Urinary tract infection in pregnant population, which empirical antimicrobial agent should be specified in each of the three trimesters?

Infekcje układu moczowego u ciężarnych – który z leków przeciwbakteryjnych zastosować w każdym z trymestrów ciąży?

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Abstract

Objective: *We aimed to investigate the bacterial profile and the adequacy of antimicrobial treatment in pregnant women with urinary tract infection.*

Material and Methods: *This retrospective observational study was conducted with 753 pregnant women who needed hospitalization because of UTI in each of the three trimesters. Midstream urine culture and antimicrobial susceptibility tests were evaluated.*

Results: *E.Coli was the most frequently isolated bacterial agent (82.2%), followed by Klebsiella spp. (11.2%). In each of the three trimesters, E.Coli remained the most frequently isolated bacterium (86%, 82.2%, 79.5%, respectively), followed by Klebsiella spp. (9%, 11.6%, 12.2%, respectively). Enterococcus spp. were isolated as a third microbial agent, with 43 patients (5.7%) in the three trimesters. The bacteria were found to be highly sensitive to fosfomycin, with 98-99% sensitivity for E.Coli and 88-89% for Klebsiella spp. and for Enterococcus spp. 93-100% nitrofurantoin sensitivity for each of the three trimesters.*

Conclusions: *We demonstrated that E.Coli and Klebsiella spp. are the most common bacterial agents isolated from urine culture of pregnant women with UTI in each of the three trimesters. We consider fosfomycin to be the most adequate first-line treatment regimen due to high sensitivity to the drug, ease of use and safety for use in pregnancy.*

Key words: **empirical antimicrobial agent** / **pregnancy** / **urinary tract infection** /

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Streszczenie

Cel pracy: *Celem pracy była ocena profilu bakteryjnego i adekwatności zastosowanego leczenia przeciwbakteryjnego u ciężarnych z infekcją układu moczowego.*

Materiał i metoda: *Badanie przeprowadzono retrospektywnie na 753 kobietach ciężarnych w każdym z trymestrów ciąży, które wymagały hospitalizacji z powodu infekcji układu moczowego. Oceniono wynik posiewu moczu oraz antybiogram.*

Wyniki: *E. coli była najczęstszą izolowana bakterią (82,2%), następnie Klebsiella spp. (11,2%). W każdym z trzech trymestrów E. coli pozostała najczęstszą izolowana bakterią (86%, 82,2%, 79,5%, odpowiednio), kolejną najczęstszą była Klebsiella spp. (9%, 11,6%, 12,2%, odpowiednio). Jako trzeci najczęstszy patogen izolowano Enterococcus spp. u 43 pacjentek (5,7%) we wszystkich trymestrach. Bakterie okazały się wysoko wrażliwe na fosfomycynę, 98-99% dla E.coli i 88-89% dla Klebsiella spp. Dla Enterococcus spp. wrażliwość na nitrofurantoinę wynosiła 93-100% w każdym z trymestrów.*

Wnioski: *E.coli i Klebsiella spp. są najczęstszymi bakteriami izolowanymi z moczu kobiet ciężarnych z infekcją układu moczowego w każdym z trzech trymestrów. Fosfomycyna jest najbardziej odpowiednim lekiem pierwszorzutowym ze względu na wysoką wrażliwość bakterii, łatwość użycia i bezpieczeństwo stosowania w ciąży.*

Słowa kluczowe: **leczenie empiryczne przeciwbakteryjne** / **ciąża** / / **infekcja układu moczowego** /

Introduction

Urinary tract infections (UTIs) are the most common infection in pregnant women [1, 2]. They are considered to be the most common hospital acquired infection, accounting for as many as 35% of nosocomial infections, and the second most common cause of bacteremia in hospitalized patients [3]. Traditionally, UTI is defined either as a lower tract (acute cystitis or urethritis) or upper tract (acute pyelonephritis) infection. Asymptomatic bacteriuria (ASB) refers to the presence of a positive urine culture in an asymptomatic person, previously reported at 2-13% prevalence in pregnant women [4-6], compared to symptomatic UTI with 1-18% prevalence during pregnancy [7].

