ASYMPTOMATIC BACTERIURIA AND PREGNANCY

Matrizaeva Kurbonbika Madrimovna*
Yusupova Mehribon Atakhanovna **
*Assistant, Department of Family Physician Training, Urgench State Medical Institute, Uzbekistan matrizayevaanamoy@gmail.com
** DSc, Head of the Department of Family Physician Training, Urgench State Medical Institute, Uzbekistan, Urgench

Annotation
Microbial colonization of the urinary tract and, accordingly, the presence of bacteria in the urine without clinical manifestations of urinary tract infection (UTI) is defined as asymptomatic bacteriuria (AB). In the female population, BD is common, but its prevalence varies widely depending on geographic region, even within the same country, gender, age, sexual activity, functional and structural disorders of the urinary system, associated conditions and diseases. Among the healthy female population, the prevalence of BD increases with age – from 1% among schoolgirls to 16% or more among women 70 years and older. In young women, it is closely associated with sexual activity (in 5% of healthy premenopausal married women, but only 0.7% of nuns). In non-pregnant women, the incidence of BD is approximately 5%; in pregnant women, it ranges from 2% to 10% or more depending on socioeconomic status and a history of previous UTIs. It typically reflects colonization of the periurethral region by microorganisms prior to pregnancy. The prevalence of significant bacteriuria, determined by a single urinary catheterization at delivery, was 2% in pregnant women of middle socioeconomic status compared with 6.5% in pregnant women of low socioeconomic status.

Keywords: Urinary tract infection, asymptomatic bacteriuria, bacteriuria, pregnancy.

Despite growing interest in BB and its clinical consequences, the causes of this phenomenon remain unclear. This review presents key principles regarding screening, diagnosis, management strategies, and current understanding of the appropriateness of antibacterial therapy for BB during pregnancy, based on the results of randomized and controlled trials and international clinical guidelines [1,2].

DIAGNOSTIC EVALUATION OF BACTERIURIA

Bacteriological diagnosis is a microbiological diagnosis based on the examination of a urine sample collected under strict sterile conditions and delivered to the laboratory as quickly as possible, thereby minimizing bacterial growth. The presence and proliferation of bacteria in urine may be due to prolonged storage before analysis, as well as poor hygiene during urine collection (bacteria contamination from the external genitalia). While healthy individuals typically have sterile urine, the detection of bacteria in urine does not necessarily indicate an infectious disease. For example, nonpathogenic microbes from the nonsterile lower urethra enter the urine during urination. At the same time, other researchers have established the presence of a community of live bacteria in urine, which constitute the residents of the female urinary microbiota [3]. The presence of bacteriuria in healthy individuals led Finucane TE, given the high importance of the microbiome, to propose the use of the term "urinary tract dysbiosis" instead of "urinary tract infection" [4].

Bacteriuria is assessed by the number of colony-forming units (CFU) of microbes per unit volume. The criterion for diagnostically significant bacteriuria is the growth of colonies in culture of >105 CFU/ml (100,000 bacteria in 1 ml of urine) with the isolation of the same bacterial strain in at least two consecutive aseptically collected midstream urine samples separated by an interval of more than 24 hours. In chronic kidney disease, difficult urination, and infection with certain atypical microorganisms (e.g., Proteus, S. saprophyticus, and Candida species), bacteriuria is detected at a lower value: ≥104 CFU/ml. Urine culture is the "gold standard" for identifying the pathogen and determining its susceptibility to antibiotics. As a rule, bacteriuria is usually dominated by one bacterial species. The presence of two or more species (Lactobacilli, Corynebacteria species, Gardnerella, alpha-haemolytic Streptococci, Aerobes) most likely indicates false bacteriuria due to contamination of urine with anogenital flora during improper sample collection [5].

