INVITED REVIEW

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URINARY TRACT INFECTIONS DURING PREGNANCY – AN UPDATED OVERVIEW

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Abstract

Urinary tract infections (UTIs) are the most common type of infection during pregnancy, affecting up to 10% of pregnant women. They are also recognized as the second most common ailment of pregnancy, after anemia. Three clinical types of pregnancy-related UTI are distinguished: asymptomatic bacteriuria (ASB), cystitis, and pyelonephritis. A particular form of ASB is the presence of Group B streptococci in the urinary tract of the pregnant woman. All clinical types of UTI may lead to serious maternal and fetal complications. Therefore, unlike in the nonpregnant female patient, all UTIs during pregnancy, including the asymptomatic infection, require treatment. In some patients, antibiotic prophylaxis should also be introduced. In the present work, we collectively summarize current practical recommendations from a number of international bodies and organizations.

Key words: asymptomatic bacteriuria, cystitis, Group *B streptococci* colonization, pregnancy, pyelonephritis, urinary tract infection

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INTRODUCTION

Urinary tract infections (UTIs) are the second most common ailment of pregnancy after anemia and, at the same time, the most common type of infection during pregnancy [1]. It is estimated that 5-10% of women develop some type of UTI during pregnancy [2], which is the cause of approximately 5% of all hospital admissions of such patients [1]. Pregnancy-related adaptive changes in the urinary tract predispose to the development of UTIs which can be asymptomatic; however, even then, they contribute to the significantly increased risk for pyelonephritis, as well as may result in serious maternal and fetal complications such as preterm labor, low birth weight, or maternal systemic infection. Therefore, such infections pose considerable diagnostic and therapeutic challenges.

The aim of the present work is to provide a concise practical overview of the latest information from international literature on the medical treatment of pregnancy-related UTIs.

TYPES OF PREGNANCY-RELATED URINARY TRACT INFECTIONS

There are three separate clinical types of pregnancy-related UTI: 1) asymptomatic bacteriuria (ASB), 2) acute cystitis, and 3) acute pyelonephritis.

ASYMPTOMATIC BACTERIURIA

ASB is the presence of a positive urine culture in a given woman without any clinical manifestations. The incidence of ASB is thought to be similar both in pregnant and nonpregnant women: 2-13% [3]. When not treated, 30% of the ASB patients develop acute pyelonephritis compared with approximately 1.8% of the ASB patients who were previously subject to medical treatment [4], whereas one in three pregnant patients suffering from acute cystitis were previously diagnosed with ASB [5]. Unlike the general female population, ASB in pregnant women always requires treatment in order to reduce the possible maternal and fetal risks.

Particular attention should be paid to the clinical type of pregnancy-related UTI that is characterized by the presence of Group B streptococci (GBS), specifically the *Streptococcus agalactiae* species, in urine culture. Such a bacteriuria occurs in 2-10% of pregnant patients [6, 7]. It is the symptom of a heavy genital tract colonization and hence is associated with a high risk for premature rupture of membranes and preterm labor. Furthermore, GBS colonization increases the risk for severe early-onset neonatal infection by approximately 25 times [4, 7]. In such cases, the antibiotic therapy should be administered in line with classical guidelines for UTI management. However, it should be kept in mind that it may not eradicate

GBS strains present in the genital and alimentary tracts but, on the other hand, eradication from these tracts is not the aim of such therapy [3, 7].

Recommended screening tests for GBS identification are based on swab samples collected for culture from both the vaginal vestibule and rectum from every pregnant woman at 35-37 weeks' gestation. Patients in whom the presence of *Streptococcus agalactiae* in the urinary tract was revealed earlier in pregnancy do not need to be sampled from the vestibule nor rectum for a following time. Once GBS bacteriuria is diagnosed at any stage of pregnancy, a peripartum antibiotic prophylaxis is recommended, even in patients with negative results of the control vaginal and rectal swab tests, if carried out [7, 8].

ACUTE CYSTITIS

Acute cystitis occurs in 1-4% of pregnant women [3]. Of note, ASB may progress to acute cystitis 3-4 times more frequently in pregnant that nonpregnant women, such an outcome being a result of the anatomical and physiological changes typical for the urinary tract during pregnancy. Consequently, as many as one in three pregnant women with ASB will develop acute cystitis [5], typical manifestations of which include: dysuria, urinary frequency, urgency, painful urination, discomfort in the lower abdomen, and hematuria with accompanying bacteriuria. Some of these symptoms are also being experienced by healthy pregnant women, for instance, frequency and urgency occur in up to 80% of patients at some stage of pregnancy. Therefore, these two symptoms are less indicative in this clinical setting [3, 4].

Similar antibiotic patterns are used for the treatment of ASB and cystitis. No advantage of any pattern of antibiotic regimen over another has been demonstrated so far. Specifically, it is recommended to apply 3- to 7-day courses of antibiotic treatment [9]. One-day treatment with fosfomycin trometamol, high concentrations of which can be detected in urine up to 3 days following the administration of a single oral dose of 3 g, is also considered highly effective. Due to the fact that up to one in three patients treated for ASB during pregnancy who did not receive a prophylactic antibiotic treatment will develop bacteriuria again, some authors recommend regular urine cultures as screening tests with the aim of considering the implementation of prophylactic treatment by means of oral nitrofurantoin given 50-100 mg p.d. in cases of chronic UTI or infections manifest following intercourse. Such a treatment has been well-studied in nonpregnant patients. However, the data confirming the effectiveness of reducing bacteriuria in pregnant women are somewhat limited. Similarly, data on the effectiveness of nonpharmacologic means, such as intake of cranberry juice, require further research [6, 9].