UTI usually begins in the sixth gestational week and peaks at 22-24 weeks of gestation due to increased bladder volume, urethral dilatation and reduced bladder tone, contributing to increased urinary stasis and ureterovesical reflux. Up to 70% of pregnant women also develop glycosuria, which contributes to bacterial growth in the urine [8]. As recognized in the literature, the predominant microbial agent that causes UTIs during pregnancy is E.Coli, accounting for 80-90% of infections [9-11]. Microbial agents vary in different geographical regions [12-14].

Many studies have described a relationship between maternal urinary tract infection, particularly asymptomatic bacteriuria, and adverse pregnancy outcomes (e.g., preterm birth, low birthweight) [15-18]. One complication found in a prospective study of a general obstetric population was also acute pyelonephritis [11]. Other complications include anemia (23%), bacteremia (17%), respiratory insufficiency (7%) and renal dysfunction (2%). The mechanism for anemia is obscure, though hemolysis, perhaps mediated by endotoxin, may have a causative role [19].

As is well known, UTIs have many complications, as described above, and treatment of UTIs is important to prevent these complications and the adverse outcomes. But the real question is "which antimicrobial agent should be assessed for initial treatment in pregnant women with UTI ?", even considering geographical differences between ethnic populations.

The current study investigates the most common bacteria that may cause UTI, the antimicrobial sensitivity of these bacteria, and suggests which antimicrobial agent should be assessed in first-line therapy of UTI in pregnant women.

Methods

Study design

The current study was conducted on 753 in-patient singleton pregnant women who were admitted to our outpatient clinic with UTI symptoms, such as dysuria, urgency, frequency, hesitancy, incontinence or incomplete voiding between October 2011 and June 2012 in the X…X…X…X. Ethics approval was obtained from our institutional review board. Socio-demographic variables (age, weight, length, gravity, parity), results of urine culture and bacterial sensitivity tests of all pregnant women were obtained from our central computerized record system.

Exclusion criteria

Patients with a history of urolithiasis, diabetes mellitus, congenital urinary anomalies and patients under antibiotic therapy for any diseases were excluded.

Sample collection and bacteriological investigation

According to hospital policy, midstream urine culture and antibiotic sensitivity of bacterial agent tests are obtained from all pregnants with symptoms of UTI and, if necessary, antibiotic therapy should be compatible with results of the antibiotic sensitivity test. Midstream urine samples were taken from all pregnants, and collected samples were immediately inoculated via calibrated wire loop (0.001ml) on 5% sheep blood agar and eosin-methylene blue agar plates with a 0.01-mL loop. All of the specimens were analyzed within an hour of collection.

After 24-48 hours of aerobic inoculation at 37°C, plates were interpreted. Colony counts of a single bacteria of >105 colony forming units (cfu)/ mL were accepted as bacteriuria. The presence of multiple bacteria or of skin flora was accepted as contamination. Identification and antimicrobial susceptibility testing of microorganisms was performed according to the Clinical and Laboratory Standards Institute Guidelines with conventional microbiological methods and confirmed by The BD Phoenix Automated Microbiology System (BD Diagnostics, Sparks, MD).

Data management and analysis

Descriptive statistics were analyzed using the Statistical Package for the Social Sciences version 19.0 (SPSS, Chicago, IL USA). Study findings were explained in words and with associated tables.

Results

A total of 753 singleton pregnant women were selected in the current retrospective observational study with an age range of 12-47 years with a mean (standard deviation) of 28 (±7.7) years. There were 200 (26.6%) pregnants in the first trimester, 275 (36.5%) in the second and 278 (36.9%) in the third trimester. Based on their parity, 248 (32%) and 505 (68%) pregnant women were nulliparous and and multiparous, respectively. The mean body mass index of the pregnant women was 27.3 with a 4.06 standard deviation. In order to not have an excessively large table, socio-demographic variables are given only in the text.

Of all the isolated bacteria, Gram-negative bacteria in 706 patients (93.7%) were more prevalent than Gram-positive (6.3%) bacteria. The most commonly isolated bacteria were E.Coli in 619 patients (82.2%), followed by Klebsiella spp., 84 patients (11.2%) in the entire study population. In the current study, no ESBL-EC was identified among all the isolated pathogens.

