The significance of maternal asymptomatic bacteriuria during pregnancy on long-term offspring infectious hospitalizations

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Abstract

Asymptomatic bacteriuria (ASB) is a well-acknowledged infectious entity during pregnancy; yet its long-term implications are not well investigated. The present study aimed to test the association between maternal ASB during pregnancy and long-term offspring infectious hospitalizations. A population-based cohort analysis was conducted, comparing the incidence of long-term infectious-related hospitalizations of offspring born to mothers who were diagnosed with ASB during pregnancy, and those who did not have ASB. The study was conducted at a tertiary medical center and included all singleton deliveries between the years 1991 and 2014. Infectious morbidities were based on a predefined set of International Classification of Disease-9 codes. A Kaplan–Meier survival curve compared cumulative infectious hospitalization incidence between the groups, and a Cox regression model was used to adjust for confounding variables. During the study period, 212,984 deliveries met inclusion criteria. Of them, 5378 (2.5%) were diagnosed with ASB. As compared to offspring of non-ASB mothers, total long-term infectious hospitalizations were significantly higher among children to mothers who were diagnosed with ASB (13.1% vs. 11.1%, OR = 1.2, 95% CI 1.11–1.30, P ≤ 0.001). Likewise, a Kaplan–Meier curve demonstrated higher cumulative incidence of infectious hospitalizations among children born to mothers with ASB (log rank, P = 0.006). In the Cox regression model, while controlling for maternal age, diabetes mellitus, ethnicity, hypertensive disorders, and gestational age, maternal ASB was noted as an independent risk factor for long-term infectious morbidity in the offspring (adjusted HR = 1.1, 95% CI 1.01–1.17, P = 0.042). ASB during pregnancy increases offspring susceptibility to long-term infectious hospitalizations.

Introduction

Asymptomatic bacteriuria (ASB) is defined by the Infectious Diseases Society of America guidelines as two sequential urine samples from women without symptoms and signs of urinary tract infection (UTI), containing 10^5 cfu/ml or more, of the same organism.1–3 The prevalence of ASB ranges between 2% and 7%.4 The predominant uropathogen in ASB, for both pregnant and non-pregnant women, is E. coli.1–7

During pregnancy marked anatomical and physiological changes occur, including in the urinary system. The smooth muscle relaxation in bladder myocytes and subsequent ureteral dilatation that accompany pregnancy are thought to facilitate the ascent of bacteria from the bladder to the kidney, resulting in the greater propensity for bacteria to reach the kidneys and cause pyelonephritis.5–10 In addition, pregnancy is considered as a special immunological state characterized by an attenuation of the acquired immune response that may also contribute to infection susceptibility.9,13

Consequently, if ASB is untreated, up to 30% of mothers develop acute pyelonephritis.2 Pyelonephritis during pregnancy is associated with significant morbidity for both the mother and the fetus.14 Recent studies showed an association between women with untreated bacteriuria and an increased risk of preterm birth, preterm premature rupture of membranes, low birth weight (LBW), increased risk of preeclampsia, low 5-min Apgar score, and even perinatal mortality.4,8,13 Therefore, proper screening and treatment of ASB are necessary to prevent complications.2,6,15 The management of ASB includes antibiotic therapy tailored to culture results and follow-up cultures to confirm sterilization of the urine.

Long-term consequences of antibiotic treatment for maternal ASB on the offspring are not systematically discussed in the medical literature. Although antibiotic treatment of ASB reduces perinatal morbidity, effects of such treatment later on in childhood should be explored. The aim of the current study was to address the possible association between maternal prenatal ASB and the risk for long-term offspring infectious morbidity requiring hospitalization.
Methods

In this population-based retrospective cohort study, all infants born between the years 1991 and 2014 at the Soroka University Medical Center (SUMC), the largest birth center in Israel, were included. SUMC is the sole tertiary hospital in the southern region of Israel (Negev), serving the entire population in this region. Thus, the study was based on nonselective population data. The research was done in accordance with the 1964 Helsinki Declaration and its subsequent modifications’ ethical principles (Helsinki Declaration 1975, revision 2013). In addition, the institutional oversight board gave their approval (SUMC IRB Committee).