ETIOLOGY AND PATHOGENESIS OF BACTERIURIA IN PREGNANT WOMEN

According to the Russian Multicenter Study of Antimicrobial Resistance of UTI Pathogens (DARMIS, 2011), the dominant microorganisms in the structure of pathogens causing community-acquired UTIs during pregnancy are representatives of the Enterobacteriaceae family (88.8%), and the proportion of

E. coli in this subpopulation is 65.8%. It should be noted that E. coli strains in BB are characterized by less virulence than strains isolated from patients suffering from clinically manifest UTIs. Other representatives of Enterobacteriaceae, such as Klebsiella pneumoniae (10.5%), Proteus mirabilis (6.6%), E. cloacae (4.6%), as well as S. saprophyticus (2.0%), E. faecalis (4.6%), are cultured less frequently.

Proteus mirabilis and Enterococcus faecalis infections are suggested as possible causes of recurrent UTIs during pregnancy [6].

In general, gram-negative bacteria have a unique structure that facilitates their attachment to the uroepithelium and prevents the removal of pathogens in the urine. It is believed that the phenomenon of BB is caused by strains of microorganisms with lower virulence, which affect the host immune system, inhibit the expression of certain genes and thereby provide themselves with a favorable habitat without microorganism invasion into the urothelium and the development of inflammation [7–9]. Recently, the possible protective role of BB has been discussed; the basis for this assumption is numerous studies demonstrating the protective role of the urinary tract microbiome [10,11].

The anatomical and physiological characteristics of the female urinary tract (a wide and short urethra, the urethra's proximity to natural reservoirs of infection—the rectum and vagina)—makes women more susceptible to UTIs, which can be considered the first suspected scenario explaining the disease's development. Furthermore, a second scenario for the increased risk of urinary tract infection is due to physiological changes during pregnancy. Specifically, urinary tract infection is facilitated by decreased muscle tone and peristalsis of the ureters, as well as bladder tone due to increased concentrations of progesterone, estradiol, and other estrogens. This is accompanied by a slower urine flow rate, an increase in residual urine, the development of vesicoureteral reflux, and dilation of the upper ureters and renal pelvis, leading to the formation of physiological hydronephrosis and hydroureter of pregnancy. Bacterial growth can be facilitated by changes in the physicochemical properties of urine, such as urine pH and osmolality, as well as pregnancy-induced glycosuria and aminoaciduria. Functional disturbances in the urinary system, additional mechanical obstruction by the growing uterus, and increased bladder pressure contribute to the ascending migration of bacteria into the upper urinary tract. Sexual activity and vaginalization of the urethra can also traumatize the uroepithelium of the distal urethra, leading to increased bacterial invasion. Furthermore, risk factors for

bacteriuria include preexisting kidney and urinary tract pathologies, previous episodes of UTIs, and a genetic predisposition.

CLINICAL OUTCOMES OF ASYMPTOMATIC BACTERIURIA

In the 1960s, Kass E. et al. [12] first described the association of untreated BD with the development of pyelonephritis during pregnancy, premature birth, intrauterine growth retardation, and increased perinatal mortality. In subsequent years, the clinical consequences of BD in premenopausal non-pregnant women were widely studied. Long-term cohort studies have established an increased incidence of symptomatic UTI in women with BD identified during screening. Thus, it was found that over the next 15 years, UTI occurred in 55% of cases (pyelonephritis developed in 7.5%), whereas in the absence of BD, these figures were 10% and 0%, respectively. An analysis of numerous independent studies has shown that BB can be the cause of a number of serious complications during pregnancy and childbirth: in its presence, the risk of premature birth increases (by 1.5–2 times), undesirable outcomes for the fetus, in particular, the birth of premature babies with low body weight (<2500 g), the development of pyelonephritis (by 20–30 times), septicemia, anemia compared to women without bacteriuria [13–17].

Women with low socioeconomic status, diabetes mellitus (DM), including gestational DM, recurrent UTIs, neurogenic bladder dysfunction, polycystic kidney disease, other congenital anomalies of the kidneys and urinary tract, and sickle cell anemia are particularly at higher risk of BD and associated complications during pregnancy [2, 17, 18].