Enterococcus spp. were isolated as a third microbial agent in 43 patients (5.7%) and other agents remained more rare in the study population. In all of the trimesters of pregnancy, in accordance with results of the entire study population, E.Coli and Klebsiella spp. were demonstrated to be the most commonly isolated bacterial agents, with 172 (86%), 226 (82.2%), and 221 (79.5%) for E.Coli in each trimester, respectively, and 18 (9%), 32 (11.6%), and 34 (12.2%) for Klebsiella spp. in each trimester, respectively (Table I, Fig. 1).

In the first trimester, E.Coli was the most commonly isolated agent and the sensitivity to amoxicillin/clavulanic acid and ampicillin was 81% and 66%, respectively. Fosfomycin sensitivity was highest with 98.3 percent. A 100% sensitivity was found for broad spectrum penicillin imipenem. Nitrofurantoin sensitivity was found to be 98%. Klebsiella spp. were the second most frequent agent, with 55% sensitivity to ampicillin, while 88% were sensitive to amoxicillin/claculanic acid. The fosfomycin sensitivity of Klebsiella spp. was 89%. Similar to E.Coli, imipenem sensitivity was found to be 100% for Klebsiella spp. The nitrofurantoin sensitivity of enterococcus spp. was 100% (Table II, Fig. 2).

In the second trimester, E.Coli was the most commonly isolated agent and the sensitivity to amoxicillin/clavulanic acid and ampicillin was 86% and 68%, respectively. Fosfomycin sensitivity was highest at 98.1 percent. A 100% sensitivity was

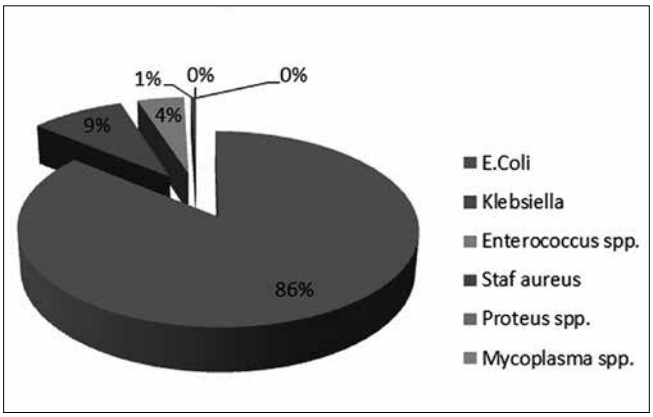

Figure 1. Bacterial factors isolated from pregnant woman with urinary tract infection.

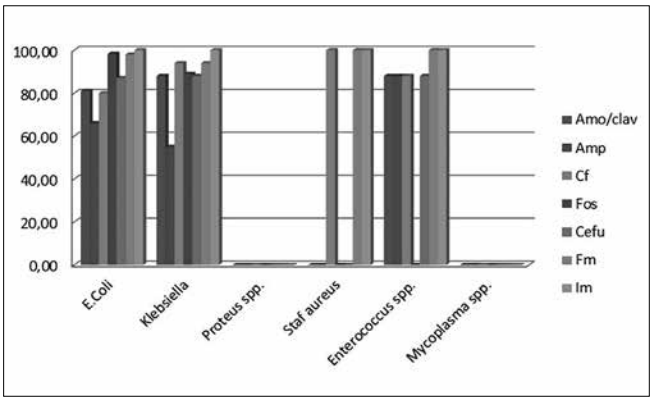

Figure 2. Aetiology and proportion of antibiotic sensivity in pregnant woman in first trimester.

Amo/clav : Amoxisilin/clavulanic acid, Amp: Ampicillin, Cf: Cefazoline, Fos: Fosfomycin, Cefu: Cefuroxime, Fm: Nitrofurantoin, Im: Imipenem, (Quinolones are excluded because they are not recommended for pregnant women).

