Jinekoloji - Obstetrik ve Neonatoloji Tıp Dergisi

The Journal of Gynecology-Obstetrics and Neonatology

Cilt/Vol: 21 • **Sayı**/No: 4 • **Aralık**/December 2024 E-ISSN 2667-7849

Özgün Araştırma / *Original Articles*

Jinekoloji-Obstetrik ve Neonatoloji Tıp Dergisi

Dergi Kurulları

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Değerli Bilim İnsanları,

Dergimizin 2024 yılındaki son sayısını sizlerle paylaşırken öncelikte 2025 yılının tüm dünyaya barış, huzur ve mutluluk getirmesini diliyoruz. Değişen basım formatımız, dinamik yayın sekreterya ekibimiz ve editör kurulumuz ile yeni yılda da sizlerin desteği ile dergimizi bilimsel platformda daha ileri seviye taşıman gayreti içinde olacağız.

Bu sayımızda sizlerden gelen birbirinden güzel ve değerli 16 makaleye yer verdik. Obstetri alanında fibrinojen-albumin oranının hiperemesis gravidarum hastalarında kullanımından; gebelikte karpal tünel sendumunun risk faktörlerine kadar çok geniş bir yelpazede yer alan ve ilgiyle okuyacağınızı düşündüğümüz 13 orijinal makaleyi sizlerin beğenisine sunduk.

Ayrıca açıklanamayan infertil çiftlerde intrauterin inseminasyonun ile ilgili 1 orijinal makale ile inflamatuvar belirteçlerin kemik mineral yoğunluğuna etkisi ve metotreksat verilen ektopik gebelik hastaların betaHCG takibini araştıran 2 orijinal makaleye bu sayımızda yer verdik.

Bir sonraki sayımızda buluşmak dileğiyle...

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Jinekoloji - Obstetrik ve Neonatoloji Tıp Dergisi
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ÖZGÜN ARAŞTIRMA / ORIGINAL ARTICLE

DOI: 10.38136/jgon.1496564

Comparison of maternal circulating collectrin levels in pregnancies complicated by oligohydramnios and fetal growth restriction

Oligohidramniyos ve fetal büyüme geriliği ile komplike olan gebeliklerde annenin dolaşımındaki collectrin düzeylerinin karşılaştırılması

Meryem CEYHAN[1], Necati HANCERLIOGULLARI[1], Selen YAMAN[1], Esin Merve KOC[1], Tuba CANDAR[2], Aytekin TOKMAK[3]

[1]Department of Obstetrics and Gynecology, Ankara City Hospital, University of Health Sciences, Ankara, Turkey
[2]Department of Medical Biochemistry, School of Medicine, Ufuk University, Ankara, Turkey
[3]Department of Obstetrics and Gynecology, School of Medicine, Kırıkkale University, Kırıkkale, Turkey

ABSTRACT

Aim: Collectrin is a transmembrane regulatory glycoprotein involved in the renin-angiotensin system and plays an important role in kidney development. It is well known that placental perfusion play essential role in maintaining amniotic fluid production and fetal development. The current study sought to assess the relationship between serum collectrin levels and fetal growth restriction (FGR) and oligohydramnios.

Materials and Methods: This observational study was done in a tertiary level maternity hospital. The study groups were comprised of pregnancies complicated with term oligohydramniosis and isolated FGR. The control group was selected from among low risk healthy pregnancies. Demographic features, obstetric characteristics, gestational age, amniotic fluid index, fetal biometric measurements, doppler indices, blood pressure, pulse, hematologic, and biochemical parameters, and serum collectrin levels were recorded for each patient.

Results: No significant differences were observed among the groups with regard to maternal age, body mass index, gesational week, and peripheral blood pressures (p>0.05). The birth weights were statistically significantly lower in the FGR group than the other 2 groups (p<0.001). There were no significant differences in the neonatal outcomes between these groups. Maternal serum hematologic parameters and biochemical markers were similar among the groups with the exception of chloride. Collectrin values were 129.8±187.7, 120.8±52.8, and 116.7±33.5 ng/ml in the controls, FGR and oligohydramnios groups, respectively (p:0.003).

Conclusion: Maternal circulating collectrin levels is lower in pregnancies complicated with oligohydramnios and FGR than in the low risk term pregnacies. Collectrin may be a valuable biomarker for diagnosing oligohydramnios and FGR which are characterized by placental hypoperfusion.

Keywords: Collectrin, fetal growth retardation, oligohydramnios, renin–angiotensin system, placenta

ÖZ

Amaç: Collectrin, renin-anjiyotensin sisteminde yer alan transmembran düzenleyici bir glikoproteindir ve böbrek gelişiminde önemli rol oynar. Plasental perfüzyonun amniyotik sıvı üretiminin ve fetal gelişimin sürdürülmesinde önemli rol oynadığı iyi bilinmektedir. Mevcut çalışma serum collectrin düzeyleri ile fetal büyüme geriliği (FBG) ve oligohidramniyoz arasındaki ilişkiyi değerlendirmeyi amaçladı.

Gereç ve Yöntemler: Bu gözlemsel çalışma üçüncü basamak bir doğum hastanesinde yapıldı. Çalışma grupları term oligohidramniyoz ve izole FBG ile komplike olan gebeliklerden oluşturuldu. Kontrol grubu ise düşük riskli sağlıklı gebelikler arasından seçildi. Her hastanın demografik özellikleri, obstetrik özellikleri, gebelik yaşı, amniyotik sıvı indeksi, fetal biyometrik ölçümler, doppler indeksleri, kan basıncı, nabız, hematolojik ve biyokimyasal parametreler ve serum collectrin düzeyleri kaydedildi.

Bulgular: Anne yaşı, vücut kitle indeksi, gebelik haftası ve periferik kan basıncı açısından gruplar arasında anlamlı farklılık gözlenmedi (p>0,05). FBG grubunda doğum ağırlıkları diğer 2 gruba göre istatistiksel olarak anlamlı derecede düşüktü (p<0,001). Bu gruplar arasında neonatal sonuçlar açısından anlamlı bir fark yoktu. Maternal serum hematolojik parametreleri ve biyokimyasal belirteçler klorür haricinde gruplar arasında benzerdi. Collectrin değerleri kontrol, FBG ve oligohidramnios gruplarında sırasıyla 129,8±187,7, 120,8±52,8 ve 116,7±33,5 ng/ml idi (p:0,003).

Sonuç: Oligohidramniyoz ve FBG ile komplike olan gebeliklerde, annenin dolaşımdaki collectrin düzeyleri düşük riskli term gebeliklere göre daha düşüktür. Collectrin, plasental hipoperfüzyon ile karakterize olan oligohidramniyoz ve FBG'nin teşhisinde değerli bir biyobelirteç olabilir.

Anahtar Kelimeler: Collectrin, fetal büyüme geriliği, oligohidramnios, renin-anjiyotensin sistemi, plasenta

Cite as: Ceyhan M, Hancerliogullari N, Yaman S, Koc EM, Candar T, Tokmak A. Comparison of maternal circulating collectrin levels in pregnancies complicated by oligohydramnios and fetal growth restriction. Jinekoloji-Obstetrik ve Neonatoloji Tıp Dergisi 2024;21(4):261–266.

Geliş/Received: 05.06.2024 • **Kabul/Accepted:** 17.06.2024

Sorumlu Yazar/Corresponding Author: Necati HANCERLIOGULLARI, Yüzüncü yıl işçi blokları 1506. Sk, Yıldız Apt. No:21/36, Çankaya 06230, Ankara, Turkey
E-mail: necatihancerliogullari@gmail.com

Çevrimiçi Erişim/Available online at: https://dergipark.org.tr/tr/pub/jgon

INTRODUCTION

Oligohydramnios is defined as diminished amniotic fluid volume (AFV) according to the gestational age. It was shown that reduced AFV is generally associated with poor fetal and neonatal outcomes (1). A physiological change in AFV is seen during the course of pregnancy. It gradually increases until the 36th week of pregnancy, afterwards it remains stable. Beyond the 40th gestational week, AFV tend to be decreased and oligohydramnios is frequently seen in postterm pregnancies. Many diseases or factors belong to the mother, placenta or fetus can cause this condition (2). However, the etiological factors cannot be defined in the half of the oligohydramnios cases and they are diagnosed during the last part of the pregnancy (3). Fetal growth restriction (FGR), on the other hand, is used to describe fetuses with an estimated fetal weight below a certain threshold for gestational age, most commonly under the 10th percentile or 2 SD according to growth curve (4, 5). The prevalence of FGR ranges between 0.5 % -5 %. It is commonly related with increased perinatal morbidity and mortality due to fetal distress, low Apgar score, and meconium aspiration syndrome, which are consequences of placental insufficiency (6, 7). It has also various etiological reasons. As in the oligohydramnios, the etiological factors cannot be defined in many of the cases and called as idiopathic FGR. It is believed that the underlying reason for this is placental insufficiency, which is pathophysiologically characterized by impaired placental development, incomplete decidual invasion of the cytotrophoblasts, and distortion of spiral arteries (7).

