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Beyond Expert Opinion: A Comparison of Antibiotic Regimens for Infectious Urinary Tract Pathology in Pregnancy

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Abstract

Objective Outside pregnancy, nitrofurantoin, ciprofloxacin and sulfamethoxazole-trimethoprim (SMZ-TMP) are first-line therapy (FLT) for lower urinary tract infections (LUTIs). Optimal antibiotics for LUTI have been extrapolated based on expert opinion. Progression to pyelonephritis and adverse obstetric outcomes were compared between women who received FLT and those given alternative antibiotics.

Methods This study includes a retrospective cohort of women with LUTI, including asymptomatic bacteriuria and acute cystitis at single health care system from July 2013 to May 2019. Women receiving FLT, defined as nitrofurantoin or SMZ-TMP, were compared with those receiving nonfirst-line therapy (nFLT). Primary outcome was progression to pyelonephritis. Secondary outcomes included pyelonephritis-related anemia, sepsis, length of stay, preterm birth (PTB), and low birth weight (LBW). Logistic regression was used to calculate odds of outcomes.

Results Of 476 women, 336 (70.6%) received FLT and 140 (29.4%) received nFLT. Women receiving FLT were more likely having BMI $\geq$ 40 ($p = 0.04$). Progression to pyelonephritis did not differ (5.8 vs. 8.2%; $p = 0.44$), nor did other pyelonephritis-related outcomes. After controlling for confounders, no difference in odds of progression to pyelonephritis was seen (adjusted odds ratio [aOR] 1.02, 95% confidence interval [CI] 0.42, 2.49). FLT was not associated with PTB or LBW (aOR 0.60, 95% CI 0.29, 1.26) after controlling for confounders.

Conclusion Receipt of antibiotics other than nitrofurantoin or SMZ-TMP for LUTI in pregnancy was not associated with increased risk of progression to pyelonephritis, PTB, or LBW.

Keywords
- asymptomatic bacteriuria
- acute cystitis
- nitrofurantoin
- pyelonephritis
- trimethoprim-sulfamethoxazole
- uropathogen
- urinary tract infections

Lower urinary tract infections (LUTIs) are one of the most common medical complications of pregnancy, occurring in 8% of U.S. women.[1] LUTIs include both asymptomatic bacteriuria (ASB) or acute cystitis (AC). Left untreated, ASB develops into symptomatic AC in 30% of patients and may progress to pyelonephritis in up to 50% of those patients.[2] It is estimated that 0.5 to 2% of all pregnant women are hospitalized for treatment of pyelonephritis.[3,4] Pyelonephritis is associated with increased risk of anemia, sepsis, acute pulmonary insufficiency, acute renal dysfunction, and

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spontaneous preterm birth (PTB).[3] Given the increased maternal morbidity of untreated LUTI, the United States Preventive Services Task Force recommends routine screening for and treatment of ASB and AC during pregnancy.[5]

Treatment of ASB and AC in pregnancy must cover the most common uropathogens, considering the altered pharmacokinetics, and must take into account teratogenicity and fetal toxicity of some antibiotics during pregnancy. The most common urinary tract pathogen is *Escherichia coli*, accounting for 80 to 90% of UTIs in pregnancy.[1] Other common UTI pathogens include Group-B *Streptococcus*, *Staphylococcus saprophyticus*, *Klebsiella pneumoniae*, and *Proteus mirabilis*. Many antibiotics offer sufficient coverage of these microorganisms; however, antibiotic toxicity in pregnancy restricts treatment options. Antimicrobial agents currently approved for use in pregnancy include nitrofurantoin, β lactams, cephalosporins, and fosfomycin trometol.[6] However, current American College of Obstetricians and Gynecologists recommendations identify nitrofurantoin and sulfonamides, primarily trimethoprim-sulfamethoxazole (SMZ-TMP), as first-line therapies for LUTI in pregnancy.[7]