The exposure group was defined as offspring to mothers with ASB that was diagnosed during routine prenatal care testing. Urine cultures are performed as part of the intensive treatment offered by Israel’s national health services to all pregnant women. Four multiple gestations were excluded from the study due to its association with earlier termination of pregnancy and small gestational age which increase morbidity. We also excluded from the registry fetuses with congenital anomalies due to their increased morbidity and mortality rates. Perinatal mortality cases were not included for long-term analysis. Additionally, mothers with a diagnosis of UTI during pregnancy or delivery, as well as women with insufficient prenatal care were excluded from the study. The latter may have incurred undiagnosed ASB, potentially causing misclassification in the registry.

The comparison conducted was between offspring born to mothers diagnosed with ASB during pregnancy and offspring born to nonexposed mothers, based on the perinatal database. A variety of adverse perinatal characteristics were investigated including gestational age, preterm delivery (<37 weeks’ gestation), cesarean delivery (CD), LBW (defined as birth weight <2500 g), low Apgar score at 1 and 5 min (defined as Apgar score <7), small for gestational age (SGA, defined as birth weight<5th percentile for gestational age and gender), and gender. Hospitalizations due to infectious disease with offspring under the age of 18 were analyzed using diagnoses predefined by a series of International Classification of Disease (ICD)-9 codes seen in the Supplementary Table 5. If any of the following happened, the follow-up was discontinued: hospitalization due to infectious morbidity, reaching the age of 18, hospitalization culminating in death, or completion of the research duration.

The study was based on two computerized data sets: the first is the perinatal database of the Obstetric and Gynecologic department in SUMC, including information that was documented by obstetricians following delivery. The second, a pool of computerized children’s hospitalizations in SUMC (Demog-ICD-9), includes demographic data and medical diagnosis during hospitalization. The two databases were crosslinked and merged based on the patients’ ID (mother and child). All diagnoses were classified by the ICD-9.

Statistical analysis

Bivariable analysis was performed to compare background characteristics between the two study groups, as well as the dependent variables. The bivariable analysis included Chi-square tests for categorical variables, and t-tests or Mann–Whitney U tests for continuous variables according to their distribution. Cumulative incidence rates were compared using Kaplan–Meier test using the log-rank test to determine significant differences. A Cox proportional hazards model was conducted to compare infectious-related hospitalizations risk among offspring born to mothers who were diagnosed with ASB during pregnancy and offspring born to nonexposed mothers. The model adjusted for potential confounders based on the bivariable analysis, and on clinical importance of the variables. Potential confounders included maternal age, parity, hypertensive disorders of pregnancy, diabetes mellitus, ethnicity, and gestational age.

The mothers in the cohort were entered as clusters to account for dependence between siblings. The final model was chosen based on best fit and minimal –2log likelihood. All analyses were two-sided, with a power = 80% and alpha = 0.05. The analysis was performed using SPSS package 23rd ed. as well as the STATA software 12th ed.

Results

There were 212,984 singleton deliveries that met inclusion criteria. Of them, 5378 (2.5%) mothers were diagnosed with ASB during pregnancy and their offspring considered the exposed group. Maternal characteristics of the study population by exposure status are presented in Table 1. The mothers who had been exposed to ASB during pregnancy were younger, and primigravidae. Bedouin women were more likely to have ASB as compared to Jewish women. Women with diabetes mellitus (pregestational or gestational) and hypertension (chronic, gestational, or preeclampsia) were more prone to develop ASB. Our cohort includes two different socioeconomic groups based on ethnicity – Bedouin and Jewish. According to data from government sources, rates of unemployment and low income prevail in the Bedouin society.