From the 6th week of pregnancy, the Renin-angiotensin system (RAS) is present in the fetal circulation and regulates blood pressure and fluid volume. All components of the RAS are located in the placenta. Circulating RAS is closely associated with villous and extravillous cytotrophoblast proliferation, extravillous cytotrophoblast invasion, cell migration and placental angiogenesis (89. Collectrin is a glycoprotein in the kidney's collecting system and functions in the RAS. It is structurally similar to angiotensin converting enzyme-2 (ACE-2). It has been shown that kidney superoxide radicals increase and nitric oxide (NO) decrease, resulting in impaired vasodilatation in collectrin knockout mice. NO is synthesized by an enzyme called endothelial NO synthase (eNOS) which is located in the vascular endtotelium. NO–eNOS formation is essential for the vascular tonus and regulates blood pressure. In the absence of collectrin, it has been observed that eNOS formation is impaired, causing hypertension (9, 10). In this study, we hypothesized that decreased collectrin levels might cause placental hypoperfusion, leading to oligohydramnios and FGR. We aimed to measure serum collectrin concentrations in oligohydramnios, FGR and low-risk term pregnancies and compare them with each other.

MATERIALS AND METHODS

Our study was planned as an observational cross-sectional study. It was performed on 125 consecutive pregnant women who applied to our hospital for pregnancy control between January and June 2021 and met the inclusion criteria. Our hospital is a state-supported 3rd level hospital and is placed in the capital city of Turkey, Ankara. All pregnant women included in the study had a confirmed pregnancy of 37 weeks and above. The patients were selected from women aged 18-44 years. Labor induction was decided for those diagnosed with oligohydramnios and FGR. Study groups consisted of isolated term oligohydramnios (group 1, n:40), idiopathic FGR (group 2, n:40) and low risk term pregnants (group 3, n:45). Exclusion criteria for the study groups were as follows; any systemic diseases such as hypertension, diabetes, renal disease, pathological obstetric conditions such as preeclampsia, preterm labor, multiple pregnancy, rupture of membranes, fetal anomalies, and placental abnormalities. AFV was determined using the amniotic fluid index (AFI) or deepest vertical pocket (DVP). A DVP value lower than 2 cm was considered as oligohydramnios. Alternatively, the abdomen was divided into four quadrants at the navel level to measure DVP in each quadrant. AFI, representing the sum of four DVPs less than 5 cm, was used to diagnose oligohydramnios (11). Fetal weight was estimated using four biometric measurements: abdominal circumference, femoral length, biparietal diameter, head circumference. Each measurement was repeated three times; the mean measurement was considered for the estimation of fetal weight according to the Hadlock method. The diagnosis of FGR was made when it was below the 10th percentile (12). The same experienced clinician performed the ultrasound scans. Each patient's blood

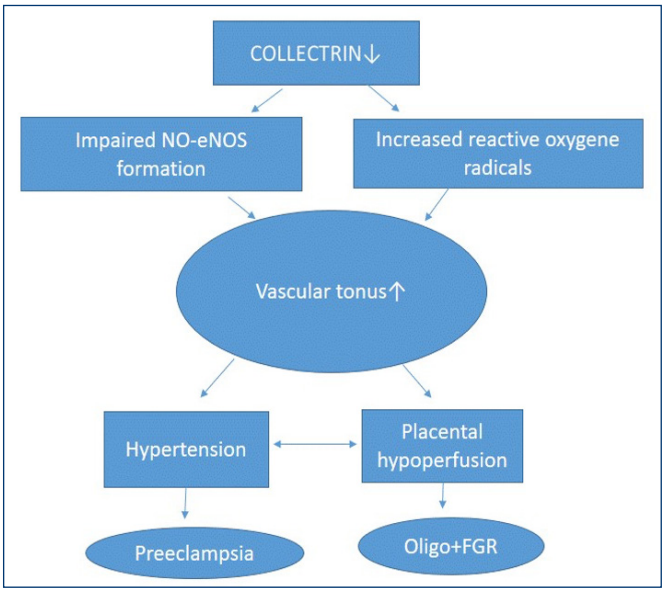

Figure 1. It shows the conditions that may develop due to changes in vascular structures in case of a decrease in collectrin level.

pressure and other vital signs were also recorded. Before active labor or labor induction, fasting venous blood samples were taken for routine tests and collectrin measurement. Blood sample for collectrin measurement was collected in an anticoagulant-free biochemistry tube, and were centrifuged for 15 seconds at 1,000 g. The serums were separated and frozen at -80 C until the working day. An enzyme-linked immunosorbent assay (ELISA) was used to determine serum colletrin levels (Human TMEM27 ELISA kit, Elabscience, catalog No. E-ELH5400, Bethesda, MD, USA). Manufacturer's instructions were followed. In the last step of the procedure, absorbance values were measured at 450 nm in a microplate reader. After drawing a standard curve from the measured absorbances against known concentrations, the collectrin levels were expressed in ng/ml. A written and verbal informed consent were taken from the all participants before the study enrollment. Institutional ethic committee approved by the study protocol (date/decision no: E2-21-455).

All data analyzes were calculated by using the SPSS software version 22.0 (Chicago, IL, USA). The normal distribution of the each variable was tested with Kolmogorov-Smirnov test. Data were presented as mean (SD) , median (range), numbaer (percentage). Comprisons of the variables among the groups were done by Kruskal wallis test, one way ANOVA with post-hoc Tukey's b test or chi sqaure test where appropraite. A P Value≤0.05 was considered statitstically significant.

RESULTS

A total of 125 pregnant women, 40 in the first two groups and 45 in the control group, were included into the study. There was no statistically significant difference in the mean maternal ages, weeks of gestation and body mass indexes in the groups (p>0.05). Gravidity, parity, number of previous misscarriges were similar. Weigh gain in pregnancy were statistically insignificant between the groups, but it is lowest in Group 2 and when compared Group 3 statistically remarkably lower (p:0.046). Number of pregnant women who smoked were comparable among the groups (p:0,272). While the mean blood pressures were similarly distributed between the groups, the values were measured within normal limits in each patient (Table 1).

Table 1. Comparison of clinical and demographic features of the groups.

GROUPS VARIABLES	Group 1 Oligohydramnios (n:40)	Group 2 FGR (n:40)	Group 3 Control (n:45)	P-value	pI-II	pI-III	pII-III
Age, (years)	26.5±5.1	26.1±5.4	26.9±5.6	0.236	0.735	0.443	0.270
Gravidity	2(1-5)	2(1-5)	2(1-5)	0.449	0.825	0.398	0.552
Parity	0(0-3)	0(0-3)	1(0-3)	0.218	0.731	0.196	0.186
Abortion	0(0-3)	0(0-2)	0(0-2)	0.667	0.532	0.593	0.896
Gestational age, (weeks)	39.2±1.0	38.8±1.2	39.4±1.0	0.110	0.095	0.742	0.067
BMI, (kg/m²)	29.8±4.6	28.5±5.2	29.5±4.9	0.720	0.564	0.880	0.876
Co-morbidity, n(%) **Hypothyroidism** **Asthma** **Arythmia**	 3(8.6) 0 1(2.9)	 3(8.6) 1(2.9) 0	 4(10) 0 0	0.479	0.428	0.334	0.456
GWG (kg)	12.9±5.4	11.2±4.6	14.1±5.3	0.059	0.356	0.589	0.046
AFI (total) (cm)	4.2±0.8	4.0±0.6	10.1±2.2	<0.001	0.668	<0.001	<0.001
Smoking, n(%)	2(5)	3(7.5)	5(11.1)	0.372	0.493	0.116	0.280
SBP (mmHg)	118.2±9.7	118.9±9.5	119.5±7.9	0.887	0.676	0.700	0.831
DBP (mmHg)	70.1±7.8	72.7±7.9	70.8±6.5	0.242	0.160	0.745	0.134
Pulse (/min)	87.7±8.5	88.7±7.9	90.1±8.1	0.480	0.864	0.272	0.340
Route of birth, n(%) **NVB** **C-Birth**	 28(70) 12(30)	 29(72.5) 11(27.5)	 27(60) 18(40)	0.588	0.982	0.269	0.216

BMI: body mass index, GWG: gestational weight gain, SBP: systolic blood pressure, DBP: diastolic blood pressure, NVB:normal vaginal birth, C-Birth: cesarean birth. Data were presented as mean±standard deviation (SD), median (range), number (percentage). A p value<0.05 was considered as statistically significant.

Table 2. Laboratory parameters and neonatal outcomes of the patients.