ACUTE PYELONEPHRITIS

Acute pyelonephritis may also occur in 1-4% of pregnant women [9]. Nonetheless, in patients with ASB, the incidence reaches 13-40% [6, 9–11] when compared with 0.4% in non-ASB patients [10]. The role of ASB as the main risk factor for developing pyelonephritis was already described in the 1960s [5]. Other risk factors include young age, tobacco smoking, low educational level, delayed medical care, multiparity, diabetes mellitus, and nephrolithiasis [11]. Acute pyelonephritis represents a rare but serious state during pregnancy due to possible complications such as: acute kidney injury, anemia, arterial hypertension, hemolysis, thrombocytopenia, sepsis, septic shock, preeclampsia, and acute respiratory distress syndrome. The aforementioned complications seem to result from the effect of bacterial/microbial exo- and endotoxins that damage the body's tissues including endothelium, although not all causal links between them are fully proven [3, 11]. Every tenth pregnant patient with pyelonephritis will eventually go into preterm labor, most often at 33 to 36 weeks [11].

Typically (in 80-90% of patients) [6, 11], this clinical type of UTI occurs in the II and III trimester of pregnancy when urinary retention is the most severe. Importantly, one out of four such patients will experience recurrence in the course of the ongoing pregnancy [4, 11]. The stage of pregnancy at the time of diagnosis does not substantially change maternal, fetal and neonatal outcomes [12]. Early treatment of bacteriuria may, however, reduce the incidence of acute pyelonephritis even by 90% [9]. An 18-year observation by Wing *et al.* revealed a small gradual increase in the incidence of the condition despite the implementation of routine screening for bacteriuria in all pregnant women in the United States [11]. Therefore, other risk factors are not without significance.

The diagnosis of pyelonephritis is based on the presence of the following clinical manifestations: fever and chills, nausea and vomiting, lumbar pain, uni- or bilateral costovertebral angle pain to percussion (positive Goldflam sign, or kidney punch) accompanied by bacteriuria and pyuria [4–6]. Urine culture test is an obligatory element of the diagnostic evaluation [5]. A study by Artero *et al.* focused on the empirical treatment of pyelonephritis showed that such an approach is unsuitable in one in ten patients. The most commonly administered drugs are amoxicillin combined with clavulanic acid (β-lactamase inhibitor), and cephalosporins, medications which turned out to be inadequate according to the antibiogram in 10.3% and 5.9% of patients, respectively [13].

Blood culture results are positive in 20-30% of patients and, based on them, the initially introduced treatment is changed in 15-20% of cases [14]. However, there is no convincing data according to which patients could be referred for routine blood culture tests, steps that would substantially increase diagnostic costs [6]. Wing *et al.* suggest that therapeutic decisions should be rather based on the clinical presentation. They believe that avoiding routine blood culture tests but instead limiting indications for performing them to selected cases (persistent symptoms despite treatment, fever extending for more than 48 hours, lack of response to the treatment and as a follow-up routine screening) would simplify the treatment and reduce costs of medical care without affecting its quality [15].

Similar to those found in nonpregnant patients, urine culture samples during pregnancy contain predominantly

Table I. Clinical types of pregnancy-related urinary tract infections.

Clinical type	Incidence	Symptoms	Treatment	Results of additional tests	Recommendations
Asymptomatic bacteriuria	2-13%	None.	1 dose of fosfomycin trometamol. Other antibiotics: 3-7 days of oral administration.	Urine culture: bacteriuria.	Screening: 12-16 wks or during the first visit in pregnancy.
GBS bacteriuria	2-7%	None.	1 dose of fosfomycin trometamol. Other antibiotics: 3-7 days of oral administration.	Urine culture: bacteriuria.	Screening: 35-37 wks. Peripartum prophylaxis.
Cystitis	1-2%	Dysuria, urinary frequency, urgency, painful urination, discomfort in the lower abdomen, hematuria.	1 dose of fosfomycin trometamol. Other antibiotics: 3-7 days of oral administration.	Urine culture: bacteriuria. General urinalysis: leukocyturia, hematuria, presence of nitrites, often change of pH to more alkaline.	Consider: periodic controls and chronic antibiotic prophylaxis.
Acute pyelonephritis	1-4%	Fever and chills, nausea and vomiting, lumbar pain, Goldflam's sign positive.	Intravenous antibiotic therapy until fever subsides, then oral administration for 7-14 days.	Urine culture – bacteriuria. Blood culture: positive in 20-30% of patients. General urinalysis – as above.	Hospitalization. Periodic screening for bacteriuria. Chronic antibiotic prophylaxis.

GBS – Group B streptococci
wks – weeks of gestation

the following pathogens: *E. coli* (63-85% of cases), *Klebsiella spp*. (8%), coagulase-negative *Staphylococci* (15%), *Staphylococcus aureus* (approximately 8%), and *Streptococcus agalactiae* (2-10%) [3, 6, 9]. When positive, blood culture tests usually revealed the presence of *E. coli* and *Klebsiella pneumoniae* [15]. Infections with less frequently occurring pathogens such as *Mycoplasma hominis, Ureaplasma parvum, Gardnerella vaginalis*, and *Chlamydia trachomatis* were also described [5, 6].

The treatment of acute pyelonephritis requires hospitalization and an intravenous (i.v.) administration of antibiotics for at least 48 hours after fever and other acute symptoms have subsided [4]. Then, the therapy should be continued by oral route for 10-14 days, combined with antiinflammatory and antipyretic drugs, as well as adequate hydration of the woman [3]. The majority of patients respond to such treatment within 48 hours [5]. First-line medications are most often β-lactam antibiotics (ampicillin or cephalosporins of II and III generation) combined with gentamicin [4, 9], or carbapenems in case of complications [3] (Table I).

DIAGNOSTIC CRITERIA

Urine culture is the gold standard in diagnosing UTI [5]. Yet, it is not recommended to carry out dipstick tests in patients with suspected UTI or rely exclusively on the urinalysis results due to an exceedingly low level of sensitivity and specificity [5, 16]. However, these tests are inexpensive and quick diagnostic methods. The sensitivity value of dipstick tests for leukocyte esterase, and presence of nitrites or blood is estimated to be 77%, whereas specificity amounts to 70%, both values being insufficient for the diagnosis of UTI in pregnant patients [6, 10, 16]. Compared to diagnostic procedures based on urinary culture, dipstick tests make it possible to detect only a half of UTIs [5]. In general urinalysis, the highest predictive value is ascribed to the presence of nitrites, leukocyturia, and hematuria [17].

