DOI: 10.17816/KMJ2022-110

Asymptomatic bacteriuria in young pregnant women in modern society

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Abstract

The article provides an overview of the literature and existing international and national Guidelines on the etiology and main pathogens' characteristics of asymptomatic bacteriuria, diagnostic criteria, management of young pregnant women with asymptomatic bacteriuria and antibacterial therapy regimens. Young pregnant women are a significant part of the society structure that requires protection. Young women in the age category of 15–17 years are identified as a group with a high risk of complications during pregnancy, delivery and the postpartum period, as well as perinatal pathologies. Women of this age group are characterized by a high risk of complications: the threatened miscarriage, premature birth as well as young pregnancies usually accompanied by sexually transmitted infections. It is important for this group of patients to be more carefully monitored by doctors in the hospitals, maternity welfare centers, during delivery and postpartum period. The main causative agents of asymptomatic bacteriuria in pregnant women are representatives of the Enterobacteriaceae family (88.0%). *E. coli, Klebsiella spp., Staphilococcus spp.* cause asymptomatic bacteriuria only in 3–10% of cases. The diagnosis is based on the Russian Clinical Guidelines for Urology and the Federal Clinical Guidelines 2020, as well as on the European Guidelines of the Urologists Association 2020. The National Guidelines indicate the main principles of asymptomatic bacteriuria treatment in high risk patients (pregnant and young). Despite the progress made in the urinary tract infections study, especially asymptomatic bacteriuria in pregnant women, and the development of practical Guidelines for the management of these patients, this issue remains important in modern society.

Keywords: asymptomatic bacteriuria, urinary tract infections, young pregnant women.

For citation: Sitdikova DG, Fatkullina IB, Lazareva AY, Fatkullina YN, Faizullina LA, Galeeva SA. Asymptomatic bacteriuria in young pregnant women in modern society. *Kazan Medical Journal.* 2022;103(1):110–118. DOI: 10.17816/KMJ2022-110.

Urinary tract infection (UTI) in pregnant women is a term used for a wide range of infectious and inflammatory diseases of the urinary system without a special location and etiological indication [1]. UTI has several forms, namely acute cystitis, pyelonephritis, and asymptomatic bacteriuria (AB).

AB is also known as asymptomatic in various international sources. AB is characterized by the absence of clinical symptoms with urinary tract bacterial colonization and the presence of bacteria in the urine. According to the Russian Clinical Guidelines, "bacteriuria is the presence of bacteria in the urine (>10^5 colony-forming units (CFU) per 1 ml of urine) that is excreted from the bladder." The diagnosis is made during outpatient or inpatient examinations [2, 3].

The Russian studies on AB revealed several data that cover certain cohorts of people, especially pregnant women. However, information on the epidemiology of AB in certain population groups is inadequate, especially on children and adolescents.

The incidence of detected AB in pregnant women is 5%–9% [2, 3]. According to epidemiological data, females are most susceptible to urinary tract inflammation. Young females are affected much more frequently than males [4–6]. At least 50% of females have had at least one episode of UTI in their lifetime [4, 7]. According to other data, every third of females who are older than 20 years old received a single antibiotic treatment for UTI [8, 9]. Unfortunately, studies reveal that despite dysuria (27%) and frequent urination (34%) episodes, many of these females do not seek medical help during the first 5 days of illness [10].

Data on the prevalence among females who used spermicidal diaphragms for contraception are of particular interest. Of these females, 50%–70% develop at least one episode of cystitis within

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Received 30.04.2021; accepted 16.09.2021; published 15.02.2022.

a year [8]. The follow-up examinations of females in Finland after a lower UTI revealed that 82% of patients may develop recurrent cystitis within a year [8]. According to other data, at least 44% of females experience a recurrent cystitis attack after the first disease episode [8].

The use of antibiotics has been significant in the development of UTIs. Females of all ages have a significantly higher probability to develop a UTI after taking antibiotics [9]. The probability of a UTI increases with age, reaching 50% in females aged 55–74 years old. Additionally, with age, the frequency of urinary system organ damage makes no gender differences. Hence, older males and females develop UTIs at the same rate [10]. UTIs pose a significant threat due to the development of serious complications, namely kidney abscess formation, urosepsis development, bacteremia, and bacterial shock [10].

