Asymptomatic bacteriuria in pregnancy from the perspective of public health and maternal health care: review and case report

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ABSTRACT
The present mini-review attempts to analyse the incidence, microbial agents and complications of asymptomatic bacteriuria (ASB) in pregnancy. Although there are regional differences in the incidence and microflora involved in ASB in different countries and geographical areas, the prevalence of ASB in pregnant women is generally high and its complications aggravate pregnancy outcomes and exacerbate maternal and foetal morbidity. This makes ASB in pregnancy particularly important from a public health perspective, suggesting that all pregnant women should be subject to routine ASB testing. Another aspect that is highlighted here is the need for general consensus guidelines for treatment of ASB in pregnancy: recommended duration of treatment, types of antibiotics suitable for use in pregnancy, adverse side effects, both maternal and foetal. Finally, this paper describes a case of ASB in a pregnant woman, with Klebsiella pneumoniae identified as the causative agent. The pregnant woman had typical ASB-associated complications combined with an atypical symptom: urinary retention in early postpartum period, which, to the best of our knowledge, is described here for the first time.

KEYWORDS
Asymptomatic bacteriuria; pregnancy; treatment

Introduction
Asymptomatic bacteriuria (ASB) is defined as the occurrence of significant bacteriuria with no clinical or laboratory findings of inflammatory process in the urinary tract.[1,2] In pregnancy, there are hormonal, metabolic and mechanical factors that provide conditions favourable for microbial growth in urine and facilitate a greater incidence of ASB in pregnant women. These include:
- changes in urine composition, i.e. higher levels of glucose, amino acid or other nutrients;
- urine retention in the bladder due to mechanical factors;
- reflux of urine from the bladder back up the ureters and to the renal pelvis due to relaxation of the vesicoureteral junction; etc.[3,4]

A review of literature on ASB in pregnancy calls attention to some open questions concerning the significance of ASB for public health and maternal health care:
- whether there are regional differences in the microbial agents that cause ASB in pregnant women in different countries and geographical areas in terms of species, incidence and antibiotic sensitivity and what treatment recommendations could be given;
- considerations in the diagnosis of ASB.

This paper attempts to address these open questions based on a review of an adequately large number of reports on ASB in pregnancy and a description of a case of ASB in a pregnant woman with many ASB-associated complications combined with an atypical symptom: urinary retention in early postpartum period, which, to the best of our knowledge, is described here for the first time.

Incidence of ASB in pregnancy
The incidence of ASB in pregnant women is generally reported to range from 2.5% to over 10%, although there are certain variations in different countries and geographical regions. For example, ASB screening in pregnant women in Turkey has suggested incidence of 8.5%, [5] and 10.7% in Nigeria,[6] 12.3% in Brazil,[7] 13.2% in India [8] and 10.4% in North-west Ethiopia.[9] It is
commonly accepted that in order for such incidence data to be reliable, an adequately large number of cases need to be analysed. The largest retrospective randomized population study on ASB in pregnancy, which was carried out in Israel, includes ASB screening in 199,093 pregnant women and reports ASB prevalence in 2.5% of cases, i.e. in 4890 pregnant women.[2] These reports demonstrate that the incidence of ASB in pregnancy may vary to a large extent in different countries and geographical regions. However, the underlying causes of this higher incidence in some populations largely remain unknown.

**ASB-associated complications in pregnancy**

The most common complications reported in pregnant women with ASB include higher incidence of preterm labour, i.e. about 13.3% as compared to 7.6% in the normal obstetric population; higher incidence of preterm amniotic sac rupture; higher incidence of oligohydramnios or polyhydramnios and higher incidence of recurrent pregnancy loss.[2,3,10–13] In this context, the costs and benefits of ASB routine screening in pregnant women have also been discussed.[14]

The most severe complication in pregnant women with ASB is acute pyelonephritis. Its incidence rate is 20%–30%, with a risk of urosepsis, higher maternal and foetal morbidity.[3] Acute antipar tumpyelonephritis is associated with adverse perinatal outcomes and specifically is an independent risk factor for preterm delivery.[15]

A recent study[16] reported data from a retrospective analysis of the incidence and complications of acute pyelonephritis in pregnancy in the United States over a period of 18 years. The women included in the study had undergone routine prenatal screening and ASB treatment. The study reports the following complications: anaemia in 26.3% of pregnant women with pyelonephritis vs. 11.4% in those without pyelonephritis, septicemia in 1.9% vs. 0.03%, acute pulmonary insufficiency in 0.5% vs. 0.04%, acute renal dysfunction in 0.4% vs. 0.03% and spontaneous preterm birth in 10.9% vs. 7.9%.[16]

These statistics indicate that, although the incidence of ASB in pregnancy varies in different countries and geographic regions, ASB could overall be considered to affect a significant number of pregnant women worldwide. Moreover, there is accumulating evidence that ASB-associated complications aggravate pregnancy outcomes and increase maternal and neonatal morbidity. ASB could be considered to be the most important risk factor for occurrence of prenatal and postnatal acute pyelonephritis with a risk of urosepsis, which may be life-threatening for the mother and foetus. In other words, an ever growing amount of data appear to suggest that ASB is diagnosed in a comparatively large number of pregnant women and often leads to serious complications, which aggravate maternal and foetal morbidity and may even be fatal to both mother and/or foetus. Therefore, ASB in pregnancy could be considered relevant from the perspective of public health and maternal health care.

