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Investigation of the relationship between genitourinary system infection in pregnancy and preterm delivery-retrospective case control study

Gebelikte genitoüriner sistem enfeksiyonu ile preterm doğum arasındaki ilişkinin incelenmesi-retrospektif vaka kontrol çalışması

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ABSTRACT

Aim: In our study, the relationship between preterm birth and genitourinary system infections during pregnancy was investigated.

Materials and Methods: Our study is retrospective. Patients who gave birth in our hospital between 2013 and 2023 were included in the study. Our study was carried out with 1005 patients, 504 cases, and 501 control groups. Births between 20 0/7 and 36 6/7 weeks of gestation were taken as preterm birth. Patients with singleton pregnancy were included in the study. SPSS (IBM SPSS for Windows, Ver.26) statistical package program was used for statistical analysis of our study.

Results: A total of 1005 patients were included in the study. The mean age of the patients was 27.98±4.8. In our study, the rate of preterm birth in the control group was **% 13**. As a result of our study, the rate of preterm birth was found to be statistically significantly higher in the group diagnosed with infection during pregnancy compared to the control group (p=0.000). The risk of preterm birth was found to be 5.6 times higher in the group diagnosed with infection during pregnancy compared to the control group (Odds Ratio: 5.593).

Conclusion: Having a genitourinary system infection during pregnancy leads to a significant increase in the risk of preterm birth.

Keywords: Preterm birth, genitourinary infection, pregnancy complication

ÖZ

Amaç: Çalışmamızda preterm doğum ile gebelik sürecinde geçirilen genitoüriner sistem enfeksiyonları arasındaki ilişki araştırılmıştır.

Gereçler ve Yöntem: Çalışmamız retrospektif bir çalışmadır. Hastanemizde 2013-2023 yılları arasında doğum yapmış hastalar çalışmaya alınmıştır. Çalışmamız 504 vaka ve 501 kontrol grubu olmak üzere 1005 hasta ile gerçekleştirilmiştir. 20 0/7 ile 36 6/7 gebelik haftaları arasındaki doğumlar erken doğum olarak alınmıştır. Çalışmaya tekil gebeliği olan hastalar alınmıştır. Çalışmamızın istatistik analizi için SPSS (IBM SPSS for Windows, Ver.26) istatistik paket programı kullanılmıştır.

Bulgular: Toplam 1005 hasta çalışmaya alınmıştır. Hastaların yaş ortalaması 27.98±4.8'dir. Çalışmamızda kontrol grubunda preterm doğum oranı %13 olarak bulunmuştur. Çalışmamızın sonucunda gebelikte enfeksiyon tanısı alan grupta kontrol grubuna kıyasla preterm doğum oranları istatiksel olarak anlamlı yüksek bulunmuştur (p=0.000). Gebelikte enfeksiyon tanısı alan grupta kontrol grubuna kıyasla preterm doğum riski 5.6 kat yüksek bulunmuştur (Odds Ratio: 5.593).

Sonuç: Gebelikte genitoüriner sistem enfeksiyonu geçirmek preterm doğum riskinde anlamlı artışa yol açmaktadır.

Anahtar Kelimeler: Preterm doğum, genitoüriner enfeksiyon, gebelik komplikasyonu

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INTRODUCTION

Preterm births affect more than 15 million pregnant women annually and are one of the leading causes of neonatal morbidity and mortality (1). Although the etiology of preterm birth is broad, genitourinary infections occupy an important place (2). Preterm labor is defined as regular and painful uterine contractions that occur at least 4 times in 20 minutes or at least 8 times in an hour between 20 0/7 and 36 6/7 weeks of pregnancy, along with progression of cervical effacement and dilatation on pelvic examination. In the presence of >1 cm cervical dilatation and ≥80% cervical effacement along with regular uterine contractions, the diagnosis is made directly. If pregnancies diagnosed with preterm labor are <24 weeks or ≥34 weeks, tocolytic treatment to stop contractions is generally not recommended (3, 4). The costs of premature birth on a country-by-country basis are considerable (3). The prevalence of preterm birth in Turkey varies between 10-15% in publications from various centers. It is reported to be around 12% throughout Türkiye (3). Preterm birth leads to severe neonatal short-term outcomes. In addition, it may have permanent effects on fetal development due to preterm birth, which may continue until adulthood (2-5). The incidence of preterm birth has been reported as 9.6% (6). Urogenital infections are quite common during pregnancy, and approximately 50% of spontaneous preterm births occur due to ascending genital tract infections (7, 8). Diagnosis and treatment of urogenital infections in the prenatal period is essential. However, the prevalence of urogenital infections in pregnant women under the threat of preterm labor in large centers, universities, and training and research hospitals should be investigated and the importance of these infections in determining pregnancy outcomes and the health of newborns should be evaluated. This study aims to determine the rates of preterm birth in pregnant women diagnosed with urogenital infection during pregnancy. We aim our study to contribute to the literature.