Table 2 demonstrates the characteristics of labor and pregnancy by contrasting pregnancy outcomes between the two groups. Mean birth weight, gestational age, and Apgar score at 5 min were lower in the ASB-exposed group. Rates of preterm delivery, CD, LBW infants, SGA, and Low Apgar score at 1 min were higher in the exposed group. Table 3 displays the hospitalization rates as well as the offspring’s long-term infectious morbidities. The incidence of otorhinolaryngological, respiratory infections, skin infections, and systemic febrile syndromes rates were significantly higher in children from the ASB-exposed group. The rates of all other infectious morbidities were similar in both categories. In the group of children born to ASB-exposed mothers, the overall infectious-related hospitalization rate was significantly higher (13.1% vs. 15.1%, OR = 1.20, 95% CI 1.11–1.30, P < 0.001). Children born to mothers who had ASB during their pregnancy had a higher cumulative rate of infectious-related hospitalizations than children born to non-ASB infected mothers, according to the Kaplan–Meier survival curve (Fig. 1 log rank P = 0.006). Table 4 illustrates the association between maternal ASB during pregnancy and the long-term probability of infectious-related hospitalizations in children (up to the age of 18 years) using the Cox regression. As is being shown in Table 4, maternal ASB during pregnancy was a significant and independent risk factor for offspring’s long-term infectious-related hospitalization with an adjusted hazard ratio of 1.08 (95% CI 1.01–1.17, P = 0.042).

Discussion

Offspring to mothers who were diagnosed with ASB during their pregnancy had an increased long-term risk for neonatal and pediatric infectious morbidity, especially otorhinolaryngological, respiratory, and skin infections as well as nonspecific febrile disease. Additional infectious complications also had a higher prevalence.
in the maternal ASB category; however these findings were not statistically significant, possibly due to a limited number of cases.

The studied association has been previously investigated by Patrick. However, in her study there was no specification on whether the mothers were symptomatic or asymptomatic.17 The findings in that paper concur with ours regarding infections in the newborn but lack data on long-term infectious morbidity. In addition, one recent study of pregnant women with symptomatic UTI showed increased otorhinolaryngological and respiratory infections in offspring.18 It is therefore plausible to suggest that bacteriuria by itself, with or without symptoms, is associated with respiratory infections in early life.

Several mechanisms may explain the association between maternal bacteriuria and offspring infections, including mother–offspring transmission of pathogens, attenuated immune response to such bacteria, or late consequences of antibiotic treatment of ASB.

Table 1. Maternal characteristics of the study population by exposure status

| Characteristics                          | ASB in pregnancy (N = 5378 (2.5%)) | No ASB in pregnancy (N = 207,606 (97%)) | Unadjusted OR; 95% confidence interval | P-value |
|-----------------------------------------|-------------------------------------|------------------------------------------|----------------------------------------|---------|
| Maternal age (mean ± SD)                | 27.59 ± 5.95                        | 28.24 ± 5.80                             | –                                      | <0.001  |
| Parity                                  |                                     |                                          | –                                      | <0.001  |
| 1                                       | 1734 (32.2)                         | 50,080 (24.1)                           | –                                      |         |
| 2–4                                     | 2522 (46.9)                         | 107,413 (51.8)                          | –                                      |         |
| 5+                                      | 1121 (20.8)                         | 50,063 (24.1)                           | –                                      |         |
| Hypertensive disorders of pregnancya    | 437 (8.1)                           | 10,656 (5.1)                            | 1.64                                   | <0.001  |
| 1.48–1.81                               |                                     |                                          |                                        |         |
| Diabetesb                               | 506 (9.4)                           | 10,985 (5.3)                            | 1.86                                   | <0.001  |
| 1.69–2.04                               |                                     |                                          |                                        |         |
| Ethnicity                               |                                     |                                          |                                        |         |
| Bedouin                                 | 2817 (2.7)                          | 103,419 (97.3)                          | 0.9                                    | <0.001  |
| Jew                                     | 2561 (2.4)                          | 104,187 (97.6)                          | 0.86–0.95                              |         |
| Gestational age (mean ± SD)             | 38.88 ± 2.14                        | 39.15 ± 1.85                            | –                                      | <0.001  |

aIncluding pregestational, gestational hypertension, and preeclampsia.
bIncluding pregestational and gestational diabetes.