GROUPS VARIABLES	Group 1 Oligohydramnios (n:40)	Group 2 FGR (n:40)	Group 3 Control (n:45)	P-value	pI-II	pI-III	pII-III
Birth weight (gr)	3380±350	2750±255	3360±290	0.000	0.000	0.880	0.000
Birth height (cm)	50.5±1.5	48.5±1.4	50.2±1.5	0.000	0.000	0.912	0.000
Fetal gender, n(%) **Girl** **Boy**	 19(47.5) 21(52.5)	 23(57.5) 17(42.5)	 25(55.5) 20(45.5)	0.560	0.492	0.378	0.890
Apgar 1.'	7(5-7)	7(4-7)	7(6-7)	0.722	0.476	0.905	0.233
Apgar 5.'	9(8-9)	9(5-9)	9(8-9)	0.494	0.430	0.798	0.274
NICU admission, n(%)	3(7.5)	4(10)	2(4.4)	0.335	0.587	0.454	0.210
Glucose , (mg/dl)	82.1±9.8	80.5±9.7	78.7±8.8	0.300	0.749	0.269	0.699
Blood urea nitrogen, (mg/dl)	17.7±4.1	17.5±4.6	16.8±4.6	0.588	0.981	0.599	0.721
Creatinine , (mg/dl)	0.5±0.1	0.5±0.1	0.5±0.1	0.375	0.877	0.354	0.656
Total protein, (mg/dl)	67.1±4.0	65.1±4.7	66.9±4.5	0.137	0.172	0.983	0.214
Albumine, (mg/dl)	40.1±2.9	39.4±3.7	40.4±4.2	0.193	0.175	0.795	0.449
Aspartate transaminase, (U/L)	17.4±5.2	17.7±5.4	17.4±5.6	0.957	0.968	1.000	0.960
Alanine transaminase, (U/L)	15.5±9.4	15.4±6.9	14.9±7.1	0.938	0.999	0.945	0.955
Total bilirubin, (mg/dl)	0.5±0.2	0.5±0.2	0.6±0.2	0.654	0.972	0.794	0.651
Direct bilirubin, (mg/dl)	0.1±0.05	0.1±0.06	0.1±0.07	0.821	1.000	0.853	0.853
Sodium, (mEq/L)	137.5±2.1	137.3±1.8	137.3±1.9	0.767	0.812	0.792	1.000
Potassium, (mEq/L)	4.0±0.3	4.1±0.3	4.0±0.2	0.098	0.202	0.964	0.109
Clorid, (mEq/L)	106.3±2.2	105.0±2.3	105.9±1.6	0.029	0.026	0.698	0.140
Protrombin time, (sec.)	11.9±0.6	11.7±0.8	11.6±0.7	0.167	0.386	0.156	0.874
INR	1.02±0.06	0.99±0.05	0.98±0.06	0.049	0.151	0.050	0.901
aPTT, (sec.)	24.4±1.9	24.3±1.7	24.2±2.2	0.958	0.995	0.956	0.980
Fibrinogen, (mg/dl)	369.2±61.9	394.7±39.1	376.9±32.1	0.060	0.054	0.743	0.216
White blood cell, (10^9/L)	9.2±2.1	9.4±2.3	9.0±2.4	0.805	0.958	0.929	0.789
Hemoglobin, (g/dl)	12.2±1.4	12.0±1.4	11.7±1.1	0,364	0.786	0.331	0.739
Hematocrit, (%)	36.9±3.5	36.2±4.2	35.2±3.0	0.155	0.700	0.134	0.514
Platelet, (x10^3/mcL)	254.3±57.7	272.9±64.0	251.1±59.0	0.254	0.401	0.972	0.264
Collectrin, (ng/ml)	116.7±33.5	120.8±52.8	129.8±187.7	0.003	0.385	0.000	0.039

NICU:neonatal intensive care unit, INR: international normalized ratio, aPTT: activated partial thromboplastin time. Data were presented as mean±standard deviation (SD), median (range), number (percentage). A p value<0.05 was considered as statistically significant.

No significant difference were obseved between the groups in terms of delivery type and baby's gender (all $p > 0.05$). Birth weight was lower in Group 2 compared to Groups 1 and 3 as expected ($p < 0.001$). However, there was no significant difference between Apgar scores and NICU acceptance rates.

Comparison of hematological and biochemical parameters is shown in Table 2. Serum chloride levels were 106.3 ± 2.2 mmol/L in Group 1, 105.0 ± 2.3 mmol/L in Group 2, and 105.9 ± 1.6 mmol/L in Group 3 (p:0.020). Maternal serum collectrin values were 116.7 ± 33.5 ng/mL in oligphydrmnios group, 120.8 ± 52.8 ng/ml in FGR group and 129.8 ± 187.7 in control group (p:0.003). When pairwise comparisons were made between the groups, it was found that Group 1 and 2 were lower than Group 3 (both $p < 0.05$) and similar between Group 1 and Group 2 (p:385).

DISCUSSION

The current study sought to assess the relationship between maternal serum collectrin levels and FGR and oligohydramnios. Collectrin plays an essential role in regulating blood pressure. Oligohydramnios and FGR are the two common obstetric conditions, mainly due to placental vascular impairment. We found that the maternal serum collectrin level is significantly lower in pregnancies complicated with oligohydramnios and FGR than in low risk pregnancies.

AFV is the result of the balance between fluid production and absorption in the gestational sac. In the first half of pregnancy, lung secretions, maternal plasma transition throughout the fetal membranes, and fetal urine make up most of the amniotic fluid

production. After the 16th week of gestation, fetal kidneys begin urine production, and fetal urine comprises the vast majority of AFV until delivery (13). Therefore, the anomalies in the fetal genitourinary system that result in oligohydramnios are usually diagnosed from the 16th to the 18th week of gestation. There are three (maternal-fetal and placental) leading causes of oligohydramnios. Oligohydramnios due to maternal causes is usually associated with some systemic diseases or obstetric conditions that cause uteroplacental insufficiency. Possible causes include particularly vascular disease such as hypertension, preeclampsia, diabetes, and substance abuse, some drugs, and hereditary or acquired thrombophilias (14). Among the fetal causes, the most common cause is premature rupture of amniotic membranes. Fetal genitourinary abnormalities are also associated with oligohydramnios. Post-term pregnancies, FGR, chromosomal abnormalities, and fetal demise are other causes of oligohydramnios (14). Placental pathologies, including placental detachment and twin transfusion syndrome, comprise the minority of cases. Idiopathic oligohydramnios is, particularly in the last trimester, the most common (higher than 50% of cases) form of oligohydramniosis and typically has a favorable obstetric outcome. There is very little data evaluating the relationship between oligohydramnios and placental histology. Acute and occult placental hypoperfusion may be an underlying reason for idiopathic oligohydramnios. In our study, compatible with the literature, idiopathic cases were diagnosed at term, and most had better neonatal outcomes. We also diagnosed oligohydramnios using MVP and AFI measurements (15).

The diagnosis of FGR is made according to an estimated fetal weight below -2 SD or below the 10th percentile on the growth curve. On the other hand, small for gestational age (SGA) is considered as birth weight under the 10th percentile for babies born at that gestational age. These two terms cannot fully correspond to each other. FGR also known as intra uterine growth restricted fetus means growth abnormality (slowing and stopping of fetal growth with or without abnormal Doppler measurements) or being a change in fetal measurement rates in follow-ups during the course of pregnancy (at least two measurements with three weeks apart) (15). Rarely, they may correspond with inadequate growth, with a weight near the 10th percentile without being SGA. Different cut-off values have been identified for the definition of FGR, such as the 10th, 5th, and 3rd percentiles. However, the severity of FGR increases when lower threshold values are used. Idiopathic FGR cases may be a mild form of the spectrum. In this study, we used the 10th percentile, and all cases were between the 5th and 10th percentiles (15).

Collectrin was first identified in the kidney as a collecting duct-specific transmembrane glycoprotein (9). It is expressed mainly in the kidneys, with the highest levels in the collecting ducts and proximal tubules. There was a 47.8% structural similarity between collectrin and ACE-2. Although collectrin has high molecular similarity with ACE-2, it does not contain any catalytic activity. Disturbances in the expression of enzymes that process angiotensin (Ang) have been observed in the placentas of pregnant women with idiopathic FGR. This causes the imbalance between the vasoconstrictor and vasorelaxant branches of the placental RAS system to be disrupted and Ang-2, which is known to have a vasoconstrictor effect, becomes dominant. Ang-(1-7) has a vasodilator effect and the opposite effect of Ang-2's vasoconstrictor effect. These two factors are associated with FGR, which occurs with the disruption of uteroplacental perfusion [9]. Placental RAS is significant in the development of the functions of the placenta. Placental RAS may also be effective in the deterioration of uteroplacental perfusion in idiopathic fetal developmental retardation (4). ACE-2 is localized in placental syncytial layer, and in case of its disruption, umbilical blood flow and placental perfusion are impaired in the FGR that occurs.[9] In FGR pregnancies, it has been observed that there is a decrease in AFV due to placental disruption.[10] Collectrin and ACE-2 are homologous molecules, but the effects of Collectrin were found to be independent of RAS (10). Collectrin adjusts vascular tonus through NO produced by eNOS; in the absence of collectrin, hypertension occurs.[9] It has been shown that endothelium-dependent vasodilation is impaired as a result of the production of less NO and more superoxide radicals in the kidneys of collectrin knock-out mice (10). L-Arginine is an essential amino acid for NO synthesis and is transported into the cell by collectrin. It has been shown that L-arginine uptake is reduced in endothelial cells of collectrin knockout mice. These findings suggest that the collectrin provides a balance between NO and superoxide by assisting the uptake of L-arginine for NO synthesis, thus having a protective role against endothelium-dependent vasoconstriction and hypertension. Çetin et al. demonstrated that serum collectrin concentrations were significantly lower in pre-eclamptic patients than in control patients, even if they found lower levels in early- onset preeclampsia than in late-onset preeclampsia (16). Similarly, a recent study conducted on pre-eclamptic women also demonstrated that collectrin was lower in early-onset preeclampsia than in late-onset preeclampsia and healthy controls. They found a significant inverse correlation between serum collectrin levels and blood pressure (17). We excluded hypertensive and pre-eclamptic patients, and all women included in the study had blood pressure within normal ranges. Therefore, we could not demonstrate such a relationship between collectrin and blood pressure.