Despite these recommendations, a recent CDC study that used MarketScan Commercial Database to find pregnancies with UTIs and filled antibiotic prescriptions, and included 450,000 pregnancies of which nearly 40,000 met inclusion criteria, found that less than half of LUTI were treated with nitrofurantoin or SMZ-TMP.[8] These data suggest nonfirst-line antibiotics are commonly used to treat LUTI in pregnancy. However, the efficacy in preventing progression to pyelonephritis of nonfirst-line antibiotics for UTI in pregnancy is unknown. The purpose of this study is to compare the rates of progression to pyelonephritis and obstetric outcomes among women treated with first-line antibiotic therapies, specifically nitrofurantoin or SMZ-TMP, with those treated with nonfirst-line therapies.

Materials and Methods

This was a retrospective cohort study of all pregnant women presenting at a single health system with LUTI, including ASB or AC, during pregnancy. Women delivering at a Duke University-affiliated hospital from July 1, 2013 to May 1, 2019 were included. Eligible patients were identified using International Classification of Diseases, 9th (ICD-9) and 10th (ICD-10) Revision codes for ASB, acute cystitis, and pyelonephritis.

Women were included if they were diagnosed with LUTI during pregnancy and delivered during the study period in the health care system. Women with missing culture data, antibiotic data, or delivery information were excluded. Women with documentation of medication nonadherence per provider records were also excluded. ASB and AC were defined as urine culture positive for a single organism $\geq 10^5$ cfu/mL without symptoms and $\geq 10^2$ cfu/mL with symptoms, respectively.[9] Pyelonephritis was defined by clinical diagnosis documented by the provider during admission.

The electronic medical record was reviewed, and demographic variables, antepartum and pregnancy complications, delivery, and postpartum data were abstracted by trained chart abstractors. The exposure of interest was receipt of a "first-line" antibiotic for the treatment of LUTI. First-line antibiotic therapy was defined as nitrofurantoin or SMZ-TMP.[10] Nonfirst-line therapy included all other antibiotics. Antibiotic choice was at the discretion of the provider.

The primary outcome was progression to pyelonephritis. Secondary outcomes included length of antibiotic course, pyelonephritis-related anemia (defined as the hematocrit nadir during the admission for pyelonephritis), sepsis, pyelonephritis length of stay, preterm delivery, and low birth weight. Preterm delivery was defined as delivery prior to 37 weeks. Short course of antibiotics was defined as less than 7 days. Maternal anemia was defined as a hematocrit nadir less than 32%.[11] Women who received first-line antibiotic therapy (FLT) were compared with those who received nonfirst-line therapies (nFLTs).

Baseline demographics were analyzed with Student's *t*-test, Wilcoxon rank sum tests, Chi-square tests, or Fisher's exact tests as appropriate. Multivariate logistic regression was used to determine significant predictors of the primary outcome. Statistical significance was defined as $p < 0.05$. Statistical analysis was performed using STATA software version 14.0. This study was approved by the Duke University IRB.

Results

Of 722 women with LUTI, 476 women met inclusion criteria with culture-confirmed LUTI and documentation of antibiotic therapy completion (►**Fig. 1**). Of these, 336 (70.6%)