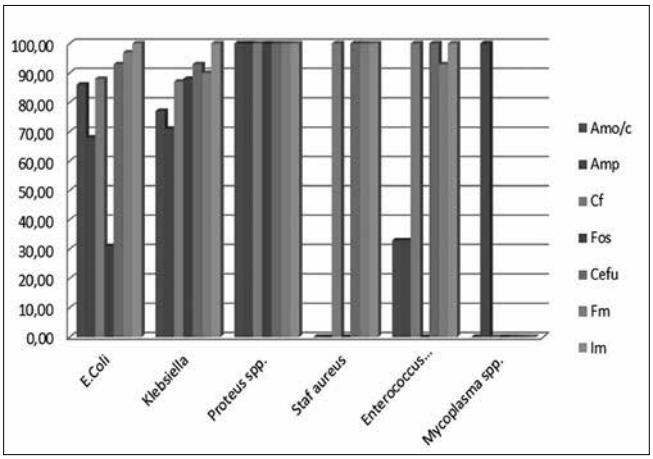

Figure 3. Aetiology and proportion of antibiotic sensivity in pregnant woman in second trimester.

Amo/clav : Amokxisilin/clavulanic acid, Amp: Ampicillin, Cf: Cefazoline, Fos: Fosfomycin, Cefu: Cefuroxime, Fm: Nitrofurantoin, Im: Imipenem, (Quinolones are excluded because they are not recommended for pregnant women).

Table I. Bacterial factors isolated from pregnant women with urinary tract infection.

	1.Trimester	2.Trimester	3.Trimester	Entire population
E.Coli	172(86)	226(82,2)	221(79,5)	619(82,2)
Klebsiella	18(9)	32(11,6)	34(12,2)	84(11,2)
Enterococcus spp.	9(4,5)	15(5,4)	19(6,8)	43(5,7)
Staf aureus	1(0,5)	1(0,4)	2(0,7)	4(0,5)
Proteus spp.	0	1(0,4)	1(0,4)	2(0,3)
Mycoplasma spp.	0	0	1(0,4)	1(0,1)

Table II. Aetiology and proportion of antibiotic sensitivity in pregnant women in first trimester.

1.Trimester	Amo/clav	Amp	Cf	Fos	Cefu	Fm	Im
Antimicrobial agent sensitivity [n=sensitive count (sensitivity rate)]							
E.Coli	81(81)	115(66)	79(80)	165(98.3)	147(87)	168(98)	171(100)
Klebsiella	16(88)	10(55)	16(94)	14(89)	14(88)	17(94)	18(100)
Proteus spp.	0	0	0	0	0	0	0
Staf aureus	0	0	1(100)	NE	0	1(100)	1(100)
Enterococcus spp.	8(88)	8(88)	8(88)	NE	8(88)	9(100)	9(100)
Mycoplasma spp.	0	0	0	0	0	0	0

Amo/clav: Amoxisilin/clavulanic acid, **Amp**: Ampicillin, **Cf**: Cefazoline, **Fos**: Fosfomycin, **Cefu**: Cefuroxime, **Fm**: Nitrofurantoin, **Im**: Imipenem, (Quinolones are excluded because they are not recommended for pregnant women), **NE**=Not examined

Table III. Aetiology and proportion of antibiotic sensitivity in pregnant women in second trimester.

2.Trimester	Amo/clav	Amp	Cf	Fos	Cefu	Fm	Im
Antimicrobial agent sensitivity [n=sensitive count(sensitivity rate)]							
E.Coli	131(86)	155(68)	134(88)	223(98.1)	210(93)	220(97)	226(100)
Klebsiella	24(77)	23(71)	27(87)	28(88)	30(93)	29(90)	32(100)
Proteus spp.	1(100)	1(100)	1(100)	1(100)	1(100)	1(100)	1(100)
Staf aureus	0	0	1(100)	NE	1(100)	1(100)	1(100)
Enterococcus spp.	14(93)	14(93)	15(100)	NE	15(100)	14(93)	15(100)
Mycoplasma spp.	0	0	0	NE	0	0	0

Amo/clav: Amokxisilin/clavulanic acid, **Amp**: Ampicillin, **Cf**: Cefazoline, **Fos**: Fosfomycin, **Cefu**: Cefuroxime, **Fm**: Nitrofurantoin, **Im**: Imipenem, (Quinolones are excluded because they are not recommended for pregnant women), **NE**=Not examined

Table IV. Aetiology and proportion of antibiotic sensitivity in pregnant women in third trimester.

