

ASYMPTOMATIC BACTERIURIA AND URINARY TRACT INFECTIONS IN PREGNANCY

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CONFLICTS OF INTEREST

None

OBJECTIVES

- Discuss potential risks associated with asymptomatic bacteriuria (ASB) and urinary tract infections (UTIs) in pregnancy
- Define ASB and UTIs
- Review screening recommendations for ASB in pregnancy
- Review treatment and follow up recommendations for ASB and UTIs in pregnancy

BACKGROUND

- Incidence of **bacteriuria** about equal in pregnant women as in non-pregnant women, but **pyelonephritis** and **recurrent bacteriuria** are more common in pregnancy
- ASB occurs in 2-15% of pregnant women
- 20-35% of pregnant women with ASB will develop symptomatic UTI
- Risk of progression to UTI may be reduced by up to 80% with treatment
- **Acute cystitis** occurs in 1-2% of pregnant women
- **Pyelonephritis** occurs in 1-2% of pregnant women
 - most common in 2nd trimester
 - one of most common medical causes of hospitalization during pregnancy

PHYSIOLOGIC CHANGES IN PREGNANCY PREDISPOSING TO UTIs

- Renal pelvis and ureters dilate and bladder displaced superiorly and anteriorly as early as 8 weeks gestational age
- **Mechanical compression** from enlarging uterus -> obstruction -> hydroureter and hydronephrosis, increased residual volume in bladder and urinary stasis
- Other contributing factors:
 - Urinary pH
 - Glycosuria
 - Progesterone-mediated smooth muscle relaxation -> decreased ureteric peristalsis, increased bladder capacity, and urine stasis -> easier for bacteria to ascend
 - Immunosuppression of pregnancy

NEGATIVE OUTCOMES ASSOCIATED WITH ASB and UTIs IN PREGNANCY

- **Pyelonephritis**
 - sepsis, shock, respiratory distress, ARDS, DIC, anemia, transient kidney dysfunction
 - Preterm labor
- **ASB**
 - Pyelonephritis
 - ? Low birth weight (LBW)?
 - ? Preterm labor?
- **Acute cystitis**
 - Pyelonephritis

***Most studies are from 1960s and 1970s, study quality was poor, and ABX treatment regimens do not reflect current practice

***Large (>4200 women), multicenter prospective study from the Netherlands (2011-2013) where screening for ASB in pregnancy is not routine showed **increased risk of pyelonephritis and symptomatic UTIs but no increased risk of preterm birth or LBW in LOW-RISK pregnancies**

- rate of pyelonephritis was 2.4% (previously thought that up to 20-30% of untreated pregnant women with ASB)

CASE: Nancy



36yo G2P1 presents for a prenatal intake. This is a desired, planned pregnancy. She has regular periods and is 8w5d by LMP. Her last pregnancy was complicated by a UTI (cystitis) in her 2nd trimester but was otherwise normal, and she delivered a 7lb 2 oz baby girl via NSVD at 40w2d.

CASE: Nancy

- What routine prenatal test will be of particular interest given this history?

Urine culture to screen for ASB

RISK FACTORS FOR ASB and UTIs in PREGNANCY

- Low socioeconomic status
- H/o ASB or UTI in pregnancy
- Pre-existing diabetes (especially 1st trimester UTI)
- Sickle cell trait (up to 40% increase in rate of ASB in pregnant women)
- Alpha and beta thalassemia trait
- Nulliparity
- Young age (<20yo)
- Smoking
- Late presentation to prenatal care
- 2nd/3rd trimesters

SCREENING FOR ASB

- ACOG and the IDSA recommend screening for ASB “early in pregnancy” with urine culture
- USPSTF “B” recommendation (evidence of moderate benefit, 2019)
- insufficient evidence to inform a recommendation for or against repeat screening during the pregnancy for a woman with an initial negative screening culture or following treatment of an initial episode of ASB

CASE: Nancy

- Ucx: 50,000 CFU/ml *E. coli*

**What is her diagnosis?
Does this require treatment with ABX?**

DEFINITIONS

- **ASB**

- the presence of 1 or more species of bacteria growing in the urine at **$\geq 10^5$ colony-forming units (CFU)/mL** irrespective of the presence of pyuria, in the absence of signs or symptoms attributable to a UTI
- normal genital/skin flora (*Lactobacillus*, *Corynebacteria*, coagulase-negative *Staphylococcus*) or multiple bacterial species suggests contamination*
- Group B Streptococcus should be treated if **$\geq 10^5$ CFU/mL**, lower levels should be documented for GBS ppx in labor but not treated
- can be found in healthy females and in patients with GU tract abnormalities

- **UTI**

- symptomatic (**dysuria**, urinary urgency, frequency, nocturia, hematuria)
- confirmed by positive urine culture (**$\geq 10^5$ CFU/mL**)*

- **Pyelonephritis**

- systemic symptoms (fever $\geq 38^\circ\text{C}$, flank pain, CVA tenderness, N/V, chills)
- +bacteriuria or pyuria

CASE: Nancy

- Ucx: 50,000 CFU/ml *E. coli*

**What is her diagnosis?
Does this require treatment with ABX?**

NO ASB -> NO ABX INDICATED

CASE: Nancy

Initial prenatal course is going well. She returns for her 20 week visit and endorses increased urinary frequency, urgency and dysuria x 2 days. VSS today. She denies F/C/N/V. Her exam is unremarkable and without CVA TTP.

