BANTAO Journal 2020; 18(1): 1-5

BJ
BANTAO Journal

Original article

Urinary Tract Infections in Pregnant Women in Second Trimester and the Risk of Preterm Birth

Katerina Nikoloska[1]

[1]University Clinic of Gynaecology and Obstetrics, Medical Faculty, Skopje, Republic of North Macedonia

Abstract

Introduction. Preterm birth, defined as delivery less than 37 weeks of gestation, is the most common cause of neonatal mortality and morbidity accounting for 11% of pregnancies worldwide. Pregnancy causes numerous changes in the woman's body that increase the risk of urinary tract infections (UTIs). Hormonal and mechanical changes can promote urinary stasis and vesicoureteral reflux, along with an already short urethra (3-4 cm in females) and difficulty with hygiene due to a distended pregnant belly, help make UTIs the most common bacterial infections during pregnancy predominantly with Escherichia coli, but also with Staphylococcus saprophyticus, Klebsiella, Enterobacter, Proteus, Enterococcus, etc. The aim of the study was to prove the relationship between UTIs in pregnancy and their risk to cause preterm birth (<37 g.w.).

Methods. This is a prospective case- control study, conducted at the University Clinic of Gynaecology and Obstetrics, Ss' Cyril and Methodius University, Medical Faculty, Skopje, Republic of North Macedonia at the Department of High-Risk pregnancy. The study included 103 patients with signs and symptoms of preterm labour.
Patients between 28-36 g.w. were followed until the end of the pregnancy. Obstetric ultrasound on Voluson 730 pro machine was performed by two experienced ultrasound observers calculating the fetal weight, estimating the gestational week and measuring the cervical length so the variations for the measurements have been minimized.
Mid-stream urine sample was sent for cytology and culture-sensitivity.

Results. All 103 patients in the study had signs and symptoms of preterm labour. Out of the total of 103 patients 65 (63%) had a positive urine sample, and 38 (36.9%) patients had negative urinalysis. The results showed that patients who had signs and symptoms of preterm birth were significantly different in women who had positive compared to those who had negative urine sample (p=0.0049). Microorganisms cultured in urine were predominantly gram-negative bacilli, although there were also gram-positive bacilli detected. E coli was the commonest microorganism cultured in the urine.

Conclusion. Urogenital infections contribute signifycantly to the preventable causes of preterm labor. The benefit of the study lies in detecting asymptomatic cases, so that this complication can be timely prevented. Making early diagnosis of urogenital infections and treating them adequately with the antimicrobials will help in decreasing the incidence of preterm labor, preterm births, and the associated neonatal and maternal morbidities.

Keywords: premature birth, urinary tract infections, Escherichia coli, pregnancy

Introduction

Preterm birth, defined as delivery less than 37 weeks of gestation, is the most common cause of neonatal mortality and morbidity worldwide, and a serious obstetric problem accounting for 11% of pregnancies worldwide and 5-9% in many other developed countries [1]. Infants are born preterm after: a spontaneous labor with intact membranes, preterm premature rupture of the membranes (PPROM), and labor induction or caesarean delivery for maternal or fetal indications [2]. Common reasons for indicated preterm births include preeclampsia or eclampsia, and intrauterine growth restriction. Births that follow spontaneous preterm labor and PPROM (commonly called spontaneous preterm births) are considered as a syndrome resulting from multiple causes, including infection or inflammation, vascular disease, and uterine over distension [3].
Preterm births can also be subdivided according to gestational age: about 5% of preterm births occur at less than 28 weeks' (extreme prematurity), about 15% at 28-31 weeks' (severe pre maturity), about 20% at 32-33 weeks' (moderate pre maturity), and 60-70% at 34-36 weeks' (near term) [3]. Maternal infection accounts for a main cause of preterm births, the exact mechanism has not been definitely clarified, however, it is believed that an inflammatory cascade is triggered resulting in an increased production of cytokines, prostaglandins