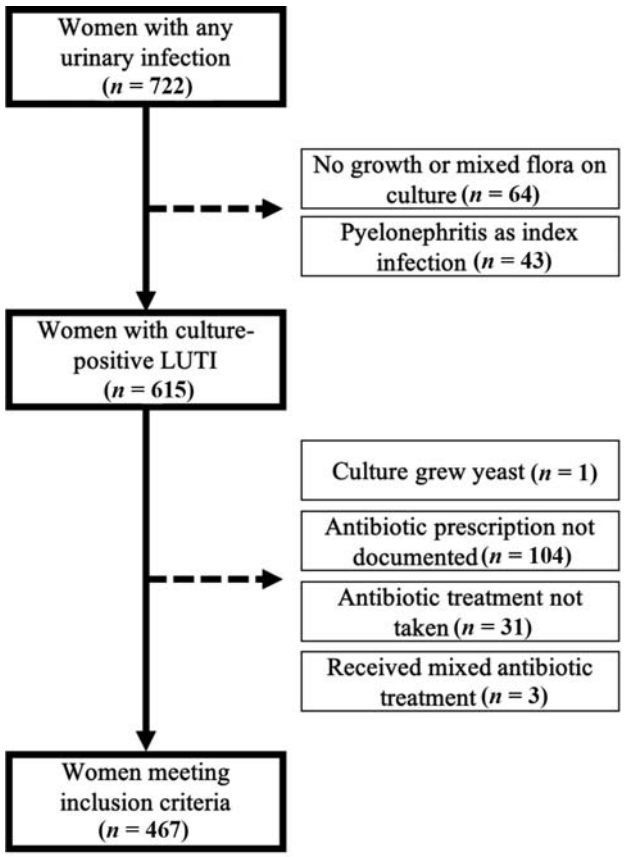

Fig. 1 Study population.

Table 1 Antibiotics received among women with UTI and ASB

Antibiotic	*N* (%)
First-line therapy	335 (71)
Nitrofurantoin	322 (68)
SMZ-TMP	13 (3)
Nonfirst-line therapy	140 (29)
Ampicillin	60 (13)
Cephalexin	49 (10)
Other	31 (6)

Abbreviations: ASB, asymptomatic bacteriuria; SMZ-TMP, trimethoprim-sulfamethoxazole; UTI, urinary tract infection.

received nitrofurantoin or SMZ-TMP and 140 (29.4%) received nFLT. The most common nFLT used was ampicillin (13%), followed by cephalexin (10%). Sixty-eight percent of women received nitrofurantoin; this was the most common treatment and the most common FLT (►**Table 1**).

Women who received FLT were more likely to have a BMI > 40 ($p = 0.04$) than those who received nFLT (►**Table 2**). Other baseline demographic data did not differ (►**Table 2**). Women who were treated with nFLT were more likely to receive a short course of their prescribed antibiotic (►**Table 2**).

E. coli was the single most common pathogen, occurring in 41.8% ($n = 199$) of all positive cultures. Among women receiving FLT, 48.5% had a culture positive for *E. coli*, compared with only 25.7% of women who received nFLT, ($p < 0.01$). Group B Strep LUTI were also common, occurring in 31.7% ($n = 151$) of all cultures. Women with GBS LUTI were less likely to receive FLT, (24.1% FLT vs. 50.0% nFLT, $p < 0.01$).

Among the 476 women included in the analysis, 35 (7.3%) developed pyelonephritis. Progression to pyelonephritis did not differ by receipt of FLT, (8.2 vs. 5.8%, $p = 0.44$). After controlling for history of UTI, culture result, treatment duration <7 days, and BMI ≥ 40, no difference in odds of progression to pyelonephritis was seen between women who received FLT and those that did not (adjusted odds ratio 1.02, 95% confidence interval 0.42, 2.49). Pyelonephritis-associated morbidities were uncommon. However, of those women who progressed to pyelonephritis in the nFLT and FLT groups, a trend toward increased rates of sepsis was seen in those who received nFLT (2/8 vs. 0, $p = 0.05$). Regarding obstetric outcomes, receipt of FLT was also not associated with earlier gestational age at delivery, PTB, or LBW (►**Table 3**), even after controlling for confounders (data not shown).

Comment

Among women with LUTI, receipt of nonfirst-line antibiotic therapy was not associated with higher odds of progression to pyelonephritis. Pyelonephritis-related sepsis was uncommon in both groups; however, it occurred in 25% of women in the nFLT compared with no women in the FLT group. No other pyelonephritis-related morbidities differed by antibiotic receipt, nor did obstetric outcomes.