Do you order any tests?

URINALYSIS INTERPRETATION

Table 2. Accuracy of Urinalysis Findings to Predict Culture-Positive Urinary Tract Infection*

Test	Result	Sensitivity (%)	Specificity (%)	PPV	NPV
Dipstick					
	Leukocyte esterase (+)	72–97	41–86	43–56	82–91
	Nitrites (+)	19–48	92–100	50–83	70–88
	Leukocyte esterase or nitrites (+)	46–100	42–98	52–68	78–98
	Protein at 3+ or higher	96	87	NA	NA
	Protein at 1+ or higher	91–100	65–99	NA	NA
Microscopy					
	More than 5 WBCs/HPF	90–96	47–50	56–59	83–95
	More than 5 RBCs/HPF	18–44	88–89	27	82
	Bacteria (any amount)	46–58	89–94	54–88	77–86

Abbreviations: PPV, positive predictive value; NPV, negative predicative value; NA, not applicable; WBC, white blood cell; HPF, high-power field; RBC, red blood cell.

*The PPV and NPV for UTI are presented as a range, because they will vary with the prevalence of UTI in the population studied. In populations with a low prevalence of UTI, the PPV decreases while the NPV increases.

Modified from Simerville JA, Maxted WC, Pahira JJ. Urinalysis: a comprehensive review [published erratum appears in Am Fam Physician 2006;74:1096]. Am Fam Physician 2005;71:1153–62.

THE ELUSIVE “CLEAN CATCH” OF PREGNANCY

- Cross-sectional study of 300 asx women attending prenatal appointments in 2018 showed **1 in 3 women** had at least 1 positive finding on U dip
 - 1/3 of women: LE+
 - 13% of women: protein+
 - 0 women: nitrite+
 - BMI is a risk factor for urine culture contamination*
 - 46% of samples were positive for multiple organisms, obese women with higher risk of mixed growth in urine
 - Maternal age, gestational age*, and parity were not significant risk factors
- Mid-stream catch most reasonable

CASE: Nancy

- Udip:
 - Leukocyte Esterase +
 - Nitrite +
 - Blood +
- Urine culture pending

Do you prescribe ABX now or wait for ucx results?

What ABX do you prescribe?

COMMON PATHOGENS

- *E. coli* (up to 80%)
- *Proteus mirabilis*
- *Klebsiella* spp.
- Gram positives (mainly Group b streptococcus)
 - more common in 3rd trimester (up to 1/4 cases of pyelo in 3rd trimester)

ANTIBIOTIC RECOMMENDATIONS

Choose ABX based on:

- urine culture results/sensitivities
- local resistance patterns
- patient's allergies/contraindications

****Avoid empiric treatment with ampicillin or amoxicillin regimens while awaiting culture results due to high levels of E. coli resistance in many areas*

****Extended-spectrum beta-lactamases (ESBL) E. coli and Klebsiella have been isolated in varying rates in pregnant patients' urine cultures across the globe*

****Choosing the appropriate ABX with narrowest spectrum and appropriate duration are essential for antibiotic stewardship*

ANTIBIOTIC RECOMMENDATIONS

- Generally safe in pregnancy: penicillins, cephalosporins, carbapenems and fosfomycin
- Reasonable in 1st trimester if no appropriate alternative available:
 - **Nitrofurantoin:**
 - possible risk of congenital anomalies although risk is likely low*
 - avoid near term (38-42 weeks) per manufacturer recs 2/2 possible increased risk of neonatal jaundice (2/2 low glutathione levels inducing hemolytic anemia)
 - avoid in pts with G-6-PD deficiency (risk of pulmonary toxicity, hemolytic anemia)
 - **Trimethoprim-sulfamethoxazole:**
 - possible association with congenital abnormalities (neural tube defects, CV malformations, urinary tract defects, oral clefts, club foot)
 - avoid near term 2/2 theoretical risk of kernicterus

TREATMENT RECOMMENDATIONS

- **ASB**

- Short (5-7 day) course po ABX

- **UTI**

- Short (5-7 day) course po ABX

- **Pyelonephritis**

- Inpatient treatment recommended
- IV ABX until improvement
- Switch to po ABX once afebrile x 48 hrs (avoid nitrofurantoin and fosfomycin)
- 14 day total course
- *Blood cultures not recommended (up to 20% positive, don't change treatment choice or duration)*