MATERIALS AND METHODS

Place and time of research

Our research was carried out in Uşak Training and Research Hospital in 2023. Our study is a retrospective case-control study.

Research population and sample

The population of the study consists of patients who gave birth in Uşak Training and Research Hospital between 01.01.2013 and 01.01.2023. The files of pregnant women who had 24513 single births in our hospital were reviewed retrospectively. Our study was designed on 1005 patients, 504 cases, and 501 control groups. Patients with a singleton pregnancy were included in the study. Births between 20 0/7 and 36 6/7 weeks of gestation were taken as preterm birth. No distinction was made for the type of birth for the study.

Study design

Age, gestational week at the time of delivery, total number of pregnancies, total number of live births, body mass index (BMI), diagnosis and treatment history of comorbidity, and genitourinary infection were obtained from patient files.

The weeks of gestation of the patients included in the study were confirmed by first-trimester Crown-rump length (CRL) measurement.

The accuracy of the diagnosis of infection in the patients included in the study and whether they received treatment were examined individually.

In our study, deliveries between 20 0/7 and 36 6/7 gestational weeks were considered premature births (9).

In our study, asymptomatic bacteriuria was diagnosed by the presence of ≥ 105 cfu/ml bacteria and pyuria in two urine cultures taken at least 24 hours apart in a non-symptomatic pregnant woman (10).

In our study, acute cystitis was taken as a symptomatic infection of the bladder, manifested by frequent urination, dysuria, urge incontinence, and foul-smelling urine, without any signs of systemic disease in the clinic. In our study, acute cystitis was diagnosed in the presence of symptoms and a positive urine culture (10).

In our study, the diagnosis of acute pyelonephritis was made by the presence of pain in the lower back or side, costovertebral angle tenderness, fever (>38ºC), nausea, vomiting, and cystitis findings, and positive urine culture (10).

In our study, the diagnosis of bacterial vaginosis (BV) was made according to the Amsel and Nugent criteria in patients who described a foul-smelling (fishy smell) discharge, an increase in this discharge after sexual intercourse and menstruation, and a burning and stinging sensation. Amsel criteria are currently used in the clinical diagnosis of BV. The clinical diagnosis of BV is the presence of a thin homogeneous gray vaginal discharge, the presence of clue cells (clue cells) on microscopic examination, a vaginal pH of 4.5 or above, a positive potassium hydroxide (KOH) test (positive amine test) three or more of these four objective criteria. more than that is sufficient for the diagnosis of BV. The Nugent scoring method is the most commonly used in the diagnosis of BV and is considered the gold standard. In this

scoring method, three bacterial morphotypes are evaluated with scoring ranging from 0-10 (11, 12).

Pelvic examination, vaginal pH and microscopy, and culture were used to diagnose Candida vaginitis. Typical discharge (thick, white, curd-like vaginal discharge), negative amine test, vaginal pH<4.5, microscopic application of potassium hydroxide (KOH), or the appearance of budding yeast, pseudohyphae or mycelial structures in fresh preparations were used for the diagnosis of candidal vaginitis. If symptoms suggest candidal vaginitis, but there are no signs (including vulvar irritation) and microscopy does not detect fungal elements, patients with positive fungal culture results were included in the study (13).

For the diagnosis of trichomonas vaginitis, the presence of motile organisms in wet preparations, pH above 4.5, and culture positivity were used (13).