Young-age pregnancy has characteristics that require close attention. The period of social maturation of girls aged 15–20 years is one of the most important stages in gender-specific role development [11]. A distinctive feature of the sexual behavior of modern adolescents is a decreased age of sexual debut (15.8–16.2 years), an increased number of intimate partners, and inadequate information about sex education, which supports an increased number of pregnancies in young females [12].

Young-age pregnancy is characterized by a high risk of complications, such as threatened abortion, severe gestational toxicosis, fetoplacental insufficiency, and preterm delivery. Complications that young females may experience during childbirth include preterm labor, premature rupture of membrane, placental insufficiency, hypotonic bleeding, retention of placental parts, and surgical intervention indications [13]. Additionally, young-age pregnancies usually take place in the context of sexually transmitted infections [14–16], which poses a significant risk for both the young mother and the unborn child.

At the Republican Clinical Perinatal Center of the Ministry of Health of the Republic of Bashkortostan (Ufa), we retrospectively analyze and evaluate 50 case histories and birth records of puerperas in the age group of 15–17 years. Obstetric pathology in these minors included preeclampsia of varying severity in 11.2% and gestational pyelonephritis in 9.6% of cases. Cesarean section was performed in 15% and vaginal delivery in 85%. Cesarean sections were due to breech presentation and a clinically narrow pelvis.

Complications in childbirth in minors were the following:

a) anomalies of labor activity in 5.4% of cases;

b) premature detachment of a normally located placenta in 2%;

c) injuries of the birth canal, particularly rupture of the perineum in 12.6%;

d) rupture of the vagina and labia in 26%;

e) cervical ruptures of various degrees in 46%, such a high incidence is presumably associated with the physical immaturity of young females, the presence of somatic pathology, and the inability to cooperate with medical personnel;

f) postpartum hemorrhage in 8%.

Childbirth support in young pregnant females should be thought out in advance due to the biological immaturity of the body, psycho-emotional instability, and incomplete development of the pelvic bone [17].

The prevalence of AB in the female population in different age groups varies. AB in children develops extremely rarely (0.2%); however, the incidence of AB is already 1% in school-age girls (7–17 years), whereas 5% in females of reproductive age (18–45 years), 9% in middle-aged (46–59 years), and 16% in elderly (60–75 years) [8].

The prevalence of AB in females with diabetes and those on dialysis is higher than in healthy females [7].

In young females aged 15–17 years, inflammatory diseases of the urogenital tract are detected in 30%–37% of cases in pregnancy during outpatient monitoring [18, 19].

The Russian multicenter study of antibiotic resistance of UTI pathogens DARMIS, which was conducted in two stages in 46 cities and issued a conclusion on June 14, 2020, concluded that the main causative agent of AB is representatives of the Enterobacteriaceae family (88.0%). *E. coli, Klebsiella spp.*, and *Staphylococcus spp.* accounts for 3%–10% [20].

The peculiarity of the structure of gram-negative bacteria allows them to attach to the urothelium and prevents them from being washed out with urine; this refers to the entire *Enterobacteriaceae* family, as well as to *E. coli* and *Klebsiella spp* [14]. The main criterion for their virulence is the presence of type 1 villi (pill), P-villi (pap), and S-villi (sfa), which are responsible for urothelium adhesion. The resulting film inside the epithelial cells protects the microorganisms, which serves as an adaptive mechanism. Colonies that are surrounded by matrix biofilm protrude into the bladder lumen in the form of cocoons that prevent the washing out of microorganisms with urine [14, 21].

In *Staphylococcus spp.*, the main pathogenicity factor is the presence of flagella, which effectively reaches the cell surface, as well as the presence of ligand-receptor interaction, through which pathogens activate transduction signaling pathways, thus receptor activation occurs [15].

G. Andersson established that it is the intracellular matrix cocoons, or rather their rupture and penetration of bacteria into the urine, which cause recurrent bladder infections, despite antibiotic therapy and body defense factors [21, 22].