The historical association between BD and pregnancy complications has led to the introduction of a “screen and treat” policy for pregnant women. However, more recent studies have found that the absolute risk of developing pyelonephritis in untreated BD is significantly lower than traditionally reported figures. A meta-analysis showed a lower incidence of pyelonephritis (OR 0.23; 95% CI 0.13–0.41) and low birth weight infants (OR; 95% CI 0.45–0.93) in pregnant women with BD who received antibiotics compared with those who did not receive antibacterial therapy. No differences in the incidence of preterm birth were found [16, 19].

A recent study of over 5,000 pregnant women in the Netherlands, where, unlike most Western countries, there is no standard policy for screening and treating BP during pregnancy, showed that the absolute risk of pyelonephritis in the absence

of treatment is low (2.4% vs. 0.6% among 4,035 women without bacteriuria). Furthermore, BP was not associated with preterm birth in women with uncomplicated singleton pregnancies. These data led the authors to conclude that screening and treatment for BP cannot be routine for all pregnant women [19, 20].

An updated Cochrane review (2015) analyzed the results of studies that compared treatment of pregnant women with beta-blockers (BBs), no treatment, or placebo. The meta-analysis of the studies showed a low level of statistical and clinical evidence for a significant reduction in adverse pregnancy outcomes with BB antibacterial therapy. No statistically or clinically significant differences were found in perinatal mortality, spontaneous abortion, neonatal sepsis, preterm birth, or fetal abnormalities [16].

The causal mechanisms explaining the association of BB with the risk of UTI and adverse pregnancy outcomes remain unresolved, while more recent studies have identified adverse effects on the child from maternal antibiotic use during pregnancy [21, 22].

BACTERIURIA SCREENING

Given the high risk of developing ascending symptomatic UTI and the negative impact of bacteriuria on obstetric and perinatal complications, most international standards recommend bacteriological examination of urine in early pregnancy (12–16 weeks or at the first antenatal visit). The Society of Obstetricians and Gynecologists of Canada recommends screening for bacteriuria in all women with a history of recurrent UTIs in each trimester of pregnancy. Repeat bacteriological examination of urine is performed in case of a positive result and during the third trimester due to the possible risk of bacteriuria recurrence in treated patients even in the absence of UTI symptoms. It is believed that in patients with two or more episodes of recurrent bacteriuria, monthly urine culture for microflora is necessary until delivery to ensure urine sterility during pregnancy. In pregnant women with no bacteriuria at the first screening, dynamic examination is not performed [2, 5, 7, 13, 14].

TREATMENT OF ASYMPTOMATIC BACTERIURIA IN PREGNANT WOMEN

Clinical trial results showing that BB treatment improved pregnancy outcomes have led to a broader interpretation of the indications for antibiotic use. Antibiotic

therapy for BB in pregnant women remains standard in numerous international guidelines [1, 4, 5].

However, clinical studies and practical experience conducted in recent years have demonstrated the lack of benefits of treating BB during pregnancy, regardless of the presence of risk factors, and the clinical appropriateness of antibacterial therapy remains controversial [4, 16]. For example, Canadian scientist Nicolle LE in the article "A paradigm shift towards non-treatment of asymptomatic bacteriuria" expressed doubts about the validity of the standard approach to the treatment of BB [17]. According to the data obtained, antimicrobial therapy of BB was recognized as an important factor contributing to the inappropriate use of antimicrobials, which is accompanied by the development of antibiotic resistance. On the other hand, arguments are presented according to which antimicrobial therapy can lead to the eradication of less virulent microorganisms and the invasion of more pathogenic ones. In particular, women experience disruption of the normal vaginal microflora (primarily lactobacilli), which facilitates colonization of the vagina by enterobacteria and fungi, which can subsequently colonize the urethra and bladder. The rise in antibiotic resistance may be due to increased drug availability, antibiotic abuse, and self-medication. Excessive and irrational use of antibiotics, aimed at eliminating all microorganisms in the urinary tract, can lead to disruption of the urinary microbiome. The literature contains reports of the development of antibiotic-associated UTI, which is a kind of equivalent to an infection associated with the proliferation of Clostridium difficile in the intestine [8, 9].