Table 2. Pregnancy and delivery characteristics by exposure status

| Pregnancy outcome               | ASB in pregnancy (N = 5378 (2.5%)) | No ASB in pregnancy (N = 207,606 (97%)) | Unadjusted OR; 95% confidence interval | P-value |
|---------------------------------|-------------------------------------|------------------------------------------|----------------------------------------|---------|
| Gestational age (mean ± SD)     | 38.88 ± 2.14                        | 39.15 ± 1.85                             | –                                      | <0.001  |
| Preterm deliverya               | 556 (10.3)                          | 13,095 (6.3)                            | 1.71                                   | <0.001  |
| Cesarian delivery               | 976 (18.1)                          | 28,596 (13.8)                           | 1.39                                   | <0.001  |
| Birthweight (mean ± SD)         | 3148.92 ± 532.66                    | 3222.07 ± 492.56                        | –                                      | <0.001  |
| Low birth weight (LBW)b         | 549 (10.2)                          | 12,705 (6.1)                            | 1.74                                   | <0.001  |
| Low Apgar score at 1 minc       | 279 (5.2)                           | 9473 (4.6)                              | 1.14                                   | 0.030   |
| Low Apgar score at 5 minc       | 64 (1.2)                            | 3216 (1.5)                              | 0.77                                   | 0.036   |
| SGAa                            | 325 (6)                             | 8876 (4.3)                              | 1.4                                    | <0.001  |
| Gender                          |                                     |                                          |                                        |         |
| Female                          | 2634 (49.0)                         | 102,003 (49.1)                          | 1.01                                   | 0.825   |
| Male                            | 2744 (51.0)                         | 105,603 (50.9)                          | 0.95–1.06                              |         |

aPreterm delivery < 37+0 weeks.
bLBW < 2500 gr.
cApgar score < 7.
dBW < 10th percentile for gestational age.
Maternal transfer of uropathogens was suggested by Patrick to be a major cause of infections after birth. In her study, maternal uropathogens were shown to be transferred to the fetus via amniotic fluid, umbilical cord blood, and placenta. Bacterial translocation was evident also in ASB. Patrick alluded that maternal uropathogens colonized fetal tissue and later on acted as pathogens. Moreover, Patrick had observed an increased rate of ASB as well as clinical pyelonephritis in infants born to bacteriuric mothers, affirming her assumption.

In addition, Cooke et al. observed nonmaternal antibodies to *E. coli* in infants of mothers with bacteriuria, indicating that the infants were exposed to the pathogens. Similarly, Brody et al. reported lymphocyte activation of the fetus in response to maternal urinary bacteria even in cases where mothers were asymptomatic. All these reports suggest that higher infection rates in children to mothers with ASB may result from prenatal colonization.

Another assumption refers to a dysregulated immune response to uropathogens due to exposure in very early life, contributing later on to increased pathogenicity of such bacteria. Studies have suggested a number of mechanisms leading to the aberrant immune response which include immune tolerance and activation of specific cytokines. The fetal innate immune system is shifted to a more antiinflammatory reaction dominated by TH2 and TH17 cells as opposed to the proinflammatory TH1 response which is critical for combating infections in mature life. Hence, exposure to uropathogens in utero induces tolerance which in turn enables invasiveness of such pathogens in later life. Moreover, chorioamnionitis increased the expression of interleukin-6, tumor necrosis factor-a, interferon-b, as well as other cytokines in uterus. These

