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

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Original Article

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This study was conducted as part of the requirements for MD degree from the Goldman Medical School at the Faculty of Health Sciences, Ben-Gurion University of the Negev.

Key points: Maternal asymptomatic bacteriuria in pregnancy is an independent risk factor for infectious hospitalizations of the offspring during childhood.

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, $P \leq 0.001$). 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.[6,8–10] 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.

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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.[4] 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 data of the obstetric and gynecologic department in SUMC, including information that was documented by obstetricians following delivery. The second, a pool of computerized children 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.[16]

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. 11.1%, 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

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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				
1	1734 (32.2)	50,080 (24.1)	–	<0.001
2–4	2522 (46.9)	107,413 (51.8)		
5+	1121 (20.8)	50,063 (24.1)		
Hypertensive disorders of pregnancy[a]	437 (8.1)	10,656 (5.1)	1.64 1.48–1.81	<0.001
Diabetes[b]	506 (9.4)	10,985 (5.3)	1.86 1.69–2.04	<0.001
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

[a]Including pregestational, gestational hypertension, and preeclampsia.
[b]Including 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 delivery[a]	556 (10.3)	13,095 (6.3)	1.71 1.57–1.87	<0.001
Cesarian delivery	976 (18.1)	28,596 (13.8)	1.39 1.29–1.49	<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 1.59–1.91	<0.001
Low Apgar score at 1 min[c]	279 (5.2)	9473 (4.6)	1.14 1.01–1.29	0.030
Low Apgar score at 5 min[c]	64 (1.2)	3216 (1.5)	0.77 0.60–0.98	0.036
SGA[d]	325 (6)	8876 (4.3)	1.4 1.29–1.61	<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	

[a]Preterm delivery < 37+0 weeks.
[b]LBW < 2500 gr.
[c]Apgar score <7.
[d]BW < 10th percentile for gestational age.

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.

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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 N = 5378 (2.5%)	No ASB in pregnancy N = 207,606 (97%)	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 Min	95% CI Max	*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

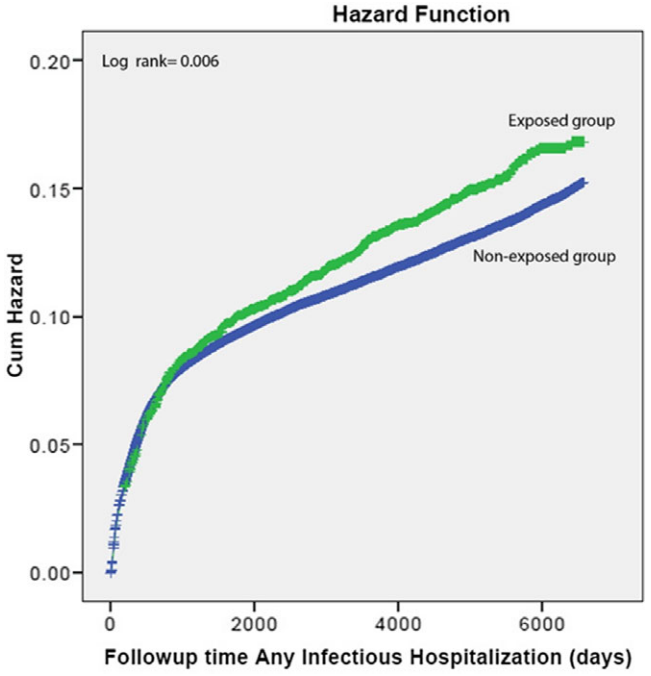

Fig. 1. Kaplan–Meier curve demonstrating the cumulative incidence of hospitalizations involving infectious morbidity in the offspring of exposed and nonexposed groups (log rank, $P = 0.006$).

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.[17] 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.[19] Similarly, Brody *et al.* reported lymphocyte activation of the fetus in response to maternal urinary bacteria even in cases where mothers were asymptomatic.[20] 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.[21–23] 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.[22] Moreover, chorioamnionitis increased the expression of interleukin-6, tumor necrosis factor-a, interferon-b, as well as other cytokines in uterus. These

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cytokines are aspirated by the fetus and cause lung injury potentially increasing susceptibility to respiratory infection.[21]

The influence of antibiotic consumption to treat ASB on infection 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 disease, 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 content 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 antibiotics, 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 susceptibility to infection and inflammation.

Such a sequence of easier bacterial airway penetration and decreased immunity may explain the higher incidence of respiratory infections we saw in our study. In addition we found that, similarly to previous studies,[4,32] ASB was associated with significantly 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 limitation is that the infectious cases we collected were only for hospitalized children, representing severe infectious cases. While the hazard ratio was significant but low (1.08), it relates to the spectrum 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 paper visit https://doi.org/10.1017/S2040174421000593

Conflicts of Interest. The authors report no conflict of interest

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