3.Trimester	Amo/clav	Amp	Cf	Fos	Cefu	Fm	Im
Antimicrobial agent sensitivity [n=sensitive count(sensitivity rate)]							
E.Coli	106(86)	157(71)	104(83)	215(98.4)	202(91)	210(97.3)	221(100)
Klebsiella	27(79)	21(61)	25(78)	230(89)	28(82)	24(70)	33(97)
Proteus spp.	1(100)	1(100)	1(100)	1(100)	1(100)	1(100)	1(100)
Staf aureus	1(50)	0	2(100)	NE	2(100)	2(100)	2(100)
Enterococcus spp.	11(57)	12(63)	12(63)	NE	11(57)	19(100)	19(100)
Mycoplasma spp.	0	0	0	NE	1(100)	1(100)	1(100)

Amo/clav: Amokxisilin/clavulanic acid, **Amp**: Ampicillin, **Cf**: Cefazoline, **Fos**: Fosfomycin, **Cefu**: Cefuroxime, **Fm**: Nitrofurantoin, **Im**: Imipenem, (Quinolones are excluded because they are not recommended for pregnant women), **NE**=Not examined

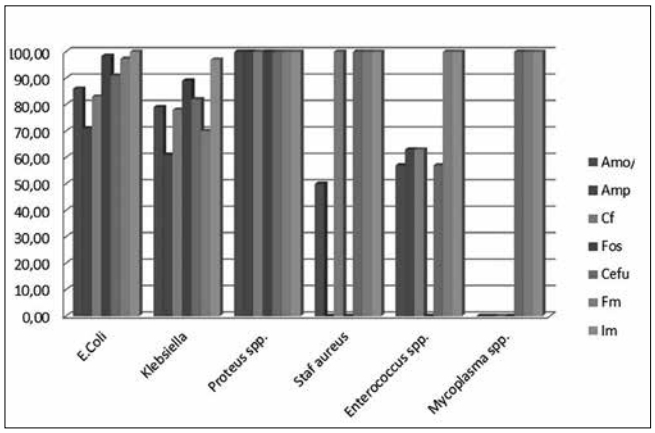

Figure 4. Aetiology and proportion of antibiotic sensivity in pregnant woman in third trimester.

Amo/clav : Amokxisilin/clavulanic acid, Amp: Ampicillin, Cf: Cefazoline, Fos: Fosfomycin, Cefu: Cefuroxime, Fm: Nitrofurantoin, Im: Imipenem, (Quinolones are excluded because they are not recommended for pregnant women).

found to broad spectrum penicillin imipenem. Nitrofurantoin sensitivity was 99 percent. Similar to the first trimester, Klebsiella spp. were the second most frequent agent, with a 71% sensitivity to ampicillin, while 77% were sensitive to amoxicillin/claculanic acid. Fosfomycin sensitivity of Klebsiella spp. was determined to be 88%. Similar to E.Coli, imipenem sensitivity was 100% for Klebsiella spp. The nitrofurantoin sensitivity of enterococcus spp. was 93% (Table III, Fig. 3).

In the third trimester, similar to the first and second trimester, E.Coli was the most commonly isolated agent, and the sensitivity to amoxicillin/clavulanic acid and ampicillin was 86% and 71%, respectively. The second most isolated were Klebsiella spp. with a sensitivity to amoxicillin/clavulanic acid and ampicillin of 79% and 61%, respectively, with 97% sensitivity to imipenem and 89% sensitivity to fosfomycin. The nitrofurantoin sensitivity of enterococcus spp. was 100 percent (Table IV, Fig. 4).

Discussion

All forms of urinary tract infection, including asymptomatic bacteriuria, are the most common health problem in pregnancy [1, 2] and may result in adverse perinatal outcomes such as preterm birth and prematurity [15-18]. Pregnant women with ASB are more likely to deliver premature or low birth weight newborns and have a 20-30 fold increased risk of UTIs, especially pyelonephritis, which can be a severe infection in pregnant women compared with non-pregnant women [15].