| Table 3. Long-term infectious morbidities requiring hospitalizations in children (up to the age of 18 years) born to mothers with and without ASB in pregnancy |
|---------------------------------------------|----------------|----------------|----------------|----------------|
| Infectious morbidity                    | ASB in pregnancy | No ASB in pregnancy | Unadjusted OR; 95% confidence interval | P-value |
|---------------------------------------------|----------------|----------------|----------------|----------------|
| Ear nose and throat infections             | 111 (2.1)       | 3111 (1.5)     | 1.39           | 1.14–1.68      | <0.001 |
| Gastrointestinal infections                | 105 (2.0)       | 3518 (1.7)     | 1.56           | 0.95–1.41      | 0.15   |
| Neonatal infections                        | 16 (0.3)        | 564 (0.3)      | 1.09           | 0.67–1.81      | 0.69   |
| Respiratory infections                     | 333 (6.2)       | 11,524 (5.6)   | 1.12           | 1.00–1.26      | 0.045  |
| Skin infections                            | 1725 (1.2)      | 63 (0.8)       | 1.42           | 1.10–1.82      | 0.008  |
| Systemic febrile syndromes                 | 18 (0.3)        | 414 (0.2)      | 1.69           | 1.05–2.70      | 0.043  |
| Urological infections                       | 40 (0.7)        | 1401 (0.7)     | 1.10           | 0.81–1.51      | 0.51   |
| Viral infections                           | 51 (0.9)        | 1814 (0.9)     | 1.09           | 0.82–1.44      | 0.56   |
| Total infections                           | 704 (13.1)      | 23,129 (11.1)  | 1.20           | 1.11–1.30      | <0.001 |

| Table 4. Multivariable analysis for the association between ASB in pregnancy and offspring long-term infectious morbidity requiring hospitalizations |
|---------------------------------------------|----------------|----------------|----------------|----------------|
| Variables                              | Adjusted HR | 95% CI | P-value |
|---------------------------------------------|----------------|----------------|----------------|
| ASB vs. no ASB                            | 1.08           | 1.01–1.17      | 0.042 |
| Maternal age                             | 0.99           | 0.990–0.994    | <0.001 |
| Gestational age                           | 0.94           | 0.94–0.95      | <0.001 |
| Diabetes mellitus                        | 1.03           | 0.97–1.09      | 0.347 |
| Hypertensive disorders of pregnancy      | 0.98           | 0.93–1.04      | 0.514 |

Fig. 1. Kaplan–Meier curve demonstrating the cumulative incidence of hospitalizations involving infectious morbidity in the offspring of exposed and nonexposed groups (log rank, *P*=0.006).
cytokines are aspirated by the fetus and cause lung injury poten-
tially increasing susceptibility to respiratory infection.21

The influence of antibiotic consumption to treat ASB on infec-
tion in later life has only recently been researched. Currently, the
most common treatment for ASB during pregnancy includes beta-
lactams, nitrofurantoin, and fosfomycin.24 25 These antibiotics
have specifically been shown to induce a sustained decrease of
gut microbiota diversity.26 Antibiotics may change the microbiome
in offspring. It is well established that gut microbiome is involved
in inflammation and immunity. As an example, the pathogenesis
of systemic inflammatory disease such as inflammatory bowel dis-
 ease, multiple sclerosis, systemic inflammatory arthritis, asthma,
and nonalcoholic fatty liver disease has been reported to be related
to the gut microbiota.27 Furthermore, microbiota process gut con-
tent and thus create antigens that shape innate immunity.28
Therefore, changes in microbiome through exposure to antibiotics
may have serious implications on the offspring’s health which are
still not clear at this time.

