episode of a well-treated APN.

- After a single episode of APN in patients with renal or excretory tract pathology (solitary kidney, renal transplant, reflux, etc.) or in patients with immunosuppression or other severe maternal medical conditions.

There are two recommended drugs:
- Cephalexin 250 mg/24 h oral (capsules, preferably administered at night) through magistral formula preparation in pharmacy.
- Fosfomycin trometamol 3 g oral every 5 days (to simplify: every 5$^{th}$, 10$^{th}$, 15$^{th}$, 20$^{th}$, 25$^{th}$ and 30$^{th}$ of each month).

It is necessary to evaluate previous cultures and antibiograms to decide which drug is the most appropriate. Cephalexin is better tolerated since it is a drug that does not pass into the colon and is entirely eliminated in the urine, so its extended use does not alter the intestinal flora.

It is recommended to perform a urine culture one month after starting prophylaxis. In 95% of the cases, it will be negative. If the urine culture is positive, assess whether the dose or type of prophylaxis should be modified with Infectious Disease Specialists