It should be emphasized that patients' values and preferences regarding screening and treatment for BB vary, depending on individual perspectives regarding the small potential benefit of antibiotics and the potential harm associated with their use during pregnancy. Women who are more concerned about the harm of antibacterial therapy may refuse screening and treatment. In such circumstances, there is a need for discussions between clinicians and pregnant women about informed decisions that are consistent with patient adherence. At the same time, it remains clear that this recommendation applies to women who are not at increased risk of complications from BB. Women with an increased risk of UTI and related complications during pregnancy should follow recommendations for high-risk groups [17, 20].

When prescribing antibacterial therapy, urine culture results, antimicrobial activity, and resistance of microorganisms should be taken into account, as

empirical therapy for BB is not performed in pregnant women. Since BB bacteria colonize exclusively the mucous membranes without tissue invasion, the antibiotic must achieve high concentrations in the urine.

Given that most microorganisms are community-acquired strains, a high level of antibiotic resistance is not expected. However, it should be noted that in recent years, many countries have seen a significant increase in the resistance of E. coli strains to aminopenicillins and inhibitor-protected penicillins. It is also important to keep in mind that the frequency of isolation of uropathogenic E. coli resistant to these drugs varies significantly. Therefore, local data on uropathogen resistance are essential for rational selection of antibacterial therapy [6].

It is especially important to emphasize that when selecting an antimicrobial drug, high fetal safety requirements, high activity and low resistance of the pathogen to the drug, high urinary drug concentrations, and compliance must be taken into account. The FDA (Food and Drug Administration) risk categories for drug use during pregnancy are widely used worldwide. In the absence of objective information confirming the safety of a drug, including antimicrobials, during pregnancy or breastfeeding, they are not prescribed. A very limited selection of safe oral antibacterial drugs in risk category B is used for the treatment of uncomplicated UTIs in pregnant women.

An analysis of international guidelines for antibacterial therapy in pregnant women with BD revealed a lack of uniform standards for both drug selection and duration of use. This is primarily due to differences in the list of registered antibacterial drugs between countries and the degree of resistance of urologic pathogens to them. A number of international clinical guidelines list fosfomycin trometamol and nitrofurantoin as the drugs of choice for treating BD in pregnant women. Cephalosporins and sulfamethoxazole/trimethoprim are considered alternative agents, while amoxicillin/clavulanic acid is mentioned as a drug "for certain categories of patients" [14, 21].

According to the study of antibiotic resistance, the oral medications with the highest activity against E. coli are fosfomycin (98.3%), nitrofurantoin (97.8%), and third-generation cephalosporins (ceftibuten and cefixime) (93.4%) [6]. Based on the results obtained, the following strategy for antibacterial therapy of UTIs during pregnancy is proposed in national clinical guidelines (Table 1).

Table 1 Antibacterial therapy regimen for asymptomatic bacteriuria during pregnancy

Antimicrobial drug	Drug dosage/administration regimen
First-line therapy	
Fosfomycin trometamol	Orally 3.0 g, once
Nitrofurantoin	Orally 100 mg 2 times a day, course 5-7 days
Alternative therapy	
Ceftibuten	orally 400 mg 1 times a day, course 5-7 days/or
Cefixime	orally 400 mg 1 times a day, course 5-7 days/or
Cefuroxime axetil	orally 250 mg 2 times a day, course 7 days
Amoxicillin/clavulanic acid	orally 625 mg 2 times a day, course 5-7 days

The primary treatment for BD at any stage of pregnancy is a single-dose regimen of 3.0 g of fosfomycin trometamol, which inhibits microbial adhesion to the urothelium and persists in high concentrations in urine for a long time after a single dose. Despite its widespread use, resistance to fosfomycin by E. coli, Proteus spp., and other members of the Enterobacteriaceae family remains very low, and there is no cross-resistance with other antibiotics used to treat UTIs.

Nitrofurantoin, a synthetic nitrofuran, interferes with bacterial carbohydrate metabolism by inhibiting acetyl coenzyme A and exhibits bactericidal activity against uropathogens such as E. coli, Staphylococcus sapr., and Enterococcus faecalis, but is inactive against Proteus spp., Serratia, or Pseudomonas. Nitrofurantoin is administered for 7 days and only up to 36 weeks of gestation. Its use after 36 weeks has been shown to cause a rare but serious complication associated with the development of hemolytic anemia in the fetus and newborn due to glucose-6-phosphate dehydrogenase deficiency. The use of nitrofurans is controversial; in some countries, they are contraindicated during pregnancy due to serious side effects.