Of note, ASB is defined as the presence of 10^5 cfu/mL or more of a single pathogen in a correctly collected urine sample, and not accompanied by clinical manifestations. Treatment should be considered also when the results are lower [9]. The Infectious Diseases Society of America defines ASB as a double-positive result of urine culture at the titer of 10^5 or more, or the titer of 10^2 in the case of catheter-derived urine, without clinical symptoms such as dysuria, frequent urination, hematuria, or discomfort in the lower abdomen. Nonetheless, for cost-effective reasons, it is recommended that a single urine culture test should be performed for screening purposes. Furthermore, it is highly advised to introduce the treatment after obtaining a single positive culture, although it may probably lead to an overestimation of the ASB incidence [3, 6]. A single urine sample allows to detect 80% of cases of ASB whereas a double urine culture detects 96%, the level comparable to results from catheter-derived urine [10]. Little attention is being paid to the technique of urine collection for culture. One should obtain a morning urine sample after rinsing the external genital organs and external urethral meatus twice or three times. This step aims to reduce, yet not completely eliminates, the impact of contamination of the skin and distal urethra with vaginal bacterial flora [10].

Some authors, for instance Salvatore *et al*., suggest that young women with symptoms of acute cystitis need to be diagnosed at the titer of 10^3/mL, an approach which would increase sensitivity but decrease specificity [17]. The clinical significance of GBS presence at any titer in the urine culture is emphasized; it seems that titer values even below 10^4/mL are indicative of the colonization of the genital tract [17].

In patients who did not demonstrate any abnormalities in their urine results at first examination in pregnancy, repeated urine cultures are still worth considering in every trimester. This is so because some of them will develop bacteriuria later on in the course of pregnancy [3].

RISK FACTORS

The single most important risk factor is the history of UTI prior to pregnancy or at an early stage of pregnancy [4]. Other risk factors include: low socioeconomic status, advanced maternal age, high level of sexual activity, multiparity, diabetes, and anomalies and defects of the urinary tract [3]. UTIs occur more frequently in women with bacterial vaginosis [18]. The importance of sickle cell anemia, advanced age, and multiparity remains controversial [3, 19]. In human immunodeficiency virus-positive women, high viremia increases the risk of UTI [20].

Pregnancy-related physiological changes are considered predisposing factors for UTI as well (see Table II). These include in particular: upper urinary tract dilatation, decreased peristalsis, smooth muscle relaxation related to relaxing effects of progesterone [6], mechanical obstruction from the gravid uterus, increased glomerular filtration rate (GFR), detrusor muscle relaxation and increased bladder capacity, as well as changes in the composition of urine (glycosuria – occurring in up to 70% of pregnant women [5] and alkaline urine pH) [3, 21]. The dilatation of the upper urinary tract becomes detectable already from 7 weeks of gestation in 90% of patients and reaches its peak around 22 to 24 weeks [5]. It can persist up to 6 weeks postpartum [9]. This phenomenon is referred to as the physiological hydronephrosis and is caused by both mechanical and hormonal factors. The distention of

Table II. Principal pregnancy-related adaptive changes of the urinary tract [3, 5, 6, 9, 21].

Pregnancy-related changes of the urinary tract
Upper urinary tract dilatation (physiological hydronephrosis)
Decreased peristalsis in the pyelocalyceal systems and ureters
Increased smooth muscle relaxation in the ureters and bladder
Increased bladder capacity
Mechanical obstruction/pressure from the gravid uterus
Changes in the urine composition (glycosuria, high urine pH)
Increased renal flow and glomerular filtration

the right ureter is usually more pronounced due to the uterine dextrorotation and protective role of the large intestine filled with masses and gas on the left side [9]. The resulting urine retention not only facilitates UTI, but also pyelonephritis and nephrolithiasis [3, 9].

Due to a higher cardiac output and lowered peripheral vascular resistance in pregnancy, renal blood flow increases by 60-80% and leads to the increase in GFR by 40-65% [6, 9, 21]. This, in turn, causes an average fall in the blood creatinine level from 0.8 to 0.5 mg/dL. Therefore, altered pharmacodynamics of drugs as a result of the altered renal metabolism should be taken into account in the treatment of pregnant patients [9].

POSSIBLE SEQUELAE OF URINARY INFECTIONS IN PREGNANCY

Notably, bacteriuria in early pregnancy can be considered as an uncomplicated UTI. However, later due to the increasing risk of complications stemming from physiological changes of the urinary tract in pregnancy, bacteriuria should be considered a complicated UTI [17].

The most serious sequelae of UTIs during pregnancy include low birth weight, preterm labor, anemia, renal failure, hypertension, and systemic infection [1, 5, 22]. Pregnancy-related UTI (either in the form of ASB, cystitis, or pyelonephritis) increases by 50% the risk of preeclampsia, probably via inflammatory mechanisms [23]. Untreated urinary infections may increase the risk of fetal developmental alterations and mental retardation. They have also been associated with an over 2-point lower intelligence quotient, or IQ, in children whose mothers had a history of pregnancy-related UTI [24]. Yazdy *et al.* concluded that there is a relationship between the incidence of UTI and fetal gastroschisis, particularly in young mothers who suffered from UTI in early pregnancy [25]. A serious complication of untreated UTI, and pyelonephritis in particular, may also be a systemic infection. Systemic infection is the most frequent cause of maternal death during both pregnancy and postpartum [26].

Finally, GBS bacteriuria is closely related to a higher risk for premature rupture of membranes, preterm labor and early-onset neonatal systemic infection [3, 7].