Pelvic inflammatory disease (PID) diagnosis is tenderness in cervical movements, uterine tenderness, adnexal tenderness, high fever (oral>38.3oC), abnormal cervical/vaginal mucopurulent discharge, presence of leukocytes in vaginal secretion in microscopy, the positivity of Chlamydia Nucleic Acid Amplification Tests (NAAT), Gonorrhea NAAT test positivity and high C Reactive Protein test (CRP) and Erythrocyte Sedimentation Rate (ESR) elevation was used (14).

Patients diagnosed with genitourinary system infection above the abortion limit of 20 0/7 weeks of gestation and before 34 0/7 weeks of gestation were included in the study. Since the 34th week of gestation is the threshold week for steroid indication for fetal lung maturation, those diagnosed with genitourinary system infection were not included in the study.

Patients diagnosed with genitourinary infection and receiving treatment were included in the study. Patients received outpatient and inpatient treatment depending on their clinical status. Asymptomatic bacteriuria was diagnosed in pregnant women whose urine culture results were positive twice in a row but had no clinical complaints or symptoms. All of these patients were treated with cefuroxime axetil (250 mg, twice a day) for 5 days if the detected agent was sensitive, but if the detected agent was not sensitive, they were treated with appropriate antibiotics. In cases of cystitis, treatment was given for 5 days: Cefdinir 2x100 mg/day or cefaclor 3x250 mg/day. Additionally, a single dose of 3 g fosfomycin was administered.

Acute pyelonephritis was diagnosed in patients who had a positive or negative urine culture result when they were admitted for routine control, but who presented with clinical complaints and findings such as fever higher than 38°C, flank pain, and costovertebral angle tenderness. All patients diagnosed with acute pyelonephritis were hospitalized and treated with parenteral antibiotics after a sample was taken for urine culture. Cefotaxime sodium (1 gr, iv, 2x1) was used as the treatment agent for these patients, and the treatment was continued until 24 hours after the clinical findings disappeared. In patients who did not respond adequately to treatment, parenteral treatment was continued with appropriate antibiotics following the culture result. In all patients treated with a diagnosis of acute pyelonephritis, treatment with oral antibiotics was continued after the acute period, and these patients were evaluated again with a urine culture 2 weeks after the completion of the treatment. Pregnant women whose culture result was positive at this control but had no clinical findings were treated prophylactically with nitrofurantoin (100 mg, per-oral, 1x1) for the remainder of their pregnancy and this treatment was continued until the 37th week of pregnancy.

Pregnant women diagnosed with bacterial vaginosis were treated with Metronidazole 2x500 mg orally for 7 days and Clindamycin ovule 100 g intravaginally, at bedtime, for 3 days. Those diagnosed with Candida vaginitis were given Clotrimazole 100 mg vaginal tablet, 7 days, and Miconazole 1200 mg vaginal suppository, single-dose treatment. Metronidazole 2 g, oral, single dose, and co-treatment were given to those diagnosed with Trichomonas vaginitis.

Pregnant women diagnosed with pelvic inflammatory disease received inpatient treatment in the hospital. Ceftriaxone 1 g intravenously once a day and Metronidazole 500 mg orally or intravenously twice a day were administered.

Patients who met hospitalization criteria received inpatient treatment. Patients who did not qualify for hospitalization received treatment as an outpatient. For study safety, patients who did not receive treatment were not included in the study.

Infection diagnoses were made precisely as mentioned above according to current diagnostic guidelines, and it was also recorded whether the patients received treatment or not. Patients with a body mass index (BMI) between 18.5 and 24.9 kg/m2 were included in our study. Weak, obese, and morbidly obese patients were excluded from the study. In addition, patients with smoking, alcohol use, and drug use were not included in the study. Patients with equal socioeconomic status were included in the study. Premature births due to placenta previa, vasa previa, and placental invasion anomalies were also excluded from the study. Deliveries due to hypertensive patients of pregnancy (Preeclampsia, eclampsia, HELLP) were also excluded from the study. Pregnant women with uterine anomalies and those with a history of cervical surgery were

excluded from the study. Multiple pregnancies were excluded from the study. Patients who developed amniotic fluid abnormalities and premature rupture of membranes were excluded from the study. In our study, the rates of preterm birth in pregnant women who had an infection and those who did not have been examined.