In contradiction to the concept of the sterile womb, newer data
support the possibility that fetal microbiota may develop in utero
via the placental barrier or through ingestion of amniotic fluids.29
Moreover, certain bacteria from the maternal gut may translocate
to extra-intestinal sites and trigger immune reactions in the fetus.
Studies have shown that memory CD4+ and CD8+ T cells can be
identified toward the end of the first trimester in human fetal gut
which in turn produce various cytokines in response to microbiota,
thereby impacting immunity in the offspring. Treating ASB with anti-
biotics, which is according to standard practice,2 6 15 could therefore
lead to altered microbiota in the mother and fetus with an abnormal
immune response to pathogens, causing susceptibility to infections in
the latter.30 Indeed, it has also been found that the metabolites derived
from microbiota can have a crucial influence on the airway cellular
level that facilitate bacterial invasion which can lead to respiratory
infection.31 These exogenous toxins and inflammatory mediators
which are derived from maternal microbiota come in contact with
fetal oropharynx and skin through the amniotic fluid and induce sus-
cceptibility to infection and inflammation.

Such a sequence of easier bacterial airway penetration and
decreased immunity may explain the higher incidence of respira-
tory infections we saw in our study. In addition we found that,
similarly to previous studies,3 2 ASB was associated with signifi-
cantly higher rates of CD. Such association may be explained by
increased rates of PROM, preterm labor, and Intrauterine
growth restriction associated with ASB.33 It is established that
off-springs born via CD have a less diverse microbiome
than those born through vaginal delivery, possibly increasing
susceptibility to infectious outcomes.34 Such an association
between increased pediatric infections and CD has been reported
previously.35

In summary, the findings in our study can be explained by
altered microbiota, easier bacterial invasion, and attenuated
immune and cytokine response leading to increase in clinical
infection.

The key downside of this research is its retrospective design. As
a result, we can suggest association but not causality. Another limi-
tation is that the infectious cases we collected were only for hospi-
talized children, representing severe infectious cases. While the
hazard ratio was significant but low (1.08), it relates to the spec-
trum of severe infections which require hospitalizations. Future
studies should explore the association between ASB and childhood
infections, which are mostly less severe, and managed in the
community.

An additional limitation is the lack of information on whether or
not any antibiotic was administered, its kind, dose and duration
of the treatment, although it is a common practice at the Health
Maintenance Organization from which the data were extracted.
Thus, it is reasonable to assume that most cases with ASB were
treated.

Indeed, environmental factors, possibly confounding the studied
association, were unavailable and unaccounted for.

Another concern is that the prevalence of ASB in our sample
was at the low range reported in the literature.36 Since the reasons
for the wide range are obscure, we cannot rule out a sampling
bias.37

Our study’s biggest attribute is its large nonselective population-
based cohort, which gives us confidence that our findings
can be inferred to the general population.

In conclusion, our findings suggest that maternal ASB in pregnancy
may have a major impact on offspring predisposition to infections requiring hospitalizations. Future research should focus on
the mechanisms leading to such infections and to prospectively
estimate the net effect of treating ASB, considering the offspring
risk for infectious morbidity.