**Microbial agents and antibiotic resistance**

Most reports on ASB in pregnancy pinpoint *Escherichia coli* as the most prevalent agent identified in screening tests. *E. coli* can readily colonize and penetrate the urinary tract endothelium. For example, it has been shown that *E. coli* isolates from pregnant women with ASB in France has similar virulence potential as *E. coli* isolates from cases of cystitis.[17] In the large-scale study in Israel,[2] *E. coli* is identified in 58.9% of ASB cases in pregnancy; *Proteus mirabilis* in 8.4%; group B Streptococcus in 4%; *Pseudomonas aeruginosa* in 5%. In Turkey,[5] screening tests for ASB in pregnant women show *E. coli* isolates in 76.6% of cases, with *Klebsiella pneumoniae* being the second prevalent agent (14.6%). Unlike these reports, in a regional study in Ethiopia,[9] the prevalent agents in ASB cases in pregnancy are coagulase-negative Staphylococcus species in 32.6% of cases, followed by *E. coli* in 26.1% and *Staphylococcus aureus* in 13%.

In Bulgaria, in 65 cases of pregnant women, treated by us in our hospital, mean age of 31.3 years, with ASB in the second and third trimester, the following microbial agents were isolated: *E. coli* in 41.9% of cases, *Streptococcus saprophyticus* in 18.4%, *S. aureus* in 13.7%, *P. mirabilis* in 9.2%, *K. pneumoniae* in 9.2%, *Enterococcus faecalis* in 4.5%, *P. aeruginosa* in 3.1%.

As a matter of fact, over the last decade, there is a growing number of ASB cases reported to be caused by *K. pneumoniae* in New York and other parts of the United States.[18,19] Indeed, most studies on the microflora involved in ASB in pregnancy report *K. pneumoniae* as the second most prevalent agent, accounting for up to 14.6% of cases, after *E. coli* (up to 76.6% of cases). Notably, in most studies, group B Streptococcus is not identified in pregnant women with ASB, but its prevalence is significant in the large-scale study in Israel.[2]

Studies on the antibiotic sensitivity of microbial agents in cases of ASB in pregnancy report considerable prevalence of isolates resistant to two or more antibiotics, which is particularly so in Gram-negative isolates. Such resistance patterns are typical in Enterobacteriaceae, and both *E. coli* and *K. pneumoniae* belong to this group.[20,21]
Treatment of ASB in pregnancy includes antibiotic(s) to which each particular isolate is sensitive. A well-designed prospective cohort study in pregnant women with ASB indicates that timely diagnosis and antibiotic treatment reduces the incidence of acute pyelonephritis, preterm labour and delivery of a lower birth weight foetus, i.e. small for gestational age.[22]

Some authors suggest that, in most patients, ASB is a benign condition and treatment is not necessary, except for cases of ASB in pregnant women and patients undergoing urologic surgery, where antibiotic treatment is necessary.[23] The effectiveness of fosfomycin trometamol used as a single-dose oral treatment has been reviewed compared to a 4- and 7-day course.[24] In case of hospitalization for treatment of K. pneumoniae urinary infections, fosfomycin trometamol can also be administered intravenously. According to another report, the antibiotic cefoperazone/sulbactam, which is effective against both Gram-negative and Gram-positive microorganisms, can be used as an empiric therapy in pregnant women with ASB.[25] Moreover, it has been emphasized that the incidence of ASB is higher in women with diabetes mellitus and pregnant women.[26] Recently, more attention has been drawn to the effects of antibiotic treatment of ASB and urinary tract infections during pregnancy which may have long-term consequences for the neonate, such as epilepsy and antibiotic resistance. More research is needed to further explore and confirm these findings.[26] In this context, what has also received attention is the potential long-term effects of antibiotic treatment of ASB during pregnancy on the neonate.[26]

Based on a review of reports addressing the microflora involved in ASB and treatment of ASB in pregnancy, the following issues could be given special consideration:

- the choice of antibiotic treatment of ASB in pregnancy, in each individual case, should be based on diagnosis of significant bacteriuria, i.e. colony-forming units (CFU) of 10 CFU/mL and more,[5] and on results from antibiotic sensitivity tests;
- empiric treatment of ASB in pregnancy is not considered appropriate. There are still no general consensus guidelines for treatment of ASB in pregnancy in terms of effectiveness, duration of treatment adverse side effects and contraindications for some antibiotics in pregnancy. The only available consensus document is the Spanish Recommendations 2012 Update on the prevention of neonatal group B streptococcal infections, which are the most common cause of early-onset neonatal sepsis.[27]

In an attempt to address these issues, Guinto et al. [28] analysed the results from five randomized studies involving 1140 pregnant women with ASB. However, it was not possible to draw any definite conclusion on the most effective and safest antibiotics for the initial treatment of ASB in pregnancy due to differences in the antibiotic regimens used in each of the five reviewed trials.

Some cost analyses strongly recommend to screen for bacteriuria in all pregnant women on the first prenatal visit in a medical centre or hospital.[29] Such screening allows early diagnosis and adequate antibiotic treatment of pregnant women with ASB. In case of lack of routine screening for ASB, diagnosis may be assumed based on history of previous pregnancies with preterm delivery between the 16th and 36th week of gestation. Risk of ASB is considered higher in pregnant women with a history of more than one preterm delivery.[29] Some authors recommend screening for ASB in pregnancy to be performed when the incidence of ASB is over 2% and that of pyelonephritis, over 13%.[29,30]

Considering the optimal time for screening for ASB in pregnancy discussed above, we hold the opinion that it is also necessary to routinely screen for ASB in all pregnant women at first diagnosis of pregnancy. In such cases, diagnosis of ASB would give grounds for adequate antibiotic treatment to prevent postnatal complications, both in mothers and neonates. This approach was taken in the case report presented below.

Case report
A pregnant woman, aged 27, in the 32nd week of gestation was hospitalized with symptoms of amniotic sac rupture within 24 hours of diagnosis. She was having a third pregnancy in a row, having delivered two live infants.

The patient’s somatic status was normal. Examination of the lungs showed vesicular breath sounds, normal heart rate of 82 beats per minute, arterial pressure of 120/70 mm Hg.

The patient did not report any previous or concomitant diseases. She did not have symptomatic high body temperature, lower back pain or miction disorders. No family case history was reported.

Regarding the obstetrical status, the external genital organs were typical of a woman who has given birth. The pelvic measurements were normal. The cervix was smooth, with 4 cm dilation. The amniotic sac was open. Regarding the anterior foetus part presentation, the head of the foetus was freely movable above the pelvic inlet.

Standard paraclinical examinations were performed at admittance. The blood count showed the following: erythrocytes 3.59 T/L, haemoglobin 120 g/L haematocrit
0.36 L/L, thrombocytes 202 G/L, leukocytes 15.7 G/L; differential blood count — neutrophils 74.2%, lymphocytes 11.3%, monocytes 3.5%, eosinophils 0%, basophils 1%. Other blood test parameters were as follows: blood group A /Rh+/, INR 1.0, fibrinogen 3.37 g/L. Urine test results were as follows: pH 6.0, protein neg., bilirubin neg., glucose neg., ketones neg., blood neg., leucocytes neg., normal urobilinogen, specific gravity 1.020 g/mL, nitrates neg.

Microbiology urine culture test revealed significant bacteriuria with *K. pneumoniae* susceptible to imipenem, gentamicin, amikacin, cefuroxime, ceftriaxone, ciprofloxacín, cefepime, ceftazidime, cefoperazone/sulbactam, ampicillin/sulbactam; and resistant to three antibiotics: cefazolin, fosfomycin, ampicillin.

The foetal ultrasound test showed a live foetus with anterior head position, biparietal diameter of 80.2 mm, abdominal circumference of 280 mm, femur length of 57.5 mm, ultrasound gestation age 31 ± 4 d, anterior placenta with a maturity of grade III, low amniotic fluid.

Non-stress-test (foetal monitor screening) showed early and late decelerations — up to 60 beats per minute. Natural delivery proceeded. Due to sluggish contractions, 5 IU oxytocin was infused in a physiological bank serum i.v. Partus prematurus cum episiotomia. A live male foetus was delivered, 2300 g in weight and 45 cm in height in a depressive condition which improved following reanimation actions. The woman in labour was prescribed amikacin 3 x 500 mg i.v. for 8 days. She did not report any symptoms for a couple of days. On the third day, the patient reported cease of spontaneous urine flow, which required bladder catheterization with evacuation of 600 mL of urine. When a urine sample was examined by a laboratory test, no pathology was shown. The prescribed therapy included atropinum sulphuricum and buscolysin (hyoscine butylbromide) injections for evacuation of urine.

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