Statistical analysis

SPSS (IBM SPSS for Windows, Ver.26) statistical package program was used for the statistical analysis of our study. Comparison of fetal outcomes, maternal and pregnancy characteristics, χ^2 test or Fisher's exact test for categorical variables, and Mann-Whitney U test for continuous variables were used. Statistical significance was accepted as $p<0.05$. Bonferroni correction was used when necessary to adjust for multiple comparisons.

Ethics committee approval

For our research, permission was obtained from the Ethics Committee of Non-Invasive Clinical Researches of Uşak University Faculty of Medicine with Date: 02.02.2023, Decision No: 70-70-24. Necessary informed consent was obtained from the patients included in the study. Our study was carried out according to the principles stated in the Declaration of Helsinki.

RESULTS

Our study was carried out on 504 pregnant women who were diagnosed with infection during their pregnancy and 501 pregnant women who were taken as the control group without a diagnosis of infection. A total of 1005 patients were included in the study. The mean age of the patients was 27.98±4.8. In our study, our patients did not have any additional diseases. In our study, the mean BMI of the patients was 22.62±1.5. In our study, the rate of preterm birth in the control group was 13%. The general characteristics of the patients are given in Table 1. A comparison of patients' infection diagnoses and preterm birth rates is given in Table 2.

Table 1. General Features

	Minimum	Maximum	Mean+Std. Deviation
Age (Year)	18	39	27.98±4.8
Gravide	1	7	2.83±1.2
Parite	1	4	2.2±0.7
Abort	0	2	0.3±0.4
Medical Termination of Pregnancy	0	2	0.4±0.5
BMI*	18.5	24.40	22.62±1.5
		Number (n)	**Percent (%)**
Additional Disease	Yes	0	0
	No	1005	100

*BMI: Body Mass İndex

Table 2. Comparison of Patients' İnfection Diagnoses and Premature Birth Rates

		Number (n)	Percent (%)
Infection in Pregnancy	Yes	504	50.1
	No	501	49.9
	Total	1005	100
Preterm Birth		489	48.7
Term Birth		516	51.3
	Total	1005	100
In the Group Without Infection Diagnosis	Preterm Birth	65	13
	Term Birth	436	87
	Total	501	100
Infection Diagnosis	Asymptomatic Bacteriuria	65	6.5
	Cystitis	115	11.4
	Pyelonephritis	65	6.5
	Vaginitis	205	20.4
	PID**	54	5.4
	Total	504	100

* PID: Pelvic Inflammatory Disease

Table 3. Preterm Birth Rates in Pregnants with and Without a Diagnosis of Infection

		Number (n)	Percent (%)	p value
Preterm Birth	Yes Infection	424	42.2	**0.000***
	No Infection	65	6.5	
Term Birth	Yes Infection	80	8	
	No Infection	436	43.3	
Total		1005	100	

* Chi-Square Tests, p<0.05 values were taken as significant at the 95% confidence interval. Odds Ratio: 5.593

Table 4. Preterm Birth Rates by Infection Type

		Number (n)	Percent (%)	p value
Infection Diagnosis	Asymptomatic Bacteriuria	65	6.5	0.061
	Cystitis	115	11.4	
	Pyelonephritis	65	6.5	
	Vaginitis	205	20.4	
	PID	54	5.4	
	Total	504	100	

* Chi-Square Tests, p<0.05 values were taken as significant at the 95% confidence interval.
* PID: Pelvic Inflammatory Disease

As a result of our study, preterm birth rates were found to be statistically significantly higher in the group diagnosed with infection during pregnancy compared to the control group (p=0.000). As a result of our study, the risk of preterm birth was found to be 5.6 times higher in the group diagnosed as having infection during pregnancy compared to the control group (Odds Ratio: 5.593). The rates of preterm delivery between the pregnant women diagnosed with infection and the control group are given in Table 3.

For study safety, patients who did not receive treatment for infection were not included in the study.

There was no statistical relationship between the week of infection and preterm birth (p=0.136).

No statistical relationship was found between the type of infection and preterm birth (p =0.061). Preterm birth rates according to infection types are given in Table 4.