Table 2 Maternal demographics among women with ASB and UTI by antibiotic treatment regimen[a]

	Non-1st line Tx $n = 140$ (%)	1st line Tx $n = 335$ (%)	*p*-Value
Median age, years (IQR)	27 (22, 32)	28 (23, 33)	0.34
African American Race	31 (22.1)	83 (24.7)	0.64
Private insurance	43 (31.4)	116 (35.1)	0.15
Limited prenatal care	7 (5.1)	14 (4.2)	0.81
Chronic hypertension	16 (11.5)	23 (6.9)	0.10
Diabetes mellitus	9 (6.5)	17 (5.1)	0.52
Tobacco use	14 (10.1)	36 (10.8)	>0.99
BMI ≥40	29 (20.7)	43 (12.8)	0.04
Median baseline hematocrit (IQR)	36.6 (35.0,39.9)	37.0 (34.6,39.0)	0.49
Depression	15 (10.7)	68 (20.2)	0.01
Multiparous	81 (57.9)	213 (63.4)	0.30
Prior preterm birth	24 (17.1)	52 (15.5)	0.68
History of pyelonephritis	4 (2.9)	14 (4.2)	0.61
History of UTI	27 (19.3)	90 (26.9)	0.10
Median GA of first infection, wk, (IQR)	11.0 (8.7,21.3)	11.6 (9.3,18.4)	0.54
Short therapy (<7 d)	16 (11.4)	12 (3.6)	<0.01

Abbreviations: ASB, asymptomatic bacteriuria; BMI, body mass index; GA, gestational age; IQR, interquartile range; Tx, therapy; UTI, urinary tract infection.

[a]Data presented as *n*(%), unless otherwise stated.

Table 3 Maternal and obstetric outcomes among women with ASB and UTI by antibiotic treatment regimen[a]

	Non-1st line Tx $n = 140$ (%)	1st line Tx $n = 336$ (%)	*p*-Value
Progression to pyelonephritis	8 (5.8)	27 (8.2)	0.44
Median pyelonephritis LOS, days, (IQR)	3.5 (2, 5)	4 (2, 5)	0.97
Median hematocrit nadir (IQR)	26.7 (24.4, 29.9)	29.9 (27.0, 31.8)	0.12
Anemia	7/9 (77.8)	21/27 (77.8)	0.99
Blood transfusion	1/8 (12.5)	0	0.23
Sepsis	2/8 (25.0)	0	0.05
Median GA delivery, weeks, (IQR)	39.3 (37.7, 40.0)	39.1 (37.9, 40.0)	0.94
Preterm birth	13 (9.3)	42 (12.5)	0.35
Low birth weight	15 (10.7)	23 (6.9)	0.19

Abbreviations: ASB, asymptomatic bacteriuria; GA, gestational age; IQR, interquartile range; LOS, length of stay; Tx, therapy; UTI, urinary tract infection.
[a]Data presented as *n*(%), unless otherwise stated.

Treatment of LUTI in pregnancy is restricted due to antibiotic safety and toxicity. Outside of pregnancy, where antibiotic selection is not limited by pregnancy-specific safety concerns, the recommended therapies for UTI in women include fosfomycin, nitrofurantoin, and SMZ-TMP.[12] Unlike β-lactams, these first-line agents in nonpregnant women have less microbial resistance and achieve higher rates of complete clearance of gram-negative microorganisms from the urine, decreasing LUTI recurrence rates.[13] In pregnancy, guidelines identify nitrofurantoin and SMZ-TMP and first-line treatment of LUTI in pregnancy based on efficacy and teratogenicity.[10] A large recent observational study of more than 450,000 pregnancies found that only 42.3% of first trimester LUTI are treated with FLTs of nitrofurantoin or SMZ-TMP.[8] In the current study, 70.6% of women were treated with first-line therapies suggesting that national rates of first-line therapy may vary by institution and provider preferences. A 2011 Cochrane review of 1,125 women treated for AC in pregnancy found no significant differences between antibiotic treatments with regards to infection cure rate, but did not assess progression to pyelonephritis.[14] This study also noted that it was not possible to draw conclusion on the best class of antibiotic nor the duration, and went on to say that "Future studies should evaluate the more promising classes of antibiotics, such as nitrofurantoin, trimethoprim-sulfamethoxazole…"[14] Thus, more data are needed. However, the findings of our study appear consistent with these results and are more current; given that existing data suggest that cure rates are similar, progression rates also likely do not differ.