Broad-spectrum drugs (ceftibuten, cefixime, cefuroxime axetil) should be used only as an alternative, when first-line drugs (standard therapy) cannot be used or are ineffective.

β-lactams are the safest class of antibacterial agents, but it should be noted that they are generally unable to eliminate pathogens in the periurethral and perivaginal areas, increasing the risk of reinfection. Pharmacokinetic changes during pregnancy reduce plasma concentrations of β-lactams by 50%. Penicillin

and cephalosporins are sometimes associated with allergic and occasionally anaphylactic reactions. International experts recommend avoiding the use of amoxicillin with clavulanic acid during the second half of pregnancy due to available data on the increased risk of necrotizing enterocolitis in newborns, especially those born prematurely.

In the past decade, recommendations for the duration and frequency of antimicrobial therapy have undergone significant changes. To assess the optimal duration of antibacterial therapy, an analysis of studies [16] comparing single-dose therapy with 4- to 7-day treatment courses was conducted. Although the quality of the studies was generally low, the analysis revealed an increased incidence of adverse events with longer courses of therapy, while single-dose antibiotics resulted in fewer side effects and better compliance.

Thus, pregnant women with BD are recommended to receive a single dose of fosfomycin trometamol or a 3- to 7-day course of antibacterial therapy. Previously, it was suggested to continue antibacterial therapy throughout pregnancy; however, modern studies have not found significant differences in the incidence of symptomatic, persistent, or recurrent UTIs when prescribing short or long courses of antibacterial drugs. After treatment, monthly urine culture should be performed to monitor for possible recurrence of bacteriuria. If bacteriuria is detected again (16–33%), retreatment is prescribed based on the sensitivity of the microorganisms detected in the urine to antibiotics and the exclusion of structural and functional disorders of the urinary system that contribute to impaired urine passage and the development of symptomatic UTI [24].

CONCLUSION

Thus, proper self-care, personal hygiene, increased awareness and health education for pregnant women, and microbiological screening for bacteriuria in early pregnancy are key measures for preventing and limiting obstetric and gynecological complications. The causal mechanisms explaining the association of bacteriuria with the risk of UTIs and adverse pregnancy outcomes remain unresolved. It has been suggested that bacteriuria may protect against superinfection with virulent uropathogens. Therefore, bacteriuria treatment is recommended only when proven beneficial to the patient. This avoids the risk of selection of resistant strains, eradication of potentially protective strains of microorganisms, and the adverse effects of maternal antibiotic use on the fetus

during pregnancy. It appears most rational to limit antibacterial therapy for bacteriuria to high-risk pregnant women, as this can significantly reduce adverse outcomes for both mother and fetus.