Supplementary material. For supplementary material accompanying this
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References
1. Rubin RH, Shapiro ED, Andriole VT, Davis RJ, Stamm WE. Evaluation of
new anti-infective drugs for the treatment of urinary tract infection. Infectious Diseases Society of America and the Food and Drug Administra-
tion. Clin Infect Dis [Internet]. 1992; 15(Suppl 1), S216–S227, http://www.ncbi.nlm.nih.gov/pubmed/1477248,
2. Nicolle LE, Gupta K, Bradley SF, et al. Clinical practice guideline for the
management of asymptomatic bacteriuria: 2019 update by the Infectious Diseases Society of America. Clin Infect Dis; 2019; 68(10), 1611–1615.
3. Schnarr J, Small F. Asymptomatic bacteriuria and symptomatic urinary tract infections in pregnancy. Eur J Clin Invest. 2008; 38(25962), 50–57.
4. Sheiner E, Mazor-Drey E, Levy A. Asymptomatic bacteriuria during preg-
nancy. J Matern Neonatal Med. 2009; 22(5), 423–427.
5. Small FM, Vazquez JC. Antibiotics for asymptomatic bacteriuria in preg-
nancy. Cochrane Database Syst Rev. doi: 10.1002/14651858.CD000490.
pub3.
6. Lin K, Fajardo K, U.S. Preventive Services Task Force. Screening for asym-
tomatic bacteriuria in adults: evidence for the U.S. Preventive Services Task
Force reaffirmation recommendation statement. Ann Intern Med [Internet]. 2006; 149(1), W20–W24, =http://annals.org/article.aspx?doi=
10.7326/0003-4819-149-1-200607010-00009-w1
7. Cortes-Penfield NW, Trautner BW, Jump RLP. Urinary tract infection and
asymptomatic bacteriuria in older adults. Infect Dis Clin North Am. 2017;
31(4), 673–688.
8. Mazor-Drey E, Levy A, Schlaeffer F, Sheiner E. Maternal urinary tract infec-
tion: is it independently associated with adverse pregnancy outcome? J Matern Neonatal Med. 2009; 22(2), 124–128.
9. Leeper C, Lutzkanin A. Infections during pregnancy. Prim Care Clin Off
Pract [Internet]. 2018; 45(3), 567–586. DOI10.1016/j.pop.2018.05.013.
10. Lai YJ, Hsu TY, Lan KC, et al. Asymptomatic pyuria in pregnant women
during the first trimester is associated with an increased risk of adverse
obstetrical outcomes. Taiwan J Obstet Gynecol [Internet]. 2017; 56(2),192–195.

https://doi.org/10.1017/S2040174421000593 Published online by Cambridge University Press
11. Nicolle LE. Management of asymptomatic bacteriuria in pregnant women. In *The Lancet Infectious Diseases*. vol. 15, 2015; pp. 1252–1254. Lancet Publishing Group.

12. Petersson C, Hedges S, Stenqvist T, Connell H, Svanborg T. Suppressed antibody and interleukin-6 responses to acute pyelonephritis in pregnancy. *Kidney Int.* 1994; 45(2), 571–577.

13. Kalinderi K, Delkos D, Kalinderis M, Athanasiadis A, Kalogiannidis I. Urinary tract infection during pregnancy: current concepts on a common multifaceted problem. *J Obstet Gynaecol (Lahore)* [Internet]. 2018; 38(4), 448–453. DOI 10.1080/01443615.2017.1370579.

14. Farkash E, Weintraub AY, Sergienko R, Wiznitzer A, Zlotnik A, Sheiner E. Acute antepartum pyelonephritis in pregnancy: a critical analysis of risk factors and outcomes. *Eur J Obstet Gynecol Reprod Biol* [Internet]. 2012; 162(1), 24–27.

15. Keating GM. Fosfomycin trometamol: a review of its use as a single-dose oral treatment for patients with acute lower urinary tract infections and pregnant women with asymptomatic bacteriuria. *Drugs*. 2013; 73(17), 1951–1966.

16. The Bedouin population in the Negev (written in Hebrew). Weissblei, E.

17. Patrick MJ. Influence of maternal renal infection on the foetus and infant. *Arch Dis Child*. 1967; 42(222), 208–213.

18. Cohen R, Gutvirtz G, Wainstock T, Sheiner E. Maternal urinary tract infection during pregnancy and long-term infectious morbidity of the offspring. *Early Hum Dev* [Internet]. 2019; 136(2), 54–59. DOI 10.1016/j.earlhumdev.2019.07.002.

19. Cooke CW, Hallock JA, Wurzel H, Oski FA, Wallach EE. Fetal and maternal outcome in asymptomatic bacteriuria of pregnancy: effects on isohemagglutinin titers. *Obstet Gynecol*. 1970; 36(6), 840–844.

20. Brody JJ, Oski FA, Wallach EE. Neonatal lymphocyte reactivity as an indicator of intrauterine bacterial contact. *Lancet*. 1968; 291(7557), 1396–1398.