The primary weakness of our study is the scarce of sample size. The cross sectional nature of the study design does not imply a cause-effect relationship. The lack of knowledge about placental

expression of collectrin levels, which would likely provide more accurate data, also limited the study hypothesis. However, our results collectively demonstrated a novel molecular biomarker that contributes to the physiopathology of idiopathic oligohydramnios and FGR. These findings may lead to new diagnostic and therapeutic insights into these two obstetric entities.

In brief, maternal circulating collectrin levels were significantly lower in pregnancies diagnosed with oligohydramnios and FGR. Collectrin may be a valuable biomarker for diagnosing oligohydramnios and FGR characterized by placental hypoperfusion. Our results should be supplemented with further molecular and immunohistochemical studies, including more cases, to reveal the precise relationships between collectrin, oligohydramnios, and FGR.

Institutional Review Board Statement
The study was conducted according to the guidelines of the Declaration of Helsinki, and approved by the Institutional Review Board of the Ankara Cİty Hospital (E2-21-455).

Author Contributions
Conceptualization, M.C. and S.Y.; Methodology, M.C.; S.Y.; E.M.K.; Software, N.H.; Validation, M.C., S.Y. and N.H.; Formal Analysis, T.C. and A.T.; Investigation, M.C.; S.Y.; N.H.; Resources, M.C and N.H.; Data Curation, A.T.; Writing – Original Draft Preparation, N.H.; Writing – Review & Editing, A.T.; Visualization, N.H. and A.T.; Supervision, A.T.; Project Administration, N.H.

Informed Consent Statement
Written informed consent has been obtained from the patients to publish this paper.

Conflicts of Interest
The authors declare no conflict of interest.

Funding
This research received no external funding.

Acknowledgments: We thank to all pregnant women who voluntarily participated in this study.

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Jinekoloji - Obstetrik ve Neonatoloji Tıp Dergisi
The Journal of Gynecology-Obstetrics and Neonatology

ÖZGÜN ARAŞTIRMA / ORIGINAL ARTICLE

DOI: 10.38136/jgon.1496614

İkinci trimester maternal serum serbest estriol seviyesinin yenidoğan umblikal arter pH değeri ile ilişkisi

The relationship between second trimester maternal serum free estriol levels and newborn umbilical artery pH values

Gülbahar OLUKÇU[1], Necati HANCERLİOGULLARİ[1], Merve Didem EŞKİN TANRIVERDİ[1], Yasemin DADAŞ[1], Aytekin TOKMAK[2]

[1]Sağlık Bilimleri Üniversitesi, Ankara Şehir Hastanesi, Kadın Hastalıkları ve Doğum Anabilim Dalı, Ankara, Türkiye
[2]Kırıkkale Üniversitesi Tıp Fakültesi Kadın Hastalıkları ve Doğum Anabilim Dalı, Kırıkkale, Türkiye

ÖZ

Amaç: Üçlü tarama testi özellikle Down Sendromu olmak üzere bazı fetal kromozomal anormalliklerini tayin etmek için kullanılır. Bunun yanısıra olumsuz gebelik sonuçları ile de bağlantılı olduğu yapılan çalışmalarda tespit edilmiştir. Çalışmamızda üçlü test parametrelerinden serum serbest estriol seviyesinin fetal distres tanısı ile sezaryene alınan hastaların bebeklerinin kan pH değerleri ile ilişkisinin olup olmadığını belirlemeyi amaçladık.

Gereç ve Yöntemler: 1 Ocak 2022-31 Aralık 2022'ye kadar Ankara Bilkent Şehir Hastanesi Kadın hastalıkları ve doğum bölümünde doğum eylemi sırasında fetal distress tanısı ile sezaryene alınan toplam 901 gebe gözden geçirilmiştir. İkinci trimester taramasını hastanemizde yaptıran 270 gebe çalışmaya dahil edilmiştir. Maternal yaş, vücut kitle indeksi (VKİ), gebelik haftası, doğum süreci ve üçlü test sonuçları ile her bir yenidoğanın doğum sonrası umblikal arter kan gazı değerleri kaydedilmiştir.

Bulgular: Hastalar estriol değerine göre 1 mom'un altı (grup 1, n:163) ve üstü (grup 2:107) olarak iki gruba ayrılmıştır. Gruplar arasında maternal yaş, VKİ, gebelik haftası, doğum indüksiyonu, APGAR skoru, mekonyum varlığı, yenidoğan cinsiyeti, yenidoğan yoğun bakım ünitesi başvuru oranları gibi parametreler arasında istatistiksel olarak anlamlı bir farklılık bulunmadı (p>0.05). Umblikal kord pH değeri grup 1'de 7,26-0,51 grup 2'de 7,32-0,08 olduğu belirlenmiştir (p:0.188).

Sonuç: Fetal distres nedeniyle sezaryene alınan gebelerin yenidoğanlarında umblikal arter pH düzeyi istatistiksel olarak anlamlı olmasa da ikinci trimester serum serbest estriol düzeyleri 1 mom'un altında olanlarda daha düşüktür.

Anahtar Kelimeler: Fetal distres, umblikal kord, yenidoğan yoğun bakım, estriol, pH

ABSTRACT

Aim: The triple screening test is used to detect certain fetal chromosomal abnormalities, especially Down syndrome. In addition, studies have found that it is also associated with adverse pregnancy outcomes. In our study, we aimed to determine whether there is a relationship between serum free estriol levels, one of the triple test parameters, and the blood pH values of the babies of patients who underwent cesarean section due to fetal distress.

Materials and Methods: A total of 901 pregnant women who underwent cesarean section due to fetal distress during labor at Ankara Bilkent City Hospital's Department of Obstetrics and Gynecology between January 1, 2022, and December 31, 2022, were included in the study. A total of 270 pregnant women who underwent second trimester screening at our hospital were included in the study. Maternal age, body mass index (BMI), gestational age, labor process and triple test results, along with each newborn's postnatal umbilical artery blood gas values, were recorded.

Results: Patients were divided into two groups based on their estriol values: below 1 mom (group 1, n=163) and above 1 mom (group 2, n=107). There were no statistically significant differences between the groups in terms of maternal age, BMI, gestational age, induction of labor, APGAR score, presence of meconium, newborn sex, and neonatal intensive care unit admission rates (p>0.05). The umbilical cord pH value was determined to be 7.26 ± 0.51 in group 1 and 7.32 ± 0.08 in group 2 (p: 0.188).

Conclusion: Although not statistically significant, the umbilical artery pH level in newborns of mothers who underwent cesarean section due to fetal distress is lower in those with second trimester serum free estriol levels below 1 .

Keywords: Fetal distress, umbilical cord, neonatal intensive care, estriol, pH

Cite as: Olukçu G, Hancerliogullari N, Eşkin Tanrıverdi MD, Dadaş Y, Tokmak A. İkinci trimester maternal serum serbest estriol seviyesinin yenidoğan umblikal arter pH değeri ile ilişkisi. Jinekoloji-Obstetrik ve Neonatoloji Tıp Dergisi 2024;21(4):267–273.

Geliş/Received: 05.06.2024 • **Kabul/Accepted:** 03.10.2024

Sorumlu Yazar/Corresponding Author: Necati HANCERLIOGULLARI, Yüzüncü yıl işçi blokları 1506. Sk, Yıldız Apt. No:21/36, Çankaya 06230, Ankara, Turkey
E-mail: necatihancerliogullari@gmail.com

Çevrimiçi Erişim/Available online at: https://dergipark.org.tr/tr/pub/jgon

GİRİŞ

Fetal distres, fetüse oksijen sağlanmasının azalması nedeniyle metabolik asidozun meydana geldiği patolojik bir durum olarak tanımlanabilir (1). Umblikal kordon kanından bakılan pH değeri doğum sonrasında neonatal hipoksiyi tayin etmek ve doğum sonrası bakım planı için en doğru kararları alabilmek için var olan en iyi parametredir (2-4). Umblikal arter kan gazı daha çok fetal metabolik durumun bir göstergesi iken umblikal venöz kan gazı değerleri doğumda fetal-plesantal oksijenizasyon için değerli ve güvenilir bilgiler verir. Ek olarak kordon kanı pH değeri ile düşük apgar skoru, yenidoğan yoğun bakım ünitesine (YYBÜ) giriş ve ileri resüsitasyon gereksinimi gibi selektif neonatal sonuçların insidansı arasında anlamlı bir ilişki gösterilmiştir (4, 5). Umblikal kordon kan gazının (UKKG) normal pH aralığı 7.40-0.20 olup, doğumda umblikal kordun arteriyel kanındaki metabolik asidoz genellikle pH <7,00 veya <7,05 ve baz açığı (BE) >12,0 mmol/L olarak tanımlanır. Bu değerlerin altındaki değerlere sahip yenidoğanlarda nöbet geçirme riski, entübasyon olasılığı, YYBU giriş riski ve mortalite artar (6). Tüm doğumlarda neonatal durum hakkında bir fikre sahip olmak ve fetusun hipoksiye maruz kalıp kalmadığını bilebilmek için UKKG analizinin kullanılması yönünde giderek artan bir tutum vardır. Fetal distres, fetal morbidite ve mortaliteyi azaltmak obstetride altın amaçtır. Aynı zamanda gereksiz sezaryen oranının azaltması da önemlidir (7). Travay sırasında yapılan fetal izlemde Non stress test (NST) ile tanımlanan fetal distres mevcudiyeti en sık sezaryen (C/S) endikasyonlarından birini oluşturmaktadır. Günümüzde fetüsün anne karnında değerlendirilmesinde; kardiyotokogram (CTG yada NST), amnion sıvı indeksi, fetal biofizik profil, fetal doppler belirteçleri, kontraksiyon stress test (CST), fetal saçlı deri kan örnekleri, kordon kanı laktat, arginin, vasopressin ve Apgar skoru sıklıkla kullanılan parametrelerdir.