Correspondence to: Katerina Nikoloska, University Clinic of Gynaecology and Obstetrics, Skopje, R. N. Macedonia; E-mail: katerinadudeska@hotmail.com

and matrix-degrading enzymes that promotes uterine contractions, cervical dilatation, preterm rupture of the membranes (PROM), as well as an easier entry of pathogens into the uterine cavity [4]. Evidence suggests that infection plays a role in pathogenesis of preterm labor and delivery. An estimated 50 % of spontaneous preterm births were associated with ascending genital tract infections and had positive urine and cervical cultures [5].
Pregnancy causes numerous changes in the woman's body that increase the risk of urinary tract infections (UTIs). Hormonal and mechanical changes can promote urinary stasis and vesicoureteral reflux, along with an already short urethra (3-4 cm in females) and difficulty with hygiene due to a distended pregnant belly, help make UTIs the most common bacterial infections during pregnancy [4]. Decidual invasion by the lower genital tract bacteria is associated with recruitment of leukocytes followed by cytokine production which trigger prostaglandin synthesis in the amnion, chorion, decidua, and myometrium [6]. This leads to contractions of the uterus, dilatation of cervix, membrane exposure, and entry of microorganisms into the uterine cavity. Local action of the lower genital tract bacteria produces enzymes sialidase or mucinase, which weakens the protective cervical mucosa and thus supports bacterial invasion of the upper genital tract [7]. In pregnancy, asymptomatic urinary tract infection is very common and is linked with preterm delivery. If bacteriuria without symptoms is not treated in pregnant women, then it may lead to acute cystitis and pyelonephritis [3,8]. The presence of urinary tract infection may be an indicator for abnormal vaginal flora because of the colonization of the vagina with the same pathogens as found in the urine [9].
Risk factors related to bacteriuria in pregnancy are: anatomic urinary tract abnormalities, functional urinary tract abnormalities, diabetes mellitus, sickle cell disease, low socioeconomic status, multiparity, increased frequency of sexual activity [10]. Pathogenic microorganisms associated with both symptomatic and asymptomatic bacteriuria are Escherichia coli, accounting for up to 86% of cases, Staphylococcus saprophyticus, Klebsiella spp, Enterobacter spp, Proteus spp, Enterococcus spp, group B Streptococcus, etc.
The aim of the study was to prove the relation between UTIs in pregnancy and their risk to cause preterm birth (< 37 g.w.).

Methods

This prospective case- control study was conducted at the University Clinic of Gynaecology and Obstetrics, Ss' Cyril and Methodius University, Medical Faculty, Skopje, Republic of North Macedonia at the Department of High-Risk pregnancy. The study included 103 patients, during the period from 10.2018-07.2019. Before entering the study, all patients gave their consent in writing for study participation. Patients were selected to enter the study after hospitalization at High risk pregnancy department with signs and symptoms of preterm labour by the UCOG criteria as four uterine contractions in 20 min or eight in 60 min plus progressive change in the cervix; cervical dilatation greater than 1 cm; and cervical effacement 80 % or greater, before 37 completed weeks. Leaking, i.e., rupture of membranes was diagnosed by per speculum examination and confirmed by litmus paper (change of color from red to blue).
All patients were between 28-36 g.w. and are being followed until the end of the pregnancy. Each woman has undergone obstetric ultrasound to determine the gestational week and to confirm there are no exclusion criteria so that the patient could enter the study.
The pregnant women were followed on Voluson 730pro ultrasound machine. Ultrasound cervicometry was done and the length of cervix was measured with a vaginal transducer and results recorded on the personal document for the patient. Each patient was taken a detailed anamnesis adapted to the needs and information needed for the research.
Two experienced ultrasound observers were included in calculating the fetus weight, estimating the gestational week and measuring the cervical length so the variations for the measurements have been minimized. The Headlock formula was used for HC (head circumference), AC (abdomen circumference), and FL (femur length) to calculate the EFW (efficient fetal weight).
Mid-stream urine sample was sent for cytology and culture-sensitivity to the Institute of Microbiology and Parasitology-Skopje. The samples were inoculated on blood agar and MacConkey's agar using semi-quantitative method of inoculation. The culture plates were incubated at 37_C for a duration ranging from 24 to 48 h. Isolates were identified by standard methods [11].
Inclusion criteria: women with singleton pregnancy, women with signs and symptoms for preterm birth.
Exclusion criteria: Women with twin pregnancy or higher-order pregnancy, women with antepartum, hemorrhage, eclampsia, preeclampsia, women with urinary infections before the pregnancy.