Bibliography

1. Nicolle LE, Gupta K, Bradley SF, Colgan R, DeMuri GP, Drekonja D, Eckert LO, Geerlings SE, Köves B, Hooton TM, Juthani-Mehta M, Knight SL, Saint S, Schaeffer AJ, Trautner B, Wullt B, Siemieniuk R. Clinical Practice Guideline for the Management of Asymptomatic Bacteriuria: 2019 Update by the Infectious Diseases Society of America. Clin Infect Dis. 2019; 68(10): e83–e110. doi: 10.1093/cid/ciy1121.
2. Glaser A.P., Schaeffer A.J. Urinary tract infection and bacteriuria in pregnancy. Urol Clin North Am. 2015; 42(4): 547–60.doi: https://doi.org/10.1016/j.ucl.2015.05.004.
3. Hilt E.E., McKinley K., Pearce M.M., Rosenfeld A.B., Zilliox M.J., Mueller E.R., Brubaker L., Gai X., Wolfe A.J., Schreckenberger P.C. Urine is not sterile: use of enhanced urine culture techniques to detect resident bacterial flora in the adult female bladder. J Clin Microbiol. 2014; 52(3): 871–76. doi: 10.1128/JCM.02876-13.
4. Finucane T. E. «Urinary tract infection» –requiem for a heavyweight. J Am Geriatr Soc. 2017; 65(8): 1650–55.doi: 10.1111/jgs.14907.
5. Grabe M. (Chair), Bartoletti R., Bjerklund Johansen TE, Cai T., Çek M., Köves B., Naber KG, Pickard RS, Tenke P., Wagenlehner F., Wullt B. Guidelines on urological infections European Association of Urology, 2015. http://uroweb.org/wp-content//uploads/19-Urological-infections.
6. Kurbanyiazova M. Z. et al. Pregnancy and diseases of the cervix: frequency, complications of gestation // ministry of health of the republic of uzbekistan republican specialized scientific and practical medical center of obstetrics and gynecology association of private practice doctors of uzbekistan clinic "MAHLIYO-SHIFO" & V "MAHLIYO-SHIFO" & V. - P. 55.Sunden F., Hakansson L., Ljunggren E., Wullt B. Escherichia coli 83972 bacteriuria protects against recurrent lower urinary tract infections in patients with incomplete bladder emptying. J. Urol. 2010, 184(1): 179–85. doi: 10.1016/j.juro.2010.03.024.

7. Kurbaniyazova, M. (2018). Bacterial vaginosis as a problem of modern women. Journal of Problems of Biology and Medicine, (3 (102), 36–39. Retrieved from https://inlibrary.uz/index.php/problems_biology/article/view/2559
8. Shamsieva, M., Negmadzhanov, B., & Kurbanyiazova, M. (2014). Optimization of management of girls with vulvitis diagnosed with intrauterine infection in women in labor at the present stage. Journal of Problems of Biology and Medicine, (4,1(81), 97–99. Retrieved from https://inlibrary.uz/index.php/problems_biology/article/view/4524.
9. Nienhouse V., Gao X., Dong Q., Nelson D.E., Toh E., McKinley K., Schreckenberger P., Shibata N., Fok C.S., Mueller E.R., Brubaker L., Wolfe A.J., Radek K.A. Interplay between bladder microbiota and urinary antimicrobial peptides: mechanisms for human urinary tract infection risk and symptom severity. PLoS One. 2014; 9(12): e114185.
10. Brubaker L., Wolfe A. The urinary microbiota: a paradigm shift for bladder disorders? Curr Opin Obstet Gynecol, 2016; 28(5): 407–12.
11. Kass E.H. Pyelonephritis and Bacteriuria. A Major Problem in Preventive Medicine. Annals of Internal Medicine. 1962; 56: 46–53. doi: https://doi.org/10.7326/0003-4819-56-1-46.
12. Turaeva, S., Negmadzhanov, B., Fattaeva, Sh., & Kurbanyiazova, M. (2016). Recurrent candidal vulvovaginitis in pregnant women. Journal of the Doctor's Herald, 1(1), 54–59. Retrieved from https://inlibrary.uz/index.php/doctors_herald/article/view/3431.
13. Wing D.A., Fassett M.J., Getahun D. Acute pyelonephritis in pregnancy: an 18-year retrospective analysis. Am J Obstet Gynecol. 2014; 210: 219.e1-6. doi: 10.1016/j.ajog.2013.10.006.
14. Ipe D.S., Sundac L., Benjamin W.H. Jr., Moore K.H. Asymptomatic bacteriuria: prevalence rates of causal microorganisms, etiology of infection in different patient populations, and recent advances in molecular detection. FEMS Microbiol letters. 2013; 346(1): 1–10. doi: 10.1111/. 1574-6968.12204
15. Smaill F.M., Vazquez J.C. Antibiotics for asymptomatic bacteriuria in pregnancy. Cochrane Database Syst Rev. 2015; 7(8): CD000490. doi: 10.1002/14651858.
16. Moore A., Doull M., Grad R., Groulx S., Pottie K., Tonelli M., Courage S., Garcia A.J., Thombs B.D. Recommendations on screening for asymptomatic bacteriuria in pregnancy. For the Canadian Task Force on Preventive Health Care. CMAJ. 2018; 190(27): E823–30. doi: 10.1503/cmaj.171325.