Östrojenler, önemli fizyolojik olayları yöneten yapısal olarak benzer steroidlerdir. Menopoz öncesi kadınlarda temel olarak overlerden üretilen 17-β-estradiol (E2) en bol ve güçlü östrojendir. E2 geri dönüşümlü olarak estrona (E1) oksitlenir ve hem E2 hem de E1, geri dönüşümsüz olarak estriol (E3)'e dönüştürülebilir ve yine doğrudan androstenediondan E3 üretilebilir. E3 zayıf östrojenik etkiye sahip bir steroid hormon bileşiğidir (8, 9). E3 gebelik sırasında plasenta tarafından üretilen başlıca östrojendir, fetoplasental ünitenin fonksiyonu hakkında en iyi bilgiyi verirken gebelik sürecinde özellikle üçüncü trimesterda hem serbest hem total estriol düzeylerinde yaklaşık 1000 kat artışlar görülür (9).

Fetüs, uterin kontraksiyonlara sekonder oluşan kısa süreli oksijen kesintisini tolere edebilmektedir. Fetal distres, oksijen yoksunluğuna bağlı asidoz semptomlarına fetal yanıtların toplamı olarak tanımlanabilse de, terminolojik olarak ilerleyici asidoz ve hipoksiye bağlı fetal hasar ve yaklaşan ölüm olarak tanımlanır. Başka bir tanıma göre ise uteroplasental kan akımının uzun veya kısa süreli olarak azaldığı veya kaybolduğu ve fetüsün hipoksi yaşadığı tablodur (10, 11). Hipoksi; oksijen eksikliği demektir, sonuç olarak metabolik asidoz gelişir. Fetal kalp hızı (FHR) kemorefleks, barorefleks ve merkezi sinir sistemi dahil olmak üzere otonom sinir sistemi tarafından düzenlenir. Uygun regülasyon, doku oksijenasyonu ile sağlanır. Bu nedenle, fetal hipoksi veya asidoz meydana geldiğinde bazal FHR fizyolojik instabilitesi azalır ve değişkenliğin azalmasına yol açar. Bazı uzmanlar fetal distresi, elektronik fetal monitörizasyonda kısa süreli değişkenlik kaybı, şiddetli değişken deselerasyonlar ya da fetal kalp atım hızının geç deselerasyonlarıyla beraber taşikardi şeklinde görmektedir (12). Diğer grup yazarlar için fetal distresin olmazsa olmazı için fetal asidoz gereklidir

Diğer bir önemli konu ise fetal asfiksi konusudur. Perinatal asfiksi, yenidoğanlarda morbidite ve mortalitenin ana nedenlerinden biridir. Hem sosyal hem de ekonomik olarak yüksek maliyetler üretir ve değiştirilebilir risk faktörleri sunar (13). Bu olaylar doğum sırasında fetal oksijen eksikliği ve/veya yetersiz doku perfüzyonu nedeniyle ortaya çıkabilir (14). Sonuç olarak asfiksi hipoksemiye sekoder oluşan organ hasarıdır diyebiliriz. Asfiksinin vereceği hasar şiddeti ile orantılıdır. Oksijenizasyondaki bozulma fetal kalp atımını etkilmekte ve fetal distrese neden olmaktadır. Düşük riskli term yenidoğan için doğumda umbilikal arter pH'ı <7,0 insidansı 1000'de 3,7'dir, bunlardan %17,2 neonatal nörolojik morbidite ile hayatta kalmıştır, %16.3 nöbet geçirmiştir ve %5,9 yenidoğan döneminde ölmüştür. Kordon pH'ı <7.0 ile doğan term bebeklerde neonatal nörolojik morbidite ve mortalite insidansı %23,1 iken hipoksik-iskemik ensefalopati insidansı 1000 canlı doğumda 2,5'tir; intrapartum hipoksi-iskemi ile ilişkili serebral palsinin oranı %14,5'tir (14).

Perinatal asfiksi, uzun dönem sekelleri dikkate alındığında hem tedavi hem bakım maliyetleri açısından aileler için maddi olarak zorlayıcı olduğu kadar manevi olarak da çok zor durumlara neden olmaktadır. Bu nedenlerle özellikle intrapartum gelişen fetal hipoksinin öngörülüp önlenebilmesi oldukça hayati önem taşımaktadır. Bu çalışmada amacımız üçlü test parametrelerinden serum serbest E3 seviyesinin fetal distres tanısı ile sezaryene alınan hastaların bebeklerinin kan pH değerleri ile ilişkisinin olup olmadığını belirlemektir.

MATERYAL VE METOT

Bu araştırma retrospektif kohort bir araştırma olarak tasarlanmıştır. Ankara Bilkent Şehir Hastanesinde takipli olup fetal distres tanısı ile sezaryene alınan hastalarımız değerlendirilmiştir. Çalışmamız için

Sağlık Bilimleri Üniversitesi Ankara Bilkent Şehir Hastanesi Klinik Araştırmalar Etik kurulu (E2-22-3030)'ndan 18/01/2023 tarihinde onay alınmıştır. 1 Ocak 2022'den 31 aralık 2022'ye kadar, Ankara Bilkent Şehir Hastanesi Kadın Hastalıkları ve Doğum Bölümü Antenatal (Gebe) Polikliniği'ne başvurup NST baz alınarak fetal distres tanısı ile sezaryene alınan 901 gebe tarandı. Bu gebelerden 270 tanesi hastanemizde ikinci trimester taramasını yaptırmış olup, tarama testini hastanemizde yaptıran gebeler çalışmaya dahil edildi. Hastalar ikinci trimester tarama testi sırasında bakılan serbest estriol mom değerlerine göre 1 altındakiler ile 1 ve üzerindeki hastalar olarak iki gruba ayrılmıştır. Maternal gebelik yaşı, son adet tarihine göre hesaplanıp 36 hafta üzeri gebeler çalışmamıza dahil edildi. Anormal fetal karyotipleri, gebelik komplikasyonları (erken doğum, gebeliğe bağlı hipertansiyon/preeklampsi, gestasyonel diyabet, intrauterin büyüme kısıtlılığı ve plasental dekolman) ve sistemik hastalıkları (kronik hipertansiyon, tip 1 ve tip 2 diyabet) olan gebeler çalışma dışı bırakıldı.

Her hastanın obstetrik öyküsü, demografik özellikleri kaydedildi. Tüm hastaların ultrasonografik muayene ve doğum eylemi kayıtları incelendi. Hastaların yaş, VKİ, sigara kullanımı, doğum sayısı, fetal cinsiyet, sezaryene alındıkları hafta, indüksiyon varlığı, doğum süresi, mekonyum varlığı, sezaryene alındığı sıradaki servikal muayene bulguları, yenidoğan Apgar skorları, UKKG pH değerleri gibi parametreler kaydedildi. Yenidoğan yoğun bakım yatış öyküsü gibi gebelik komplikasyonları araştırılıp kayıt altına alındı. UKKG örnekleri bebek doğar doğmaz umblikal arterlerden yaklaşık 2 cc heparinize enjektörlere alınarak, en kısa sürede (en geç 20 dk içinde) kan gazı çalışılması için laboratuvara teslim edilmiştir. Takip edilen her bir gebenin estriolü de içeren ikinci trimester üçlü tarama testi sonuçları kaydedildi.

İstatiksel Analizler

Gravide, parite, anestezi şekli, bebeğin cinsiyeti, tanı gibi demografik bilgilerde bireylerin dağılımını göstermede sayı (n) ve yüzde (%) değerleri kullanıldı.Çalışmada yer alan sürekli değişkenlerin normal dağılıma uygunluğu grafiksel olarakve Shapiro-Wilks testi ile değerlendirildi. Sürekli değişkenlerin hiçbirinin normal dağılıma uymadıkları belirlendi. Değişkenlerin tanımlayıcı istatistiklerinin gösteriminde Ortalama±SS(standart sapma) ve Medyan (Çeyreklikler Arası Genişlik-ÇAG Interquartile Range - IQR)değerleri verildi.Estroil sınıflamasına göre pH, Yaş, BMI değerlerinin karşılaştırmalarında Mann-Whitney U testi kullanıldı. Tanı gruplamasına göre pH değerinin karşılaştırılmasında Kruskal Wallis non-parametrik varyans analizine başvuruldu.Estroil sınıflaması ve pH sınıflamasına göre kategorik değişkenlerin karşılaştırılmasında çapraz tablolar oluşturuldu, sayı (n), yüzde (%) ve ki kare (χ^2) testistatistiği verildi. Doğum süresi ile pH değeri arasında yapılan korelasyon analizinde spearman non-parametrik korelasyon katsayısı verildi. İstatistiksel analizler ve hesaplamalar için IBM SPSS Statistics 21.0 (IBM Corp.Released 2012. IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY: IBM Corp.) ve MS-Excel 2007 programları kullanılmıştır. İstatistiksel anlamlılık düzeyi $p<0.05$ olarak kabul edilmiştir.