Statistical analysis

A database in the statistical program SPSS for Windows 23.0 was created for the purpose of analyzing the results obtained in the research.
The numerical, i.e. the quantitative parameters are shown with an average, standard deviation, median and interquarter rank.
Qualitative i.e. attributive parameters are shown by distribution frequencies.
Mann-Whitney test was used for comparing women who gave premature birth and those who gave term birth.
Statistically significant differences were set at the level of $p<0.05$.

Results

All 103 patients in the study had signs and symptoms of preterm labour. Out of the total of 103 patients 65 (63%) had a positive urine sample, and 38(36,9%) patients had negative urinalysis. The results showed that patients who had signs and symptoms of preterm birth were significantly different in women who had positive compared to those who had negative urine sample (p=0.0049). Microorganisms cultured in urine were predominantly gram-negative bacilli, although there were also gram-positive bacilli detected. E coli was the commonest microorganism cultured in the urine.

In those patients who had positive urinary tract sample, the mean gestational week at birth was 33, 2 and in those who had negative urinary tract sample the mean gestational week was 35,4. The mean leant of the cervix was 28 mm (26.0±3.5) in those patients with positive urinary tract sample, and 31mm (30.0±3.5) in patients with negative urinary tract sample. The BMI was 25,2 kg/m^2 in patients with UTI and 24,4 in patients with negative urinary tract sample.

From 65 patients who had positive urinary tract sample with detected UTI, pathogenic microorganisms associated with both symptomatic and asymptomatic bacteriuria were Escherichia coli, accounting for up to 86% of cases, Staphylococcus saprophyticus, Klebsiella spp, Enterobacter spp, Proteus spp, Enterococcus spp and group B Streptococcus (Figure 1).

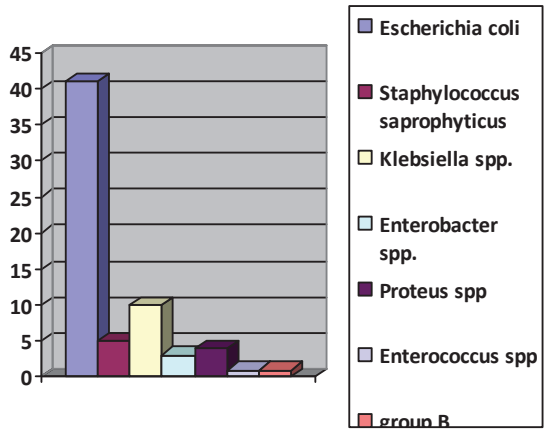

Fig. 1. Isolated microorganisms in the urinary tract samples

From the total number of 103 patients including all samples (positive and negative) in 41 urine samples we isolated Escherichia coli, in 5 samples we isolated Staphylococcus saprophyticus, in 10 Klebsiella spp was isolated, Enterobacter spp was isolated from 3 samples, Proteus spp from 4 samples, Enterococcus spp from 1 sample and group B Streptococcus was isolated from 2 samples (Table 1).

Table 1. Isolated microorganisms in urine sample by number of patients and gestational week

Isolated microorganisms	No of positive samples	Mean gestational week at birth
Escherichia coli	41	33,1
Staphylococcus saprophyticus	5	32,3
Klebsiella spp	10	32,5
Enterobacter spp	3	32
Proteus spp	4	32,5
Enterococcus spp	1	30,4
groupB Streptococcus	1	33.4

Discussion

Pregnant women are at an increased risk of acquiring urinary tract infection due to functional and anatomical changes in pregnancy. In most cases the urinary tract infection is asymptomatic. The purpose of our study was to evaluate partly the possible association between maternal UTI during pregnancy and the increased risk of preterm birth, and in addition birth outcomes such as gestational age and isolated microorganisms. The results obtained in this study, support the expected hypothesis that the positive urine sample can increase the risk of preterm birth and affect the outcome of the pregnancy i.e. its presents leads to premature birth. The examination is more valuable since we know that 5-18% in total of the full number of births in our Clinic belongs to this group. The results have confirmed that risk factors for premature birth include vaginal and cervical infection [12], shortened cervix and presence of urinary tract infection [13].