17. Renko M., Tapanainen P., Tossavainen, P., Pokka T., Uhari M. Metaanalysis of the significance of asymptomatic bacteriuria in diabetes. Diabetes Care. 2011; 34, 230–35. https://doi.org/10.2337/dc10-0421.

18. Kazemier BM, Koningstein FN, Schneeberger C., Ott A., Bossuyt PM, de Miranda E., Vogelvang TE, Verhoeven CJ, Langenveld J., Woiski M., Oudijk MA, van der Ven JE, Vlegels MT, Kuiper PN, Feiertag N., Pajkrt E., Mol BW, de Groot C.J. Geerlings SE Maternal and neonatal consequences of treated and untreated asymptomatic bacteriuria in pregnancy: a prospective cohort study with an embedded randomized controlled trial. Lancet Infect Dis. 2015; 15(11): 1324–33.doi: 10.1016/S1473-3099(15)00070-5.

19. Angelescu K., Nussbaumer-Streit B., Sieben W., Scheibler F., Gartlehner G. Benefits and harms of screening for and treatment of asymptomatic bacteriuria in pregnancy: a systematic review. BMC Pregnancy Childbirth. 2016; 16(1): 336.doi: 10.1186/s12884-016-1128-0.

20. Wright A.J., Unger S., Coleman B.L., Lam P.P., McGeer A.J. Maternal antibiotic exposure and risk of antibiotic resistance in neonatal early-onset sepsis: a case-cohort study. Pediatr Infect Dis J. 2012; 31: 1206–08. doi: 10.1097/INF.0b013e31826eb4f9.

21. Nordeng H., Lupattelli A., Romøren M., Koren G. Neonatal outcomes after gestational exposure to nitrofurantoin. Obstet Gynecol 2013; 121: 306–13. doi: http://10.1097/AOG.0b013e31827c5f88.

22. Nicolle L.E., Bradley S., Colgan R., Rice J.C., Schaeffer A., Hooton T.M. Infectious Diseases Society of America guidelines for the diagnosis and treatment bacteriuria in adults. Clin. Infect. Dis. 2005; 40(5): 643–54.

23. Bonkat G., Pickard R., Bartoletti R., Cai T., Bruyère F., Geerlings SE, Köves B., Wagenlehner F., Pilatz A., Pradere B., Veeratterapillay R. European Association of Urology. EAU Guidelines on Urological Infections; Update 2019; https://uroweb.org/wp-content/uploads/EAU-Guidelines-on-Urological-infections-2019.pdf

24. Koves B., Cai T., Veeratterapillay R., Pickard R., Seisen T., Lam T.B. et al. Benefits and harms of treatment of asymptomatic bacteriuria: a systematic review and meta-analysis by the European Association of Urology Urological Infection Guidelines Panel. Eur. Urol. 2017; 72(6): 865–68. doi: 10.1016/j.eururo.2017.07.014.

25. Wingert A., Pillay J., Sebastianski M., Gates M., Featherstone R., Shave K., Vandermeer B., Hartling L. Asymptomatic bacteriuria in pregnancy:

systematic reviews of screening and treatment effectiveness and patient preferences. BMJ Open. 2019; 9: e021347. doi: 10.1136/bmjopen-2017-021347
26. Nicolle L.E. The paradigm shift to non-treatment of asymptomatic bacteriuria. Pathogens. 2016; 5(2): E38–44.doi: 10.3390/pathogens5020038.
27. Brubaker L., Wolfe A. The urinary microbiota: a paradigm shift for bladder disorders? Curr Opin Obstet Gynecol, 2016; 28(5): 407–12. doi: 10.1097/GCO.0000000000000298.
28. Zakharova I.N., Osmanov I.M., Machneva E.B., Mumladze E.B., Kasyanova A.N., Aisanova M.R. From bacteriuria to the urinary tract microbiome: evolution of the vi