BULGULAR

Bu çalışmaya 270 hasta dahil edildi. Çalışmaya katılan bireylerin yaş ortalaması 28.39±4.61 yıl, VKİ ortalaması 29.17±4.08 kg/m^2 olduğu belirlenmiştir. Bireylerin %31.5'inde (n=85) mekonyum var iken, %68.5'inde (n=185) mekonyum yoktur. Sigara kullanan birey bulanmamaktadır. Bireylerin %30.4'ünde (n=82) anestezi şekli genel, %69.6'sında (n=188) spinaldir. Bebeklerin cinsiyetine baktığımızda %57.8'i (n=156) erkek, %42.2'si (n=114) kız olduğu belirlenmiştir. Ayrıca bebeklerin Apgar skoru ortalaması 7.47±0.83'dir. Bireylerin gebelik haftası ortalaması 40.49±20.59, HCG mom ortalaması 0.90±0.45, E3 mom ortalaması 0.95±0.35, pH ortalaması 7.28±0.40 olduğu tespit edilmiştir. Bireylerin tanılarına baktığımızda %11.9'unda (n=32) gün aşımı, %12.2'sinde (n=33) güven vermeyen NST %21.1'inde (n=57) membran rüptürü (MR), %35.2'sinde (n=95) miadında sancılı gebelik (MSG), %15.9'unda (n=43) oligohidramnios, %2.2'sinin (n=6) taşikardi olduğu saptanmıştır. Augmentasyon olan 124 birey (%45.9), propes olan 31 birey (%11.5) bulunmaktadır. Ortalama doğum süresi 9.39±8.82 saat olduğu belirlenmiştir. Yoğun bakıma kabul olan 33 yenidoğan (%12.2) bulunmaktadır. Çalışmamızda E3 değerine göre 1 mom altı ve 1 mom ve üzeri olamak üzere iki gruba ayrılmıştır. Estroil sınıflamasında 1'in altında olan bireylerin pH ortalaması 7.26±0.51, 1 ve üzerinde olan bireylerin pH ortalaması 7.32±0.08 olduğu belirlenmiştir. Grupların pH değerleri arasında istatistiksel olarak anlamlı bir farklılık tespit edilmemiştir (p=0.188)..

Ayrıca E3 sınıflamasına göre pH 7,0 olarak baz alındığında (<7,00 - ≥7,00) dağılımı açısından istatistiksel olarak anlamlı bir farklılık tespit edilmemiştir (p=0.218) yine E3 sınıflamasına göre indüksiyon alma dağılımı açısından istatistiksel olarak anlamlı bir farklılık saptanmamıştır (χ^2=0.239**,** p=0.625). Estroil değeri 1'in altında olan bireylerde pH sınıflamasına göre augmentasyon, propes, ve augmentasyon ve propes olma dağılımı açısından istatistiksel olarak anlamlı bir farklılık tespit edilmemiştir (p>0.05). Estroil sınıflamasında 1'in altında olan grupta doğum süresi ile pH değerleri arasında istatistiksel olarak anlamlı bir ilişki bulunmamaktadır (p>0.05). Ayrıca Estroil sınıflamasında 1 ve üzerinde olan grupta doğum süresi ile pH değerleri arasında da istatistiksel olarak anlamlı bir ilişki bulunmamaktadır. Estroil sınıflamasına göre yoğun bakıma kabul dağılımı açısından istatistiksel olarak anlamlı bir farklılık tespit edilmemiştir (p=0.576**,** p=0.448) Estriol sınıflamasına göre

Tablo 1. Estroil seviyelerine göre gruplarda halinde demografik özellikler ve teslimat sonuçları

		ESTRİOL		
Parametre		**<1 mom (n=163)**	**≥1 mom (n=107)**	**p**
PH		7.26±0.51	7.32±0.08	0.188
Anne yaşı, yıl*		28.6±4.5 (19-41)	28.0±4.8 (19-42)	0.219
BMI, kg/m^{2*}		29.3±4.1 (21-41)	28.9±4.1 (18-40)	0.576
Parite, n**		0 (0) (0-5)	0 (1) (0-4)	0.052
Doğumda gebelik yaşı, hafta*		39.2±1.4 (36-41)	39.3±1.1 (36-41)	0.670
Bebek cinsiyeti, n	Erkek	99	57	0.258
	Kız	64	49	
Mekonyum, n (%)		53 (%32.5)	31 (%29.2)	0.572
Yeni doğan kabul, n (%)		18 (%11.0)	15 (%14.2)	0.448
Doğum indüksiyonu Augmentasyon, n (%)		78 (%47.9)	46 (%43.4)	0.474
Doğum indüksiyonu Propes, n (%)		21 (%12.9)	10 (%9.4)	0.387
Doğum indüksiyonu Augmentayon+Propes, n (%)		88 (%54.0)	54 (%50.9)	0.625
	Günasımı	21	11	0.897
	Gvnst	17	16	
	MR	37	20	
	MSG	56	38	
	Oligohidramnios	26	17	
	Taşikardi	4	2	
	Diğer	2	2	

*Ortalama±SS (Min-Max)
**Medyan (ÇAG) (Min-Max)

5. dakika Apgar skoru sınıflamasının dağılımı açısından istatistiksel olarak anlamlı bir farklılık tespit edilmemiştir (p=2.927**,** p=0.087). pH sınıflamasına göre 5. dakika apgar skoru sınıflamasının dağılımı açısından ise istatistiksel olarak anlamlı bir farklılık tespit edilmiştir (p=0.005). Estroil sınıflamasında 1'in altında olan bireylerin %11.0'inde (n=18) yoğun bakıma kabul olmuş, estroil sınıflamasında 1 ve üzerinde olan bireylerin %14.2'sinde (n=15) yoğun bakıma kabul olmuştur. Estroil sınıflamasına göre yoğun bakıma kabul dağılımı açısından istatistiksel olarak anlamlı bir farklılık tespit edilmemiştir (p=0.448).

Estroil değeri 1'in altında olan bireylerde, mekonyum var olanların %21.6'sının (n=11) pH değeri <7,25, %78.4'nün (n=40) pH değeri ≥7.25, mekonyum olmayan bireylerin %17.3'nün (n=19) pH değeri <7,25, %82.7'sinin (n=91) pH değeri ≥7,25'dir. Estroil değeri 1'in altında olanlarda, mekonyum durumuna göre pH (<7,25 - ≥7,25) dağılımı açısından istatistiksel olarak anlamlı bir farklılık tespit edilmemiştir (p=0.424**,** p=0.515). Estroil değeri 1 ve üzerinde olan bireylerde, mekonyum var olanların %9.7'sinin (n=3) PH değeri <7.25, %90.3'nün (n=28) pH değeri ≥7,25, mekonyum olmayan bireylerin %14.7'sinin (n=11) pH değeri <7,25, %85.3'ünün (n=64) pH değeri ≥7,25'dir. Estroil değeri 1 ve üzerinde olanlarda, mekonyum durumuna göre pH (<7,25 - ≥7,25) dağılımı açısından istatistiksel olarak anlamlı bir farklılık tespit edilmemiştir (p=0.424**,** p=0.515).

Estroil sınıflamasında 1'in altında olan grupta doğum süresi ile pH değerleri arasında istatistiksel olarak anlamlı bir ilişki bulunmamaktadır (p>0.05). Ayrıca estroil sınıflamasında 1 ve üzerinde olan grupta doğum süresi ile pH değerleri arasında da istatistiksel olarak anlamlı bir ilişki bulunmamaktadır (p>0.05) (Tablo 2).