However, the reported cultivation data and the results of our previous studies [14,15] showed a similar spectrum of microorganisms associated with significant bacteriuria. The type of microorganisms isolated in our study was quite similar to those isolated in other studies [14], but the gestational week of delivery tended to be higher in the other studies [16]. Maybe the reason for this is the fact that in those studies the parameters compared were mainly related to the risk of premature birth as cervical length, vaginal and cervical swabs and other risk factors [17-19]. In our study, E. coli was the most common organism isolated. This is in agreement with other studies carried in other countries in which E. coli was the most common organism isolated [20, 21]. E. coli is also a common microorganism in the perineum and failure to maintain personal hygiene may increase the risk of infection with E. coli [22]. In addition, gram negative bacteria have a distinct structure which enables the organism to attach, grow and invade the uroepithelium. This may result in invasive infection and pyelonephritis [21]

The benefit of our study lies in detecting the asymptomatic cases, so that this complication can be timely prevented. Also, a prenatal check in the first trimester for detecting asymptomatic cases can increase the UTIs in pregnant women, at the same time increasing the com-

plication of UTIs in the second trimester and adverse pregnancy outcomes such as pyelonephritis, preterm birth or low birth weight [23]. However, an emerging evidence in the past few years shows the microorganisms inhabiting many sites of the body, including the urinary tract, which has been assumed sterile in healthy individuals, might have a role in maintaining urinary health. Studies of the urinary microbiota have identified remarkable differences between healthy populations and those with urologic diseases [24]. So maybe the future studies can make difference for detecting the urinary microbiota. We live in the era of antimicrobial resistance and may live in other eras like the era of the microbiome. Thus, new insights might also provide an opportunity to prevent the overuse and misuse of antibiotics and could enable the development of innovate managing strategies [25].

Conclusion

Patients with UTI have more common complications in pregnancy especially in the second trimester. Our study has confirmed the reasons for examining UTIs as a method to discover risk in patients who have signs and symptoms of premature birth.

The patients with UTI have more common complications with an increased risk of premature termination of the pregnancy. The benefit of our study lies in detecting asymptomatic cases, so that this complication can be timely prevented. We recommend that women coming for first antenatal checkup should be investigated for the presence of asymptomatic UTI. Making early diagnosis of UTIs and their adequate antibiotic treatment helps decreasing the incidence of preterm labor, preterm births, and the associated neonatal and maternal morbidities. Moreover, an early diagnosis would lower the hospital admittance rate and associated costs, and reduce the premature births It would be useful to create an algorithm for multidisciplinary treatment of these patients enabling the development of innovative therapeutic strategies.

Conflict of interest statement. None declared.