SCREENING AND TREATMENT RECOMMENDATIONS

Due to the risk of acute pyelonephritis, it is recommended to screen the patients for ASB in early gestation. According to the American College of Obstetricians and Gynecologists, a urine culture test should be performed at 16 weeks of pregnancy in all patients [9]. The US Preventive Services Task Force and the American Academy of Family Physicians (AAFP) recommend to perform urine culture between 12 and 16 weeks of gestation or during the first visit in pregnancy [6, 27]. There are no detailed indications as to further screening, if the first urine culture is negative [3]. Some authors recommend to repeat the test in every trimester in order to increase the detection rate of ASB [4]. This kind of routine is particularly worth considering in patients with a history of recurrent UTIs and urinary tract anomalies [28]. Nevertheless, the Polish Gynecological Society did not include routine urine culture tests in the recommendations for maternal care [29]. Apart from microbiological evaluation, the screening should also include the history of UTIs before and during pregnancy since such a history has been considered the most significant singular pregnancy-related UTI risk factor [4].

Schaeffer and co-workers recommend to perform control urine culture tests in all patients diagnosed with UTI. In their opinion, such verifications need to be repeated post-treatment and then periodically until delivery. They also suggest to consider introducing antibiotic prophylaxis, especially in patients with the history of acute pyelonephritis [6, 28].

Clinical and therapeutic decisions are influenced by numerous factors. Apart from the knowledge about most common local pathogens causing UTIs, these are also: awareness of pregnancy-related adaptive changes affecting drug metabolism, stage of pregnancy, transplacental distribution of medications, and possible influences on the fetus. To date, there is still no consensus on the choice of particular drugs and duration of treatment for bacteriuria in pregnant women [4].

It is universally agreed that the drug classification by the Food and Drug Administration (FDA), an American federal agency, should be implemented. This system embraces 5 principal drug categories: A, B, C, D, and X (Table III).

In December 2014, FDA published an evaluation report on that classification system, considering it no longer practical and sufficient for clinical use in certain groups of patients, such as pregnant and breastfeeding women. New, more rational rules of drug classification and description were suggested to facilitate clinical decision-making. This new classification became obligatory for drug manufacturers in June 2015 [30]. According to the new rules, the Summary of Product Characteristics (SPC) should contain information on the scope of use of a given drug in pregnancy and on pregnancy risks in the following four categories: structural abnormalities, fetal and/or infant mortality, functional impairment, and alterations to growth. The document is also supposed to provide data, if available, on the risks of congenital anomalies and miscarriages as compared to their incidence in general population [30]. Consequently, new SPCs should be a vital and immediate source of information for clinicians.

A Cochrane-type analysis presented by Vasquez and Abalos in 2011 [31], along with a study by Ortega-González and Castro-Diaz from 2014 [32], demonstrated no particular advantage of any specific antibiotic, or pattern of its intake, over another in the treatment of pregnancy-related UTIs. Optimally, the given antibiotic should be selected depending on the safety profile and local drug susceptibility, availability as well as economic factors [4, 6]. Recommendations of some countries are different. In Canada, first-line treatment includes trimethoprim and nitrofurantoin whereas penicillins and cephalosporins are recommended in the United Kingdom. Studies carried out in Scandinavia showed that physicians most often choose β-lactam antibiotics, nitrofurantoin, and sulfonamides, even

Table III. The Food and Drug Administration (FDA) classification of drugs according to pregnancy risk categories [37].

Pregnancy risk category according to the FDA	Definition in terms of safety of use in pregnant women
A	Controlled studies have failed to demonstrate a risk to the fetus in the I trimester of pregnancy. The possibility of fetal malformation seems to be unlikely.
B	Animal studies have failed to demonstrate a risk to the fetus and there are no adequate and well-controlled studies in pregnant women. Studies on animals demonstrated no adverse effects on the fetus. Studies on a group of pregnant women did not confirm any fetal risk.
C	Animal studies have shown teratogenic or lethal effects on the fetus. No controlled studies in pregnant women have been carried out or neither animal nor human studies have been carried out.
D	There is positive evidence of human fetal risks based on adverse reaction data, but potential benefits may warrant use of the drug in pregnant women despite potential risks (e.g. in life-threatening conditions or diseases that could not be treated with other safe drugs, or such treatment is ineffective).
X	Studies in animals or humans have demonstrated fetal abnormalities following drug administration or there is positive evidence of human fetal risk based on adverse reaction data and the risks involved in use of the drug in pregnant women clearly outweigh potential benefits. **Drug is contraindicated during pregnancy.**

if the latter are being considered unsuitable during pregnancy due to their negative influence on folate metabolism [33]. Fosfomycin trometamol has also significantly gained relevance due to its high effectiveness, easy administration and, therefore, high compliance. Nitrofurantoin, β-lactam antibiotics, cephalosporins, penicillin derivatives as well as fosfomycin trometamol are all drugs considered as safe in pregnancy and recommended for use as first-line treatment [17].

Interestingly, Turkish studies revealed some differences in drug susceptibility of uropathogens depending on trimesters of pregnancy. The most frequently detected pathogens: *E. coli* and *Klebsiella spp*. showed the highest i.v. drug susceptibility for imipenem, accounting for 100%, regardless of the advancement of pregnancy. Among orally administered drugs, the highest susceptibility was observed for fosfomycin trometamol (reaching in the I, II, and III trimester 98.3%, 98.1% and 98.4% of cases, respectively) and for nitrofurantoin (in the I, II, and III trimester – 98.0%, 97.0% and 97.3%, respectively) [34]. This is another argument for the use of the above-mentioned drugs as first-line treatment.