Use of nFLT for treatment of LUTI in pregnancy does not appear to carry increased risk of progression to pyelonephritis or worse obstetric outcomes. These findings suggest that antibiotic choice for LUTI in pregnancy may not need to be limited to the recommended first-line therapies. Thus, the choice of antibiotics for treatment of LUTI can be based on other factors including provider or patient preference, local resistance patterns, and side effect profiles. Further larger studies are needed to assess rates of progression to pyelonephritis among individual antibiotics within the FLT and nFLT groups. Additionally, prospective randomized control trials could provide more data on ideal FLT in pregnancy.

This study has multiple strengths. First, the study was conducted over 6 years at a large health care system allowing for a representative sample of antibiotic therapies used for LUTI in pregnancy. Additionally, the study population was diverse across metrics of age, race, ethnicity, and socioeconomic status making it generalizable to the broader population. We also recognize several limitations of the study. In this study, antibiotic therapies were simplified into only two groups: FLT and nFLT. Individual antibiotics within the respective groups may not share the same outcomes as others in the group. Given the limited sample size of this cohort, we were only able to analyze between general therapy groups. The sample size thus limits the ability to differentiate among therapies and provide detailed outcomes for each individual therapy. We also recognize that among gram-negative infections in this cohort, there is some degree of antibiotic resistance; however, in the adjusted analysis, we controlled for infectious pathogen to mitigate this to some extent. Another limitation concerns the rate that a test of cure was performed within 2 weeks of treatment, only 12% of the time, which limits our ability to comment on effectivity of treatment. However, a larger analysis could be completed to evaluate outcomes of each antibiotic independently. We are also limited by a small sample size. With the current sample size, a significance level of 0.05, and assuming an increase from 5 to 10% incidence of pyelonephritis as a clinically important difference to detect, the power of this study to exclude a type II error is 45%. Achieving 80% power and assuming the same clinically important difference to detect would require 474 subjects per group. Thus, there is a chance of type 2 error. Additionally, very few women, only 12%, had a test of cure within 2 weeks of completion of therapy, limiting our ability to comment on bacterial clearance. We are also unable to explain antibiotic prescribing that varied from our standing protocols which recommend nitrofurantoin, cephalexin, or SMZ-TMP, as this occurred at the discretion of the provider (of which there are

over 100 involved in the care of pregnant women at our institution). Lastly, the rate of progression to pyelonephritis in this study was found to be 7.3% whereas prior large analyses demonstrate the rate of 1.4%.[15] This could suggest that our population of patients was at higher risk of pyelonephritis than seen nationally regardless of the treatments used, making the results less generalizable.

LUTIs in pregnancy treated with nonfirst-line antibiotics do not appear to progress to pyelonephritis at higher rates than those treated with nitrofurantoin or SMZ-TMP. Additionally, no difference was seen in obstetric outcomes in women treated with first-line antibiotics versus nonfirst-line antibiotics. Future studies are required to determine whether individual antibiotics used in pregnancy, regardless of first-line or nonfirst-line status, result in higher rates of adverse obstetric outcomes or rates of progression to pyelonephritis.

Highlights

- As per expert opinion, nitrofurantoin and sulfamethoxazole-trimethoprim (SMZ-TMP) are first line for lower urinary tract infections (LUTI) in pregnancy.
- Nonfirst-line drugs do not increase the rate of LUTI progression to pyelonephritis.
- Pyelonephritis and obstetric outcomes are similar regardless of antibiotic choice.

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None to disclose.

Meeting Presentation Disclosure

This work was presented as a poster presentation at the Society for Maternal-Fetal Medicine's 40th Annual Pregnancy meeting in February 2019 in Dallas, Texas.

Condensation

Receipt of antibiotics other than nitrofurantoin or trimethoprim-sulfamethoxazole for LUTI in pregnancy is not associated with increased risk of progression to pyelonephritis.

Disclosure Statement

The authors report no conflict of interest.

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