References

1. Suff N, Story L, Shennan A. The prediction of preterm delivery: what is new? *Seminars in Fetal and Neonatal Medicine* 2018.
2. Romero R, Miranda J, Chaiworapongsa T, *et al*. A novel molecular microbiologic technique for the rapid diagnosis of microbial invasion of the amniotic cavity and intra-amniotic infection in preterm labor with intact membranes. *Am J Reprod Immunol* 2014; 71: 330-358.
3. Robert L Goldenberg, Jennifer F Culhane, Jay D Iams, Roberto Romero. Epidemiology and causes of preterm birth. *Lancet* 2008; 371: 75-84.
4. Dinarello CA, Gelfand JA, Wolff SM. Anticytokine Strategies in the Treatment of the Systemic Inflammatory Response Syndrome. *JAMA* 1993; 269: 1829-1835.
5. Mercer BM, Goldenberg RL, Moawad AH, *et al*. The preterm prediction study: effect of gestational age and cause of preterm birth on subsequent obstetric outcome. National Institute of Child Health and Human Development Maternal-Fetal Medicine Units Network. *Am J Obstet Gynecol* 1999; 181: 1216.
6. Kim CJ, Romero R, Chaemsaithong P, *et al*. Acute Chorioamnionitis and Funisitis: Definition, Pathologic Features, and Clinical Significance. *American journal of obstetrics and gynecology*. 2015; 213(40): S29-S52.
7. Alijahan R, Hazrati S, Mirzarahimi M, *et al*. Prevalence and risk factors associated with preterm birth in Ardabil. 2014.
8. Anderson BL, Simhan HN, Simons KM, *et al*. Untreated asymptomatic group B streptococcal bacteriuria early in pregnancy and chorioamnionitis at delivery. *American Journal of Obstetrics and Gynecology* 2007; 196: 524.e1-525.
9. Bachman JW, Heise RH, Naessens JM, et al. A study of various tests to detect asymptomatic urinary tract infections in an obstetric population. *JAMA: The Journal of the American Medical Association* 1993; 270: 1971-1974.
10. Kalinderi K, Delkos D, Kalinderis M, *et al*. Urinary tract infection during pregnancy: current concepts on a common multifaceted problem, Journal of Obstetrics and Gynaecology 2018.
11. Collee JG, Miles RS, Watt B. Tests for identification of bacteria. In: Fraser AG, Marmion BP, Simmons A, editors. Mackie and McCartney's practical medical microbiology. *14th ed. Edinburgh: Churchill Livingstone* 1996; 131-149.
12. Kim SM**,** Romero R, Lee JJ, *et al*. About one-half of early spontaneous preterm deliveries can be identified by a rapid matrix metalloproteinase-8 (MMP-8) bedside test at the time of mid-trimester genetic amniocentesis. *J Matern Fetal Neonatal Med* 2016; 29(15): 2414-2422. Published online 2015 Dec 7.
13. Winstanley TG, Limb DI, Eggington R, Hancock F. A 10-year survey of the antimicrobial susceptibility of urinary tract isolates in the UK: The Microbe Base Project. *J Antimicrob Chemother* 1997; 40: 591-594.
14. Czeizel AE, Hancsok M, Margitay Becht D, *et al*. Incidence of significant bacteriuria during pregnancy. *Orvosi Hetilap* 1967; 108: 684-686.
15. Czeizel AE, Hancsok M, Ormay L, Philipp G. The connection between significant bacteriuria during pregnancy and premature births. *Orvosi Hetilap* 1967; 108: 101-102.
16. Czeizel AE, Berecz M, Gerofi J, *et al*. Study of asymptomatic significant bacteriuria in a population section of Budapest. *Orvosi Hetilap* 1968; 109: 1985-1987.
17. Czeizel AE, Petik D, Vargha P. Validation studies of drug exposures in pregnant women. *Pharmacoepid Drug Safety* 2003; 12: 409-416.
18. Lee J, Romero R, Xu Y, *et al*. A signature of maternal anti-fetal rejection in spontaneous preterm birth: chronic chorioamnionitis, anti-human leukocyte antigen antibodies, and C4d. *PLoS One* 2011; 16:806-36.
19. Chaemsaithong P, Romero R, Korzeniewski SJ, *et al*. A point of care test for interleukin-6 in amniotic fluid in preterm prelabor rupture of membranes: a step toward the early treatment of acute intra-amniotic inflammation/infection. *The Journal of Maternal-Fetal & Neonatal Medicine* 2016; 29:3, 360-367.
20. Glaser AP, Schaeffer AJ. Urinary Tract Infection and Bacteriuria in Pregnancy. *Urol Clin North Am* 2015; 42(4): 547-560.
21. Ali IE, Gebrecherkos T, Gizachew M, Menberu MA. Asymptomatic bacteriuria and antimicrobial susceptibility pattern of the isolates among pregnant women attending Dessie referral hospital, Northeast Ethiopia: A hospital-

based cross-sectional study. *Turkish journal of urology* 2018; 44(3): 251-260. PMID: 29733799.
22. Oli AN, Okafor CI, Ibezim EC, *et al*. The prevalence and bacteriology of asymptomatic bacteriuria among antenatal patients in Nnamdi Azikiwe. University Teaching Hospital Nnewi; South Eastern Nigeria. *Nigerian journal of clinical practice* 2010; 13(4): 409-412.
23. Nteziyaremye J, Iramiot SJ, Nekaka R, *et al*. Asymptomatic bacteriuria among pregnant women attending antenatal care at Mbale Hospital, Eastern Uganda. *PLoS ONE 2020*; 15(3): e0230523.
24. Whiteside SA, Razvi H, Dave S, *et al*. The microbiome of the urinary tract-a role beyond infection. *Nat Rev Urol*. 2015; 12(2): 81-90.
25. Lee SJ. Recent advances in managing lower urinary tract infections. *F1000Res*. 2018; 7: F1000 Faculty Rev-1964. Published 2018 Dec 21.