In the current study, we demonstrated that Gram-negative bacteria (93.7%) were more prevalent than Gram-positive (6.3%) bacterial agents in the each of the three trimesters. This ratio was higher than the result of a recent study conducted on pregnants with ASB, which showed a frequency of 47.5% [12].

In other studies, A. Artero, et al [20] found a frequency of 70% in pregnants with pyelonephritis and Celen S. et al [14]. found a rate of 76.6% for pregnants with ASB. The different ethnic populations could have caused the difference in these results, but the important point from our study is that in acute infections, E. Coli may be more prevalent in each of the three trimesters.

Extended-spectrum [beta]-lactamase producing Escherichia coli (ESBL-EC) are emerging as pathogens world-wide [21-23], but in our study no ESBL-EC was identified from among all the isolated pathogens. From the perspective of antibiotic sensitivity, E.Coli was 98%, 99% and 98.4% sensitive to fosfomycin in the each of the three trimesters. The sensitivity to ampicillin was significantly less than to amoxicillin/clavulanic acid in each of the three trimesters. The sensitivity to imipenem was 100% in all trimesters. A 87%, 93% and 91% sensitivity rate of cefuroxime in each of the three trimesters seems to offer another choice for oral therapy for pregnant women with UTI.

Previously, ampicillin was offered and prescribed for UTI as a first-line therapy among oral antibacterial agents for pregnants, but in the current study, according to the results, it does not seem to be effective as a first-line therapy because of the low sensitivity rates, 66%, 68% and 71% in each of the three trimesters, respectively. In a recent study, nitrofurantoin was recommended as a first-line therapy in pregnant women with ASB [24], and also cefuroxime can be an adequate first-line therapy with 87%, 93% and 91% sensitivity rates, which are comparable to cefazolin sensitivity rates of 80%, 88% and 83% in each of the three trimesters, respectively.

Judging by the results of drug susceptibility of the second most frequently isolated bacteria, Klebsiella spp. is encountered and high fosfomycin sensitivity rates were observed, as 89%, 88% and 89% in each of the three trimesters. Cefuroxime had the nearest sensitivity rates to fosfomycin (88%, 93% and 82% in each of the three trimesters) and may be an adequate first-line oral therapy for UTI in pregnant women. In first and second trimesters, the sensitivity to imipenem was 100%, while a 97% sensitivity ratio was found in the third trimester for Klebsiella spp.

Gram-positive microbial agents were also identified with low percentages of 5.7% Enterococcus spp. and 0.5% staphylococci in the current study, with nearly the same ratios in the study of Celen et al. (5.8%) [14] and lower ratios in the study of Enayat et al. (16.8% ratio for coagulase negative staphylococci) [25].

Conclusion

Periodic and continuous follow-up are principles for the preventation of UTI in pregnant women. Midstream urine samples should be obtained from all pregnants with or without UTI symptoms, and urine culture should be performed and patients with ASB or UTI detected should be treated according to the antimicrobial susceptibility test results. Midstream urine culture is mandatory for detection of bacteriuria, though sometimes this cannot be performed because of technical problems or inadequacy of the facility. In these cases, the knowledge of the most frequently isolated microorganisms and antimicrobial susceptibility can lead the way for initial treatment of UTI.

We have demonstrated that E.Coli is the most commonly isolated microorganism in the obstetric population with UTI. It has a high sensitivity to fosfomycin. We would consider to recommend fosfomycin oral therapy before urine culture or where urine culture could not be performed, due to its high sensitivity, ease of use and safety for use in pregnancy (Teratogenic Effects: Pregnancy Category B).

Authors' Contribution

1. Bekir Serdar Unlu – concept, study design, analysis and interpretation of data, article draft, corresponding author, revised article critically.
2. Yunus Yildiz – acquisition of data, analysis and interpretation of data, article draft, revised article critically.
3. Ibrahim Keles – study design, analysis and interpretation of data, revised article critically.
4. Metin Kaba – analysis and interpretation of data, article draft.
5. Halil Kara – study design, article draft.
6. Cuma Tasin – data collection/entry, literature analysis/search.
7. Selcuk Erkilinc – data collection/entry, literature analysis/search.
8. Gulcin Yildirim – data collection/entry, literature analysis/search.

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