Below we provide brief descriptions of most commonly used medications for the treatment of pregnancy-related UTIs:

Amoxicillin is a β-lactam compound from the oldest group of penicillin-derived antibiotics [6], characterized by its bacteriolytic effect based on inhibiting bacterial cell wall synthesis. It is among the most commonly prescribed drugs in pregnant women [35, 36], often administered as first-line treatment against UTI [3] at dosage 3 times p.d. for 3-7 days. Its activity spectrum includes such penicillinase-negative strains as: *Streptococcus spp., Enterococcus spp.* (strains of *Enterococcus faecium* are often resistant), *Staphylococcus aureus* and *Staphylococcus epidermidis* (only approximately 10% of these staphylococcal strains are penicillinase-negative), *Neisseria meningitidis, Neisseria gonorrhoeae, Listeria monocytogenes, Haemophilus influenzae, E. coli, Proteus mirabilis, Salmonella spp., Shigella spp., Helicobacter pylori, Fusobacterium spp., Prevotella melaninogenica, Clostridium spp.,* and some *Bordetella, Borrelia, Brucella*, and *Actinomyces* strains. Animal studies applying doses 10 times higher than those used in humans showed neither negative effects on the course of pregnancy, nor any increased incidence of congenital anomalies in the offspring. Amoxicillin has been assigned to the FDA's pregnancy category B [37, 38].

Amoxicillin combined with clavulanic acid is a drug with a spectrum of activity similar to that of amoxicillin, yet due to the addition of clavulanic acid this activity is

extended against β-lactamase producing strains as well as amoxicillin- and ampicillin-resistant strains. It has also been assigned to pregnancy category B by the FDA. Observational studies showed a slightly higher incidence of spina bifida following the I trimester exposure to clavulanic acid. The causal link is possible, although the influence of other factors cannot be excluded [37]. The drug administered in pregnant women with preterm premature rupture of membranes increases the risk of neonatal necrotizing enterocolitis [39]. Treatment of UTI consists of dosages given every 8-12 hours for 3-7 days [3]. Resistance of most common uropathogens to this combined medication can reach from 19% for *E. coli* to 23% for *Klebsiella spp.* [34].

Ampicillin belongs to β-lactam antibiotics that act by inhibiting the synthesis of bacterial cell wall. Its activity spectrum includes penicillinase- and β-lactamase-negative strains and, when combined with sulbactam (assigned also to pregnancy category B by the FDA), is extended to penicillinase- and β-lactamase-positive strains. Ampicillin is widely recognized as a safe drug. Neither harmful effects on the course of pregnancy, nor higher incidence of congenital anomalies were observed upon its use [37]. The drug is indicated for peripartum prophylaxis in GBS carriers as first-line treatment, being administered every 4 hours [8]. In patients solely with UTI, it is recommended to administer ampicillin every 6 hours, which may reduce compliance [6, 37, 38]. Of note, up to 30% of *E. coli* and 45% of *Klebsiella* strains (second most common uropathogen in pregnant women) may be resistant to ampicillin [34].

Cephalosporins are a broad class of β-lactam antibiotics divided into five generations with a wide spectrum of bacteriolytic activity resistant to microbial penicillinase and β-lactamase (second to fifth generations). They are also assigned to pregnancy category B by the FDA. Generally, the use of these drugs is considered safe during pregnancy, although observational studies revealed a slightly higher incidence of cardiovascular congenital anomalies, cleft lip and cleft palate. The causal link is possible, however, the influence of other factors cannot be excluded [37]. Treatment against UTIs consists of oral or parenteral administration of cephalosporins 1-4 times *p.d.* depending on drug generation. Cephalexin belongs to the first generation of cephalosporins and, like amoxicillin, it is recommended as the first-line treatment in pregnant patients with UTI: on average 500 mg every 6-12 hours [3]. Furthermore, it is recommended for a prolonged prophylaxis in patients with recurrent pyelonephritis at dosages of 250-500 mg before night rest [3]. Apart from the mentioned cephalexin, the most commonly used cephalosporins are: cephazolin (represents first generation), cefuroxime axetil and cefuroxime (second generation), and ceftriaxone (third generation). For peripartum prophylaxis of GBS carriers, cephazolin is the drug of choice at doses administered every 8 hours [8].

Fosfomycin trometamol is a synthetic derivative of phosphoric acid. Its antibacterial activity relies on inhibiting bacterial wall synthesis and exerting antiadhesive effects (inhibition of microbial adhesion to the urothelium) [40]. The activity spectrum includes Gram-positive and Gram-negative organisms (including penicillinase-producing bacteria) such as: *E. coli, Citrobacter spp., Klebsiella spp., Proteus spp., Staphylococcus spp.,* including methicyllin-resistant *Staphylococcus aureus* (MRSA) strains, *Salmonella spp., Streptococcus faecalis, Serratia spp., and Enterococcus* strains (including vancomycin-resistant strains) [6, 40]. Particular clinical relevance is assigned to the high susceptibility of microorganisms that are often detected in hospital infections, such as *Klebsiella spp., Proteus spp.* (indole-negative strains), *Serratia spp.,* MRSA, and *Staphylococcus faecalis* [40]. Fosfomycin is conveniently given as a single oral dose of 3 g. In recurrent infections or infections induced by *Pseudomonas spp., Enterobacter spp.,* and indole-positive *Proteus spp.*, administration of the second dose is recommended in 24 hours [40]. No negative influence of fosfomycin on the course of pregnancy and fetal development was observed. The drug has been assigned to pregnancy category B by the FDA [40]. Approximately 89-98% of pathogens are sensitive to fosfomycin [2, 34, 41]. Resistance of *E. coli*, the most common uropathogen, may occur in rare cases, however, it has not been on the increase. Importantly, the drug does not induce cross-resistance with other antibiotics and seldom causes side effects [40]. Due to the ease of its use and high potency in comparison with other treatment patterns (amoxicillin with clavulanic acid and cefuroxime axetil administered twice *p.d.* for 5 days achieving 77% and 82% compliance, respectively), fosfomycin may be considered a preferred drug during pregnancy [42]. Of note, it should be used for the treatment of the lower UTIs only [6].