ASB and CYSTITIS TREATMENT RECOMMENDATIONS

Antimicrobial	Regimen	Considerations
Nitrofurantoin	100 mg orally every 12 h for 5–7 d	Reasonable to offer in the 1st trimester if no appropriate alternatives are available Avoid as treatment for pyelonephritis due to inability to reach therapeutic levels in the kidney
Cephalexin*	250–500 mg orally every 6 h for 5–7 d	
Sulfamethoxazole-trimethoprim	800/160 mg every 12 h for 5–7 d	Reasonable to offer in the 1st trimester if no appropriate alternatives are available In areas with more than 20% resistance to trimethoprim-sulfamethoxazole, avoid if initiating treatment before culture results are available
Fosfomycin	3 g orally once	Avoid as treatment for pyelonephritis due to inability to reach therapeutic levels in the kidney
Amoxicillin*	500 mg orally every 8 h for 5–7 d 875 mg orally every 12 h for 5–7 d	High degree of resistance; avoid if initiating treatment before culture results are available
Amoxicillin—clavulanate*	500 mg orally every 8 h for 5–7 d 875 mg orally every 12 h for 5–7 d	High degree of resistance; avoid if initiating treatment before culture results are available

*For patients with a β -lactam allergy for whom other classes of antibiotic are inappropriate, further investigation regarding the severity of allergic reaction is necessary. For patients at low risk for anaphylaxis, treatment with cephalosporins would be appropriate; however, individuals at high risk for anaphylaxis would need to be treated with an alternative regimen.

Modified from:

1. Matuszkiewicz-Rowińska J, Małyszko J, Wieliczko M. Urinary tract infections in pregnancy: old and new unresolved diagnostic and therapeutic problems. *Arch Med Sci* 2015;11:67–77. doi: 10.5114/aoms.2013.39202
2. Wang T, Wu G, Wang J, Cui Y, Ma J, Zhu Z, Qiu J, Wu J. Comparison of single-dose fosfomycin tromethamine and other antibiotics for lower uncomplicated urinary tract infection in women and asymptomatic bacteriuria in pregnant women: a systematic review and meta-analysis. *Int J Antimicrob Agents* 2020;56:106018. doi: 10.1016/j.ijantimicag.2020.106018

PYELONEPHRITIS TREATMENT RECOMMENDATIONS

Table 3. Antibiotic Regimens for Treatment of Pyelonephritis

Antimicrobial	Regimen
Ampicillin + gentamicin	2 g IV every 6 h 1.5 mg/kg IV every 8 h 5 mg/kg IV every 24 h
Ceftriaxone	1 g IV every 24 h
Cefepime	1 g IV every 12 h
Aztreonam (appropriate in patients with β -lactam allergy)	1 g IV every 8–12 h

Abbreviation: IV, intravenously.

Data from:

1. Wing DA, Hendershott CM, Debuque L, Millar LK. A randomized trial of three antibiotic regimens for the treatment of pyelonephritis in pregnancy. *Obstet Gynecol* 1998;92:249–53. doi: 10.1016/s0029-7844(98)00156-2
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CASE: Nancy

Ucx from previous pregnancy showed >100K CFU E. coli, pan-sensitive. You confirm Nancy has NKDA and prescribe 5 days of nitrofurantoin 100 mg po BID while awaiting pending ucx results.

Does she need to f/u sooner than her scheduled 4 week visit at 24 weeks?

FOLLOW UP RECOMMENDATIONS

- **ASB**
 - Can consider test of cure (TOC) 1-2 weeks after treatment
 - Can consider repeat testing for high-risk women (h/o UTI in pregnancy, urinary tract anomalies, diabetes, hemoglobin S, preterm labor)
- **UTI**
 - Can consider TOC 1-2 weeks after treatment **vs** symptoms-based testing
- **Pyelonephritis**
 - **TOC recommended**
 - Can consider daily prophylactic ABX until 4-6 weeks postpartum **and** monthly screening urine cultures

CASE: Nancy

- TOC 1 week after completion of ABX:
negative ucx
- She remains asx until her 28 week visit at which time she endorses similar sx (dysuria, increased frequency, urgency) as well as hematuria x 1 day.

**What labs do you order?
Do you treat empirically? If so, with what?**

CASE: Nancy

- Udip:
 - Leukocyte Esterase +
 - Nitrite +
 - Blood +
- Urine culture pending
- Same ABX as previous UTI until culture results.

Do you need to see Nancy back sooner than her 32 week appointment?

Do you need to do anything additional for her UTI this time?

MANAGEMENT OF RECURRENT UTIs IN PREGNANCY

- No consensus
- Can consider:
 - monthly urine culture
 - treat based on symptoms
 - prophylactic low-dose ABX (daily vs post-coital)
 - Nitrofurantoin 50-100 mg
 - Keflex 250-500 mg

CASE: Nancy

Through shared decision making, you and Nancy decide to start daily prophylactic ABX with nitrofurantoin 100 mg daily. She does not have any further UTI sx for the duration of her pregnancy.

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Questions?

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THANK YOU!