The physiological and anatomical aspects of the body of females (compared to men) create a predisposition to UTI as follows [23]:

– a decreased rate of urine passage;

– the proximity of the urethra to the rectum and vagina;

– decreased tone of the bladder and ureters;

– increased residual urine volume;

– noticeable urethral shortening and dilatation;

– high estrogen concentration;

– development of vesicoureteral reflux;

– change in the urine acidity, "physiological hyperventilation," which causes alkalosis and bicarbonaturia;

– increased concentration of protein, glucose, steroid hormones; urine becomes persistently alkaline;

– the formation of physiological hydronephrosis is due to increased upper ureters and renal pelvis, which leads to an increased risk of AB and pyelonephritis in the later stages.

These indicators almost do not differ in young pregnant females from adult females due to puberty acceleration [24].

Factors intensifying bacterial invasion usually include an active sexual life and lower UTIs. The migration of bacteria to the upper urinary tract is usually due to a growing uterus and increased bladder pressure [25].

The Russian Clinical Guidelines for Urology and the Federal Clinical Guidelines 2020, as well as the European Guidelines of the Association of Urology 2020, proposed screening of pregnant females for AB, and with its detection, antibiotic therapy is administered [26]. Additionally, Professor Edgar Lerm [27], in his work on AB (2021), revealed that bladder catheterization in young females has no clinical significance.

Bacteriuria in the majority of pregnant females is detected at their early registration, although approximately 1%–3% of cases are detected in the later stages [28].

This diagnosis is particularly important at a term of 9–17 weeks of gestation. The risk of bacterial vaginosis in pregnant females in 29%–35% of cases should be considered [29, 30], which is not detected promptly by doctors. No typical complaints or symptoms are revealed during a medical examination in AB [29].

Significant changes in the concept of AB occurred after the article by Thomas E. Finucane entitled "Urinary tract infections as a requiem for a heavyweight" [31]. This catchy title clarifies that views on the pathogenesis and treatment of UTIs have dramatically changed, and what previously seemed reliable started to be questioned. The author says that all people in a normal state have bacteriuria. Additionally, UTI is a diagnosis that is often unreasonably used. The term "bacteriuria" has also been criticized, and the author proposes to replace it with "urinary tract microbiome."

Modern research methods determine that the urinary tract is represented by a complex microbial community. Accepting the presence of a urinary microbiome, which was previously unrecognizable using standard culture methods, allows a new perspective on the issue of UTIs and particularly AB. The author argued that most people treated for UTIs would better avoid treatment at all and called for the optimization of therapy and the exclusion of unreasonable antibiotic use [31].

The following are the types of AB diagnostics:

a) Griess nitrite test, when, under the influence of bacteria, nitrites are reduced to nitrates and are determined using the Griess reagent;

b) Gram-staining of a smear from urine sediment;

c) counting chambers;

d) slide-plate centrifuge method;

e) methods for sequencing the urinary microbiota genes;

f) express method for determining pyuria with test strips for leukocyte esterase;

g) the "gold standard" for detecting pathogen and establishing its sensitivity to antibiotics is urine culture that is taken extremely sterile and quickly sent to the laboratory, which prevents the growth of microorganisms to a greater extent [32].

Following the clinical guidelines of the Russian Society of Obstetricians and Gynecologists, the American Society for Infectious Diseases, and the European Association of Urology, the diagnosis of AB in the absence of clinical symptoms of UTI was established by isolating the bacteria in $\geq 10^5$ CFU/ml in two consecutive urine samples taken at an interval of 3–7 days (minimum 24 h), with similarly detected bacteria [25].

The Russian pharmacoepidemiological study on diagnostics and treatment of UTIs in pregnant females (2020) published the results of a bacteriological study, where *Ent. faecalis* (31.4%) and *E. coli* (25.7%) ranked first, *Str. agalactiae* (17.1%) ranked second, the *Kl. pneumoniae* and *Staph. haemolyticus* (8.6%) ranked third [33].

However, test result errors are possible when non-pathogenic microorganisms enter the urine from the lower urethra [34]. The appearance of bacteria in the urine is probably caused by the violation of urine collection hygiene. The bacteria in the

urine are isolated using chemical tests and microscopy, as well as bacteriological tests. According to McIsaac, a false positive response with a single culture can be >50% [33, 34].