Nitrofurantoin is a bacteriostatic medication. Its activity is based on inducing lipid oxidation, as well as damage to bacterial cell walls, ribosomal proteins and DNA strands. It is preferred in the treatment of UTIs mainly due to its pharmacokinetic parameters. Therapeutic concentrations of nitrofurantoin are achieved solely in the lower urinary tract and not in other tissues. Therefore, the drug is specifically indicated for the management of lower UTIs and not recommended for pyelonephritis [6]. Additionally, nitrofurantoin demonstrates antiprotozoal and antifungal activity. Usual dosage is twice *p.d.* for 5-7 days [3]. In the peripartum period (38 to 42 weeks of gestation), its administration is related to the potential risk of evoking hemolytic anemia in newborns, particularly in those with glucose-6-phosphate dehydrogenase (G6PD) deficiency, but also in healthy neonates. Therefore, this agent should not be used in this time frame [37]. Since its possible influence on the development of fetal malformations (such as hypoplastic left heart syndrome) in the I trimester cannot be ruled out [43], nitrofurantoin should be avoided in this period [3, 44]. In Poland, furazidin is a popular and available over-the-counter derivative of nitrofurantoin that has similar limitations; however, the two substances are not equivalents [37, 43]. For prolonged UTI prophylaxis, small oral daily doses (50-100 mg) of nitrofurantoin are recommended [9]. Similarly to fosfomycin, nitrofurantoin

shows the strongest antibacterial activity in uncomplicated UTIs. Bacterial resistance remains very low (over 98% susceptibility for *E. coli* and 94% susceptibility for *Klebsiella pneumoniae*) [34, 40].

Sulfonamides used for the treatment of UTIs are the combination of sulfamethaxozole and trimethoprim. Sulfamethoxazole belongs to pregnancy category C by the FDA and, during the peripartum period, is recognized as a pregnancy category D drug due to the risk of inducing hyperbilirubinemia and kernicterus in the neonate [6]. Since sulfonamides may impair the fetal metabolism of folate, a higher risk of incidence of cardiovascular, neural tube, and urinary tract anomalies, together with cleft palate and clubfoot should be taken into account. This becomes particularly important when sulfonamides, in combination with trimethoprim or alone, are used before the end of the third month of pregnancy [37]. Therefore, they may be prescribed in the I trimester only if no alternative treatment method is available [6, 44]. In children from mothers with G6PD deficiency, sulfonamides may induce anemia [9]. However, the risk of fetal cardiovascular anomalies in pregnant women on sulfonamides who received folic acid supplementation was not significantly increased. The studied groups were also too small to evaluate other types of malformations [37, 38]. As to the dosage regimen, patients should take a sulfonamide twice *p.d.* for 5-7 days [3]. An increase of *E. coli* resistance against sulfonamides has been observed [9]. Overall, in view of the above-mentioned possible risks and uncertainties, sulfonamides should not be used during pregnancy [6].

Erythromycin belongs in a group of drugs called macrolides. Its bacteriostatic effect results from the inhibition of bacterial protein synthesis. The drug is particularly recommended for the treatment of Gram-positive cocci and atypical pathogens (chlamydia, mycoplasma, ureaplasma) whereas it demonstrates lower activity against Gram-negative bacteria [6, 38]. It is used as a third-line treatment recommended for the peripartum prophylaxis of GBS colonization in patients with hypersensitivity to penicillins and cephalosporins [8]. Erythromycin may induce symptoms of cholestasis in pregnant women [9]. Observational studies have revealed a higher incidence of pyloric stenosis in the offspring when erythromycin was used in early gestation [37]. Nevertheless, macrolides are generally recognized as safe and their use is allowed during pregnancy [6]. Erythromycin was assigned to pregnancy category B by the FDA as was its newer close derivative azithromycin that is used for the treatment of chlamydia, mycoplasma, and ureaplasma infections, also in pregnant women. Azithromycin is better tolerated and causes fewer gastrointestinal side effects than erythromycin [6, 37, 38].

Clindamycin belongs to lincosamides and is characterized by bacteriostatic or bacteriolytic effects depending on its concentration in the tissue. The medication's activity is based on inhibiting bacterial protein synthesis. The FDA assigned pregnancy B category it to. Clindamycin's antibacterial activity includes *Staphylococcus spp.*, among other strains, yet remains inactive against *Enterococcus spp.* and the majority of Gram-negative aerobic bacteria [6]. The drug is considered a safe alternative for GBS prophylaxis in patients with hypersensitivity to penicillins and cephalosporins [8]. No harmful influence on the course of pregnancy, nor increased incidence of birth defects following its administration were observed [37]. One in ten patients may develop diarrhea and, rarely, pseudomembranous colitis [6]. Quite frequent doses every 6-8 hours may reduce compliance [37].

Vancomycin is a glycopeptide antibiotic. Its bacteriolytic activity stems from the inhibition of cell wall biosynthesis and the effects on the permeability of bacterial cell membranes and ribonucleic acid synthesis. Vancomycin is active against Gram-positive aerobic cocci, *Clostridium difficile*, and *Clostridium jeikeium*. It is particularly useful for the treatment of infections induced by MRSA and other multidrug resistant Gram-positive bacteria, e.g. *Enterococcus spp.* [6]. No cross-resistance of vancomycin to antibiotics from other groups has been observed. The drug is also an alternative for patients with hypersensitivity to penicillins and cephalosporins. It is available only in the i.v. form and has been assigned to pregnancy C category by the FDA. Data on the application scope is very limited. No animal studies were carried out. Potential nephrotoxic and ototoxic side effects were not confirmed in few studies evaluating the use of vancomycin in pregnant women. However, the effects in the I trimester were not assessed [6, 37]. The medication may be used for GBS infection prophylaxis against strains resistant to macrolides, lincosamides and streptogramins B (MLSB) and in cases of hypersensitivity to penicillins and cephalosporins when alternative treatment is not possible [8, 37].

Regarding the follow-up management, control urine cultures should be performed in all pregnant women treated for UTIs 1-2 weeks following the treatment [3]. Then, the tests should be repeated at least once a month until delivery. One in three patients may develop recurrent infection [6], more frequently when short 3-day patterns of treatment were applied earlier [5]. The treatment of persistent or recurrent bacteriuria should be continued, usually as a prolonged administration of first-line drugs, until an unremarkable urine culture is obtained. Some women (such as those with a history of immunodeficiency and recurrent urinary infections) may require prophylaxis extended to term (for instance, nitrofurantoin 50-100 mg in the evening, or following intercourse if the recurrence has been related to sexual activity). Consequently, during such a prophylaxis, urine cultures should be carried out only in the III trimester [9]. According to recommendations by the AAFP, a control test should be performed in the III trimester in all patients treated earlier for pregnancy-related UTIs [5].