21. Zhu T, Zhang L, Qu Y, Mu D. Meta-analysis of antenatal infection and risk of asthma and eczema. *Medicine (United States)*. 2016; 95(35), e4671.

22. Padeh E, Wainstock T, Sheiner E, Landau D, Walfisch A. Gestational age and the long-term impact on children’s infectious urinary morbidity. *Arch Gynecol Obstet* [Internet]. 2019; 299(2), 385–392. DOI 10.1007/s00404-018-4973-4.

23. Keski-Nisula L, Katila MI, Remes S, Heinonen S, Pekkanen J. Intrauterine bacterial growth at birth and risk of asthma and allergic sensitization among offspring at the age of 15 to 17 years. *J Allergy Clin Immunol*. 2009; 123(6), 1305–1311.

24. Enbom JA. Bacteriuria in pregnancy. Therapeutic considerations. *Postgrad Med*. 1971; 49(5), 216–220.

25. Pedler SJ, Bint AJ. Management of bacteriuria in pregnancy. *Drugs*. 1987; 33(4), 413–421.

26. Xu L, Surathu A, Raplee I, et al. The effect of antibiotics on the gut microbiome: a metagenomics analysis of microbial shift and gut antibiotic resistance in antibiotic treated mice. *BMC Genomics*. 2020; 21(1), 1–18.

27. Uchiyama K, Naito Y, Takagi T. Intestinal microbiome as a novel therapeutic target for local and systemic inflammation. In *Pharmacology and Therapeutics*. vol. 199, 2019; pp. 164–172. Elsevier Inc.

28. Gensollen T, Iyer SS, Kasper DL, Blumberg RS. How colonization by microbiota in early life shapes the immune system. *Science*. 2016; 352(6285), 539–544.

29. Walker RW, Clemente JC, Peter I, Loos RJF. The prenatal gut microbiome: are we colonized with bacteria in utero? *Pediatr Obes*. 2017; 12, 3–17.

30. Nyangahu DD, Jaspan HB. Influence of maternal microbiota during pregnancy on infant immunity. *Clin Exp Immunol*. 2019; 198(1), 47–56.

31. Arrieta MC, Stiensma LT, Dimitriu PA, et al. Early infancy microbial and metabolic alterations affect risk of childhood asthma. *Sci Transl Med*. 2013; 5(307), 307ra152.

32. Gehani M, Kapur S, Madhuri SD, et al. Effectiveness of antenatal screening of asymptomatic bacteriuria in reduction of prematurity and low birth weight: evaluating a point-of-care rapid test in a pragmatic randomized controlled study 2021.http://creativecommons.org/licenses/by/4.0/.

33. Byna P, Muova N, Kolli S, Shaik M. A study of risk factors and consequences of asymptomatic bacteriuria in pregnant women and feto-maternal outcome. *Int J Reprod Contracept Obstet Gynecol*. 2015; 4, 1300–1305.

34. Reyman M, van Houten MA, van Baarle D, et al. A study of risk factors and consequences of asymptomatic bacteriuria in reduction of prematurity and low birth weight: evaluating a point-of-care rapid test in a pragmatic randomized controlled study. *Pediatr Infect Dis J*. 2019; 38(2), 176–180.

35. Wainstock T, Walfisch A, Shoham-Vardi I, et al. Term elective cesarean delivery and offspring infectious morbidity: a population-based cohort study. *Pediatr Infect Dis J*. 2019; 38(2), 176–180.

36. Whalley P. Bacteriuria of pregnancy. *Therapeutic considerations*. 1987; 33(4), 413–421.

37. Garnizov TM. Asymptomatic bacteriuria in pregnancy from the perspective of public health and maternal health care: review and case report. *Biotechnol Biotechnol Equip*. 2016; 30(3), 443–447. DOI 10.1080/13102818.2015.1114429.