Preis et al. experimented in 2016, where they isolated two *E. coli* isolates from two female patients. Case 1 had cystitis (E78) while case 2 had no UTI symptoms (E75). Their results revealed that the strain of the microorganism from the female without UTI signs (E75) is similar to the strain of the avian pathogen, and the strain isolated from the woman with cystitis (E75) is often found in the human bladder [35]. The work of Yaroslav Zdziarsky (sequencing of the *E. coli* genome) revealed that more than half of the strains leading to AB developed from uropathogenic *E. coli* strains that lost their virulence genes [36].

The conclusion "antibiotic resistance is the main scourge of our time" was made by the Canadian scientist L.E. Nicolle in his article entitled "A paradigm shift towards no treatment of asymptomatic bacteriuria" [37]. However, understandably, the question of prescribing antibiotic therapy should not be in high-risk groups [38].

A Cochrane study [39] revealed that antibiotic therapy in AB reduces the incidence of pyelonephritis, preterm delivery, and low birth weight babies [39].

However, the authors point to the unjustified prescription of screening programs, since determining the degree of effects due to the low level of an evidence base is difficult [39].

The Russian National Clinical Guidelines for the Treatment of UTIs stated that treating AB after 12–15 weeks of gestation is desirable. In antibiotic therapy prescription, the findings of urine culture for flora, antibiotic sensitivity, and microorganism resistance are considerably necessary [40].

The treatment of choice is phosphonic acid, thioctic acid, and nitrofurans. Phosphonic acid is the main drug of therapy, which blocks the adhesion of microorganisms to the urothelium and does not lose its concentration in the urine for a long time after administration. Nitrofurans are characterized by the ability to destroy microorganisms and interfere with the metabolism of bacterial carbohydrates, thereby inhibiting acetyl-coenzyme A. They are prescribed for 7 days and only up to week 36 of pregnancy. Admission later than this can lead to hemolytic anemia of the fetus and newborn [41–43].

Nikirovsky (2020) revealed that 46.8% of physicians considered fosfomycin as the drug of choice, 26.6% preferred amoxiclav, 25.3% chose drugs from the cephalosporin group, and 1.3% chose herbal drugs [33].

In the future, a monthly culture of the urine should be performed to control possible relapses after treatment. In 16%–33% of cases, the disease recurs, and ruling out structural and functional disorders in the urinary system and treatment based on the sensitivity of microorganisms to antibiotics is necessary [33, 44, 45].

Attention should also be paid to the studies conducted by Gessner in 2016 on mice [46]. He proved the protective effect on the intestinal microbiota of a herbal medicinal product of combined action, which includes centaury herb, medicinal lovage root, and Rosmarinus officinalis leaves. During its intake, the microbiota is represented by a wider variety of species.

S.V. Shkodkin conducted a clinical study in 2020–2021, where preliminary obtained results suggested that the use of a combined herbal medicinal product in pregnant females with AB can be an effective alternative for antibiotics [45].

A decisive end to the creation of rational methods of treating AB cannot be marked yet. Currently, on the territory of the Russian Federation, antibacterial therapy is recognized as the only effective method of treating AB, included in Order No. 1130n [39]. Treatment is empirically performed, considering the tolerability of drugs during pregnancy, as well as the safety criteria; all this is based on antibiotic resistance and sensitivity [38, 47, 48].

Conclusion

Thus, the analysis of contemporary literature demonstrates a high level of infection and prevalence of AB in pregnant females, which confirms the relevance of the problem. Timely diagnostics and treatment of AB in young pregnant females are an important part of urinary system disease prevention, especially the kidneys. The relationship between AB and the high incidence of complications in pregnancy and childbirth justifies the need for further research in the issues of early diagnostics and prognosis of AB using modern technologies. The high probability of obstetric and perinatal complications due to AB in young females requires the prevention of AB starting from early pregnancy.

Author contributions. D.G.S. wrote the manuscript; I.B.F. was the research supervisor; D.G.S., Yu.N.F., L.A.F., and L.A.G. conducted the research, collected the material, and performed its statistical processing, performed data analysis; D.G.S. analyzed and interpreted the data obtained, edited the draft and final versions of the manuscript; D.G.S., A.Yu.L., S.A.G., and L.A.G. edited the final version of the manuscript.

Funding. The study had no external funding.

Conflict of interest. The authors declare no conflict of interest.

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