A separate issue is the peripartum UTI prophylaxis in GBS carriers, for which the drugs of choice are penicillins or ampicillin. Cephazolin is recommended in patients with the history of allergy to penicillin. In patients with allergy to cephalosporins, the use of erythromycin, clindamycin,

or vancomycin is advised depending on the susceptibility of a given strain [8]. Dosage regimens for i.v. prophylaxis include: penicillin G 5 million units as a bolus and later 2.5-3 million units every 4 hours; ampicillin 2 g initially and later 1 g every 4 hours; cephazolin 2 g and later 1 g every 8 hours; clindamycin 900 mg every 8 hours; vancomycin 1 g every 12 hours. The above prophylaxis is accurate when the first dose of the antibiotic is administered at least 4 hours before the labor. Then, it reduces the risk of neonatal GBS colonization to approximately 1%, as compared with as many as 50% in case of labors not subjected to preventive measures [7, 8].

CONCLUSIONS

Collectively, in spite of the implementation of efficient screening procedures, UTIs are still among the most common pregnancy-related disorders in the vast majority of countries and, unfortunately, their incidence has not been on a decrease. The symptoms may be nonspecific and often include these present also in healthy pregnant women. Unlike in general population, asymptomatic infections during pregnancy require treatment in line with current practical recommendations from a number of international bodies and organizations. Early diagnosis and adequate treatment of asymptomatic infections allows to significantly reduce the risk of maternal and fetal complications. The most common pathogens causing UTI demonstrate sensitivity to many drugs that can be safely administered during pregnancy, also in the I trimester. In order to reduce the number of complications, urine culture tests should be performed as a routine maternal care already from the I trimester and continue later in pregnancy.

REFERENCES

1. Amiri M, Lavasani Z, Norouzirad R, Najibpour R, Mohamadpour M, Nikpoor AR, Raeisi M, Zare Marzouni H. Prevalence of urinary tract infection among pregnant women and its complications in their newborns during the birth in the hospitals of Dezful City, Iran, 2012–2013. Iran Red Crescent Med J, 2015, 17, e26946.
2. Souza RB, Trevisol DJ, Schuelter-Trevisol F. Bacterial sensitivity to fosfomycin in pregnant women with urinary infection. Braz J Infect Dis, 2015, 19, 319-323.
3. 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.
4. Schnarr J, Smaill F. Asymptomatic bacteriuria and symptomatic urinary tract infections in pregnancy. Eur J Clin Invest, 2008, 38 (Suppl 2), 50-57.
5. Delzell JE, Lefevre ML. Urinary tract infections during pregnancy. Am Fam Physician, 2000, 61, 713-720.
6. Glaser AP, Schaeffer AJ. Urinary tract infection and bacteriuria in pregnancy. Urol Clin North Am, 2015, 42, 547-560.
7. Centers for Disease Control and Prevention: Prevention of Perinatal Group B Streptococcal Disease: Revised Guidelines from CDC, 2010. Recommendations and Reports, 2010 (November 19), 59 (RR10), 1-32.
8. Polskie Towarzystwo Ginekologiczne: Rekomendacje Polskiego Towarzystwa Ginekologicznego dotyczące wykrywania nosicielstwa paciorkowców grupy B (GBS) u kobiet w ciąży i zapobiegania zakażeniom u noworodków. Ginekol Pol, 2008, 79, 221-223.
9. Thomas AA, Thomas AZ, Campbell SC, Palmer JS. Urologic emergencies in pregnancy. Urology, 2010, 76, 453-460.
10. Teppa RJ, Roberts JM. The Uriscreen Test to detect significant asymptomatic bacteriuria during pregnancy. J Soc Gynecol Investig, 2005, 12, 50-53.
11. Wing DA, Fassett MJ, Getahun D. Acute pyelonephritis in pregnancy: an 18-year retrospective analysis. Am J Obstet Gynecol, 2014, 210, 219.e1-219.e6.
12. Archabald KL, Friedman A, Raker CA, Anderson BL. Impact of trimester on morbidity of acute pyelonephritis in pregnancy. Am J Obstet Gynecol, 2009, 201, 406.e1-406.e4.
13. Artero A, Alberola J, Eiros JM, Nogueira JM, Cano A. Pyelonephritis in pregnancy. How adequate is empirical treatment? Rev Esp Quimioter, 2013, 26, 30-33.
14. Gomi H, Goto Y, Laopaiboon M, Usui R, Mori R. Routine blood cultures in the management of pyelonephritis in pregnancy for improving outcomes. Cochrane Database Syst Rev, 2015, (2), CD009216.
15. Wing DA, Park AS, Debuque L, Millar LK. Limited clinical utility of blood and urine cultures in the treatment of acute pyelonephritis during pregnancy. Am J Obstet Gynecol, 2000, 182, 1437-1440.
16. Khasriya R, Khan S, Lunawat R, Bishara S, Bignall J, Malone-Lee M, Ishii H, O'Connor D, Kelsey M, Malone-Lee J. The inadequacy of urinary dipstick and microscopy as surrogate markers of urinary tract infection in urological outpatients with lower urinary tract symptoms without acute frequency and dysuria. J Urol, 2010, 183, 1843-1847.
17. Salvatore S, Salvatore S, Cattoni E, Siesto G, Serati M, Sorice P, Torella M. Urinary tract infections in women. Eur J Obstet Gynecol Reprod Biol, 2011, 156, 131-136.
18. Hillebrand L, Harmanli OH, Whiteman V, Khandelwal M. Urinary tract infections in pregnant women with bacterial vaginosis. Am J Obstet Gynecol, 2002, 186, 916-917.
19. Bencaiova G, Krafft A, Breymann C. Sickle cell trait and urinary tract infection in pregnancy. Int J Gynaecol Obstet, 2006, 92, 128-129.
20. Park JC, Buono D, Smith DK, Peipert JF, Sobel J, Rompalo A, Klein RS. Urinary tract infections in women with or at risk for human immunodeficiency virus infection. Am J Obstet Gynecol, 2002, 187, 581-588.
21. Fiadjoe P, Kannan K, Rane A. Maternal urological problems in pregnancy. Eur J Obstet Gynecol Reprod Biol, 2010, 152, 13-17.
22. Morken NH, Gunnes N, Magnus P, Jacobsson B. Risk of spontaneous preterm delivery in a low-risk population: the impact of maternal febrile episodes, urinary tract infection, pneumonia and ear–nose–throat infections. Eur J Obstet Gynecol Reprod Biol, 2011, 159, 310-314.
23. Chang E, Armstrong DM, Ebeling M, Hulsey T, Newman R. Urinary tract infections are associated with an increased risk of preeclampsia. Am J Obstet Gynecol, 2005, 193, S71.
24. McDermott S, Callaghan W, Szwejbka L, Mann H, Daguise V. Urinary tract infections during pregnancy and mental retardation and developmental delay. Obstet Gynecol, 2000, 96, 113-119.