Tablo 2. Estroil sınıflamasında doğum süresi ile pH arasındaki ilişki

	11'in altında		**1 1 ve üzeri**	
	Doğum Süresi		**Doğum Süresi**	
	r	**p**	**r**	**p**
PH	0.009	0.911	-0.149	0.128

r: Spearman İlişki Katsayısı

Tablo 3. Estriol sınıflamasına göre yoğun bakım kabul durumlarının karşılaştırılması

	Estriol sınıflaması			
	11'in altında n (%)	1 1 ve üzeri n (%)	Test istatistiği	
			χ^2	p
Yoğun Bakım Kabul				
Evet	18 (110)	15 (14.2)	0.576	0.448
Hayır	145 (89.0)	91 (85.8)		

Tablo 4. Estriol sınıflamasına göre APGAR skoru sınıflamasının karşılaştırılması

	PH SINIFLAMASI			
	<7.25 n (%)	≥7.25 n (%)	Test istatistiği	
			χ^2	p
APGAR Skoru Sınıflaması				
6 ve altında	8 (18.2)	11 (4.9)	-	**0.005***
7 ve üzeri	36 (81.8)	212 (95.1)		

	Estriol sınıflaması			
	11'in altında n (%)	1 1 ve üzeri n (%)	Test istatistiği	
			χ^2	p
APGAR Skoru Sınıflaması				
6 ve altında	8 (4.9)	11 (10.4)	2.927	0.087
7 ve üzeri	155 (95.1)	95 (89.6)		

Estroil sınıflamasında 1'in altında olan bireylerin %11.0'inde (n=18) yoğun bakıma kabul olmuş, %89.0'unda (n=145) yoğun bakıma kabul olmamış, estroil sınıflamasında 1 ve üzerinde olan bireylerin %14.2'sinde (n=15) yoğun bakıma kabul olmuş, %85.8'inde (n=91) yoğun bakıma kabul olmamıştır. Estroil sınıflamasına göre yoğun bakıma kabul dağılımı açısından istatistiksel olarak anlamlı bir farklılık tespit edilmemiştir (p=0.576**,** p=0.448) (Tablo 3).

Estroil sınıflamasına göre Apgar skoru sınıflamasının dağılımı açısından istatistiksel olarak anlamlı bir farklılık tespit edilmemiştir (χ^2=2.927**,** p=0.087) (Tablo 4). pH sınıflamasında <7,25 olan bireylerin %18,2'sinde (n=8) 5. dakika apgar skoru 6 ve altında, %81.8'inde (n=36) Apgar skoru 7 ve üzerinde, pH sınıflamasında ≥7,25 olan bireylerin olan bireylerin %4,9'unda (n=11) Apgar skoru 6 ve altında, %95,1'inde (n=212) Apgar skoru 7 ve üzerindedir. pH sınıflamasına göre apgar skoru sınıflamasının dağılımı açısından istatistiksel olarak anlamlı bir farklılık tespit edilmiştir (p=0.005)

Estroil değeri 1'in altında olan bireylerde, pH sınıflamasında <7,25 olanların %13.3'ünde (n=4) bebeğin Apgar skoru 6 ve altında, %86.7'sinde (n=26) bebeğin Apgar skoru 7 ve üzerinde, pH sınıflamasında ≥7,25 olan bireylerin olan bireylerin %3,1'inde (n=4) apgar skoru 6 ve altında, %96.8'inde (n=127) Apgar skoru 7 ve üzerindedir. Estroil değeri 1'in altında olanlarda, pH sınıflamasına göre apgar skoru sınıflamasının dağılımı açısından istatistiksel olarak anlamlı bir farklılık tespit edilmiştir (p=0.040).

TARTIŞMA

Gebelikte fetal sağlık için E3 önemli bir belirteçtir. Çünkü E3 fetomatrnal ünite tarafından üretilir. Fetal adrenal gland E'ün temel prekürsörlerini üretir (androstenodion gibi) ve plasenta bu prekürsörleri estriole çevirir. Bir çalışmada E3 için eşik değeri 0,6 mom kullanıldığında bu değerin altında unkonjuge E3 düzeyi ile oligohidramniyos, erken membran rüptürü (EMR), preterm eylem, eklampsi, preeklampsi, hipertansiyon, intrauterin gelişme geriliği (IUGG) arasında anlamlı bir ilişkinin mevcut olduğu gösterilmiştir (15).

Ölçülemez düzeyde estriol saptanması (<0,25 ng/ml); dışardan gebelikte steroid alınması, anensefali, adrenal yetmezlik, doğumsal

adrenal hipoplazi, doğumsal panhipopitüarizm, konjenital adrenal hiperplazi 17α-hydroxylase lipoid adrenal hyperplasia Antley-Bixler syndrome ve diğer metabolizma defektleri (steroid sulfataz defekti, multiple sulfataz defekti – zellweger sendromu, Smith-Lemli-Opitz sendromu, Aromataz defekti) ile ilişkilendirilmiştir (15). Hamilelik sırasında E3 seviyeleri düşük tespit edilirse bu hastalıkları araştırılıp, aile bilgilendirimeli ve araştırma sonuçları normal çıkarsa doğum sonrası erken dönemde inceleme önermekte fayda vardır.

Baska bir çalışma gebeliğin ikinci trimesterinde çok düşük konjuge olmayan estriol seviyeleri, erken ölüm ve plasental sülfataz eksikliği riskinde artış ile ilişkili bulmuştur (16). Çalışmalar, nedeni bilinmeyen düşük ikinci trimester maternal serum estriolu olan gebelerin, yüksek veya düşük maternal serum AFP veya hCG düzeylerinin gestasyonel diyabet, gestasyonel hipertansiyon, erken membran rüptürü ve erken doğum insidansında artış olduğunu göstermektedir (17). Estriol yüksekliğinin klinik önemi ise belirlenememiştir. Bu çalışmadaki amacımız ikinci trimesterda yapılan üçlü testte maternal kanda bakılan serbest estriolün seviyesinin fetal monitörizasyondaki bulgular nedeniyle fetal distres tanısıyla sezaryene alınan olguların UKKG pH değeri üzerine etkisini değerlendirmektir.

Fetal distres ya da olumsuz gebelik sonuçlarının öngürülmesi hem maternal hem de fetal sağlık açısından önemlidir. Günümüzde fetal distres ya da gebelik komplikasyonlarını öngörebilmek için çeşitli markerların kullanılıdığı çalışmalar mevcuttur. Bu amaçla Avşar ve arkadaşları birinci trimesterda bakılan tarama testi parametrelerinden PPAP-A düşüklüğünün (<0,5 mom) fetal distresi ön görmedeki etkisini değerlendirmiş ve intrapartum fetal distres gelişme olasılığı ve fetal distres nedenli sezaryen riski ile ilişkili olarak bulmuşlardır (18). Huerta ve arkadaşları açıklanamayan yüksek AFP değerlerinin, bazı komplikasyonların (örn. erken fetal ölüm, fetal büyüme geriliği, preeklampsi) riskinde artış olan gebelikler için bir belirteç olabileceğini savunmuştur (19). Yazdani ve arkadaşları kötü gebelik sonucları ve üçlü test markerlarını değerlendiren bir başka çalışmada IUGG, EMR, erken doğum tehdidi arasında ilişki bulunmuştur (20). McPherson ve arkadaşları AFP ve inhibin seviyesi yüksekliği, E3 düşüklüğünün IUGG ile ilişkisi bildirilmiştir (21). Bir diğer çalışmada AFP, HCG ve inhibin A yüksekliği ve E3 düşüklüğünün IUGG ile ilişkisi belirtilmiş ve yine aynı çalışmada AFP yüksekliği preeklampsi ile ilişkilendirilmiştir (22). Bir başka çalışmada Polat ve arkadaşlarının ikinci trimeter tarama testlerinde bakılan parametlerin eşik değerleri ve gebelik komplikasyonlarını karşılaştırdıklarında E3 değeri 0.6 mom veya küçük olanlarda komplikasyon görülme sıklığının E3 değeri 0,6'nın üzerinde olanlardan daha yüksek olduğunu, ancak bu farkın istatistiksel olarak anlamlı olmadığını göstermişlerdir (14). Başka bir çalışma Schleifer ve arkadaşları E3 değeri 1 mom'un altında olan gebelerde gebeliğin erken döneminde fetal ölüm ve plasental sülfataz eksikliği riskinde artış ile ilişkili bulmuştur (16).

Biz uE3 cutt of değerini belirlerken hastaların estriol değeri standart değer olan 1 mom olarak baz aldık. Estriol için çeşitli çalışmalarda farklı eşik değerler kullanılmıştır. Polat ve arkadaşları 0,6 mom'u baz almış ve değerlerinin bölgesel olarak değerlendirilmesini savunmuştur (14). Yücel ve arkadaşları fetal ağırlık ve ikinci trimester tarama testi markerlarını karşılaştırdıkları çalışmada E3 için 0,5 ve 1,5 mom aralığını kullanmıştır (23).

Çalışmamızda estriol değeri 1 mom'un altında olan bireylerin pH ortalaması 7,26±0,51, 1 ve üzerinde olan bireylerin pH ortalaması 7,32±0,08 olduğu belirlenmiştir. Estriol değeri 1 mom altı grupta pH değeri daha düşük olsa da estroil düzeyi ile arasında istatistiksel olarak anlamlı bir farklılık tespit edilmemiştir.

İki grup arasında hastaneye yatış tanıları açısından fetal pH değerleri arasında istatistiksel anlamlı farklılık olmasada özellikle gün aşımı (7,02-7,33) ve oligohidramnios (7,20-7,31) tanıları ile yatırılan gebelerin ortalama fetal pH değerleri estriol değeri 1'in altında olan grupta daha az saptanmıştır. Demirtürk ve arkadaşları yenidoğan asidemisini öngörmede amniotik sıvı indeksinin en yüksek spesifisiteye (%98) sahip olduğunu göstermiştir (24).