DISCUSSION

Our study aims to examine whether infection during pregnancy is related to preterm birth. As a result of our study, the rate of preterm birth was found to be statistically significantly higher in the group diagnosed with infection during pregnancy compared to the control group (p=0.000). The risk of preterm birth was found to be 5.6 times higher in the group diagnosed with infection during pregnancy compared to the control group (Odds Ratio: 5.593).

The etiology of preterm labor is multifactorial. Today, there are publications in the literature showing that localized or systemic infection and/or inflammation is one of the most important factors for preterm delivery (15). Existing literature data support our study.

According to microbiological studies, genital tract infections are reported to be associated with one-third of preterm deliveries (16). In the final result of our study, the rate of preterm birth was found to be high in the group diagnosed with the infection.

Hosny et al. enrolled 117 pregnant women (45 as controls and 72 cases) without risk factors for preterm labor at Kasr Al Aini Hospital between December 6, 2009, and June 2010, to examine the relationship between genitourinary tract infection and preterm birth. They identified certain types of pathogens as risk factors for preterm birth, including Trichomonas vaginalis, Mycoplasma hominis, coryneform, and Gram-negative bacilli. In addition, infection-related determinants such as vaginal pH above 5, positive whiff test and heavy vaginal bleeding, young age (under 20 years of age), and poor obstetric history were also risk factors for preterm delivery (17). Adolescents were not included in our study in terms of

study stability. Again, those over the age of 40 were not included in the study. Similarly, in our study, a relationship was found between infection and preterm birth.

In a prospective controlled observational study conducted by S V Barinov et al. in 355 pregnant women, high rates of recurrent pregnancy loss, threat of miscarriage, premature rupture of membranes, and preterm delivery were found in women with a high risk of chronic infection (18). It supports our work.

In a meta-analysis conducted by Marinjho Emely Jonduo et al. on genital mycoplasmas, they concluded that there is no clear data on the effect of mycoplasmas alone or in combination with bacterial vaginosis on adverse pregnancy and delivery outcomes (19).

Again, there are studies in the literature indicating that infection screening and treatment programs for pregnant women before the 20th week of pregnancy can reduce preterm labor (20). In our study, the rate of preterm birth was high in pregnant women with a diagnosis of infection.

Current publications have shown that Lactobacillus species are the predominant vaginal bacteria contributing to a healthy environment in the lower genitourinary tract of women (21, 22). In our study, the rate of preterm delivery in the non-infected group was 13%. These data indicate that infection is an important cause of preterm birth.

Studies have reported that the regeneration of vaginal microbiomes also improves obstetric outcomes (23, 24). Considering all these, prevention of infection during pregnancy is of great importance to prevent preterm births.

In the current literature, there are studies advocating that culture samples should be taken from the genitourinary system and appropriate treatment should be given in pregnancy follow-up (25-27).

In different studies, it has been suggested that the success rates do not change with direct empirical treatment without taking a culture (28-30).

Urogenital infections cause preterm labor and because most of them are asymptomatic, early screening and treatment are necessary. Early treatment of these infections will reduce the incidence of premature birth and related neonatal and maternal morbidity. In patients with a routine preterm birth threat, sometimes no samples other than urine culture are taken, however, culture should be given importance and routine in these patients. Genitourinary infections, which are an important cause of preterm births, should be screened and treated closely.

CONCLUSION

The rate of preterm delivery is significantly higher in pregnant women who had urinary and/or vaginal infections during pregnancy compared to those who did not. Infection in pregnancy poses an obvious risk for preterm birth. Preterm birth was found to be 5.6 times higher in pregnant women with a history of infection.

Limitations of the Study

Our study is a single-center multidisciplinary study. Although it has the advantage of being a retrospective study, the number of patients is small. There is a need for multicenter, multidisciplinary studies with more patients in this regard.

Ethics Approval and Consent to Participate

Permission was obtained from the Ethics Committee of Uşak University Faculty of Medicine, Non-Invasive Clinical Research with Date: 02.02.2023, Decision No: 70-70-24. Necessary informed consent was obtained from the patients included in the study. Our study was carried out according to the principles stated in the Declaration of Helsinki.

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