25. Yazdy MM, Mitchell AA, Werler MM. Maternal genitourinary infections and the risk of gastroschisis. Am J Epidemiol, 2014, 180, 518-525.
26. Bamfo JE. Managing the risks of sepsis in pregnancy. Best Pract Res Clin Obstet Gynaecol, 2013, 27, 583-595.
27. United States Preventive Services Task Force (USPSTF) Final Recommendation Statement. Asymptomatic Bacteriuria in Adults: Screening, July 2008. Website: http://www.uspreventiveservicestaskforce.org/Page/Document/RecommendationStatementFinal/asymptomatic-bacteriuria-in-adults-screening Accessed on August 09, 2016.
28. Macejko AM, Schaeffer AJ. Asymptomatic bacteriuria and symptomatic urinary tract infections during pregnancy. Urol Clin North Am, 2007, 34, 35-42.
29. Polskie Towarzystwo Ginekologiczne: Rekomendacje Polskiego Towarzystwa Ginekologicznego w zakresie opieki przedporodowej w ciąży o prawidłowym przebiegu. Ginekologia Po Dyplomie, 2006, 8, 56-59.
30. Food and Drug Administration. Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products — Content and Format Guidance for Industry. Website: http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm450636.pdf Accessed on August 09, 2016.
31. Vazquez JC, Abalos E. Treatments for symptomatic urinary tract infections during pregnancy. Cochrane Database Syst Rev, 2011, (1), CD002256.
32. Ortega-González Y, Castro-Diaz D. Antibiotic considerations for urinary tract infections in pregnancy. Current Bladder Dysfunction Reports, 2014, 9, 167-174.
33. Christensen B. Use of antibiotics to treat bacteriuria of pregnancy in the Nordic countries. Which antibiotics are appropriate to treat bacteriuria of pregnancy? Int J Antimicrob Agents, 2001, 17, 283-285.
34. Unlu BS, Yildiz Y, Keles I, Kaba M, Kara H, Tasin C, Erkilinc S, Yildirim G. Urinary tract infection in pregnant population, which empirical antimicrobial agent should be specified in each of the three trimesters? Ginekol Pol, 2014, 85, 371-376.
35. Thorpe PG, Gilboa SM, Hernandez-Diaz S, Lind J, Cragan JD, Briggs G, Kweder S, Friedman JM, Mitchell AA, Honein MA for the National Birth Defects Prevention Study. Medications in the first trimester of pregnancy: most common exposures and critical gaps in understanding fetal risk. Pharmacoepidemiol Drug Saf, 2013, 22, 1013-1018.
36. Dillon P, O'Brien KK, McDonnell R, Donnelly-Swift E, Galvin R, Roche A, Cronin K, Walsh DR, Schelten R, Smith S, Fahey T. Prevalence of prescribing in pregnancy using the Irish primary care research network: a pilot study. BMC Pregnancy Childbirth, 2015, 15, 67.
37. Friese K, Mörike K, Windorfer A, Neumann G, Fuchs T (Red.). Leki w ciąży i laktacji, przewodnik dla lekarzy i farmaceutów. MedPharm Polska, Wrocław, 2010, str. 103-109, 113, 115-116, 275-276.
38. DailyMed, a public service of the U.S. National Library of Medicine. Website: https://dailymed.nlm.nih.gov/dailymed/ Accessed on August 09, 2016.
39. Kenyon S, Taylor DJ, Tarnow-Mordi WO on behalf of ORACLE Collaborative Group. ORACLE – antibiotics for preterm prelabour rupture of the membranes: short-term and long-term outcomes. Acta Paediatr, 2002, 91 (Suppl. 437), 12-15.
40. Jóźwik M. Skuteczność lecznicza preparatu MONURAL® w zwalczaniu zakażeń układu moczowego u kobiet. Ginekol Prakt, 2005, 13, 24-28.
41. Krcmery S, Hromec J, Demesova D. Treatment of lower urinary tract infection in pregnancy. Int J Antimicrobial Agents, 2001, 17, 279-282.
42. Usta TA, Dogan O, Ates U, Yucel B, Onar Z, Kaya E. Comparison of single-dose and multiple-dose antibiotics for lower urinary tract infection in pregnancy. Int J Gynaecol Obstet, 2011, 114, 229-233.
43. Goldberg O, Moretti M, Levy A, Koren G. Exposure to nitrofurantoin during early pregnancy and congenital malformations: a systematic review and meta-analysis. J Obstet Gynaecol Can, 2015, 37, 150-156.
44. American College of Obstetricians and Gynecologists. American College of Obstetricians and Gynecologists Committee on Obstetric Practice. ACOG Committee Opinion No. 494: Sulfonamides, nitrofurantoin, and risk of birth defects. Obstet Gynecol, 2011, 117, 1484-1485.

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