Son zamanlarda anöploidi taramasında kullanılan ve en sık ölçülen maternal serum belirteçlerinin bir veya daha fazlasının anormal şekilde yükselmesi veya azalmasıyla ilişkili obstetrik sonuçları gözden geçirildiği birtakım yayınlar mevcuttur. İlk trimesterde, açıklanamayan düşük PAPP-A (<0,4 mom) ve/veya düşük hCG (<0,5 mom), istenmeyen obstetrik sonuçların sıklığındaki artışla ilişkili olduğuna dair yayınlar mevcutsa da, tedavi için spesifik bir protokol mevcut değildir. İkinci trimesterde, maternal serum AFP'de (> 2,5 mom), hCG'de (>3,5 mom) inhibin-A'da (>2,0 mom) açıklanamayan bir artış veya azalmış maternal serum AFP düzeyi (<0,25 mom) ve/veya konjuge olmayan estriol (<0,5 mom), advers obstetrik sonuçların artan sıklığı ile ilişkili bulunmuştur ve şu anda tedavi için spesifik bir protokol mevcut değildir (25).

Çalışmamız retrospektif tasarım ile sınırlıdır; bu nedenle, sonuçlarımızı doğrulamak için prospektif çalışmalara ihtiyaç vardır.

Sonuç olarak, E3 seviyesi 1 mom altında olanlarda fetal pH değerleri, estriol değeri 1 mom üzerinde olanlardan düşük olsa da; istatistiksel olarak pH'lar arasında anlamlı farklılık bulunamadı. Yine estriol değeri 1'in altı gebelerde gün aşımı ve oligohidramnios tanıları ile yatırılan gebelerde yenidoğan bebeklerin fetal kordon pH değerleri daha düşük, mekonyum varlığı daha fazla, yenidoğan yoğun bakıma kabülleri daha fazla, indüksiyon alma oranları daha fazla izlenmiş olup farklılıklar istatistiksel olarak anlamlı bulunmamıştır. İkinci

trimester taraması sırasında maternal kanda bakılan serbest E3 düşüklüğünün olumsuz gebelik sonucu açısından veya fetal distresi öngörmesi açından dikkate alınması gereken bir marker olduğunu düşünüyoruz.

Etik Kurul Onayı
Çalışma için Sağlık Bilimleri Üniversitesi Ankara Bilkent Şehir Hastanesi Klinik Araştırmalar Etik kurulu (E2-22-3030)'ndan 18/01/2023 tarihinde onay alınmıştır.

Disclosure Statement
No potential conflict of interest was reported by the authors.

Funding
The authors have not disclosed any funding.

Data Availability
Data availability is supplied up on request.

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The Journal of Gynecology-Obstetrics and Neonatology

ÖZGÜN ARAŞTIRMA / ORIGINAL ARTICLE

DOI: 10.38136/jgon.1440611

Evaluation of preeclampsia outcomes in de novo preeclampsia and superimposed preeclampsia: A case-control study from a tertiary center

De novo preeklampsi ve süperempoze preeklampside preeklampsi sonuçlarının değerlendirilmesi: Üçüncü basamak bir merkezden vaka kontrol çalışması

Göksun İPEK[1], Atakan TANAÇAN[1], Zahid AĞAOĞLU[1], Ayça PEKER[1], Gülcan OKUTUCU[1], Dilek ŞAHİN[2]

[1]Division of Perinatology, Department of Obstetrics and Gynecology, Turkish Ministry of Health Ankara City Hospital, Ankara, Turkey.
[2]Division of Perinatology, Department of Obstetrics and Gynecology, Turkish Ministry of Health Ankara City Hospital, University of Health Sciences, Ankara, Turkey

ABSTRACT

Aim: To compare de novo and superimposed preeclampsia outcomes and evaluate the role of chronic hypertension in preeclampsia outcomes

Materials and Method: The present retrospective case-control study was conducted on 250 pregnant women diagnosed with preeclampsia, including 100 patients in the superimposed preeclampsia group and 150 in the de novo preeclampsia group. The control group comprised 200 low-risk pregnant women consecutively delivered in the same timeline. The demographic specialties and obstetric and neonatal outcomes of the de novo and superimposed preeclampsia groups were compared with the control group and also between preeclampsia groups. Parameters were then evaluated using the literature findings.

Results: Early onset preeclampsia and preterm delivery rates were higher in the superimposed preeclampsia group, with p-values of 0.046 and 0.026, respectively. Prodromal symptoms were lower in the superimposed preeclampsia group than in the de novo preeclampsia group (p=0.029). Fetal growth retardation was higher in both preeclampsia groups than in the control group, with a p-value of <0.001. Severe preeclampsia rates were similar in the preeclampsia groups, with a p-value of 0.278.

Conclusion: The presented study showed in a single tertiary center experience that chronic hypertension is an individual risk factor for early-onset preeclampsia occurrence and preterm delivery. Because the prodromal symptoms are seen less in a superimposed preeclampsia group than in the de novo preeclampsia group, obstetricians must be careful with severe preeclampsia in such a specific patient group.

Keywords: Superimposed preeclampsia outcomes; preeclampsia outcomes; adverse outcomes; chronic hypertension

ÖZ

Amaç: De novo ve superempoze preeklampsi sonuçlarını karşılaştırmak ve kronik hipertansiyonun preeklampsi sonuçlarındaki rolünü değerlendirmek.

Gereçler ve Yöntem: Mevcut retrospektif vaka-kontrol çalışması, 100'ü süperempoze preeklampsi grubunda, 150'si de novo preeklampsi grubunda olmak üzere, preeklampsi tanısı alan 250 hamile kadın üzerinde gerçekleştirildi. Kontrol grubu, aynı zaman aralığında ardı ardına doğum yapan 200 düşük riskli hamile kadından oluşuyordu. De novo ve süperempoze preeklampsi gruplarının demografik özellikleri, obstetrik ve neonatal sonuçları kontrol grubu ile karşılaştırıldı. Sonuçlar preeklampsi subgrupları arasında da karşılaştırıldı ve daha sonra parametreler literatür bulgularıyla birlikte değerlendirildi.

Bulgular: Erken başlangıçlı preeklampsi ve erken doğum oranları, süperempoze preeklampsi grubunda p değerleri sırasıyla 0,046 ve 0,026 ile daha yüksekti. Prodromal semptomların varlığı, süperempoze preeklampsi grubunda de novo preeklampsi grubuna göre daha düşüktü (p=0,029). Fetal büyüme geriliği her iki preeklampsi grubunda da p değeri <0,001 ile kontrol grubuna göre daha yüksekti. Şiddetli preeklampsi oranları preeklampsi gruplarında p değeri 0,278 ile benzerdi.

Sonuç: Sunulan çalışma, üçüncü basamak tek merkez deneyiminde, kronik hipertansiyonun erken başlangıçlı preeklampsi oluşumu ve erken doğum için bağımsız bir risk faktörü olduğunu göstermiştir. Süperempoze preeklampsi grubunda prodromal semptomlar de novo preeklampsi grubuna göre daha az görüldüğü için, bu spesifik hasta grubunda şiddetli preeklampsi konusunda kadın doğum uzmanlarının dikkatli olması gerekmektedir.

Anahtar Kelimeler: Süperempoze preeklampsi, preeklampsi sonuçları, olumsuz gebelik sonuçları, kronik hipertansiyon

Cite as: İpek G, Tanaçan A, Ağaoğlu Z, Peker A, Okutucu G, Şahin D. Evaluation of preeclampsia outcomes in de novo preeclampsia and superimposed preeclampsia: A case-control study from a tertiary center. Jinekoloji-Obstetrik ve Neonatoloji Tıp Dergisi 2024;21(4):274–278.

Geliş/Received: 21.02.2024 • **Kabul/Accepted:** 13.06.2024

Sorumlu Yazar/Corresponding Author: Göksun İPEK, Üniversiteler Mahallesi, 1604. Cadde, No: 9. Çankaya, Ankara, Türkiye
E-mail: drgoksunipek@gmail.com

Çevrimiçi Erişim/Available online at: https://dergipark.org.tr/tr/pub/jgon

INTRODUCTION

Preeclampsia is accepted as a pregnancy-specific multisystem disorder accompanied by hypertension, permeability increase, and microvascular thrombosis (1). Preeclampsia prevalence is 5-8% and is the leading cause of both fetal and maternal morbidity and also mortality (2). There are two possible ways in which it can occur: in previously healthy women by de novo preeclampsia or pregnancies with chronic hypertension called superimposed preeclampsia (3).

Prediction of de novo preeclampsia in healthy pregnancies before it occurs is challenging. Some risk factors for having preeclampsia in pregnancies were determined, and high-risk pregnancies are defined by ACOG guidelines (4). Recently, studies have been continuing to predict and prevent preeclampsia, focusing on clinical and laboratory markers. However, the only preventive situation whose effectiveness is accepted today is starting aspirin from 12 weeks onwards in patients with risk factors and performing appropriate blood pressure and pregnancy checks (5).

Chronic hypertension has become one of the most frequent diseases seen in the reproductive age, with increasing maternal age. All chronic hypertension patients are candidates for superimposed preeclampsia. Superimposed preeclampsia develops in up to 30% of chronic hypertensive pregnancies. Diagnosis is made by new onset of proteinuria or worsening preexisting proteinuria, blood pressure control, and/or laboratory abnormalities (3). Generally, superimposed preeclampsia occurs earlier and is more severe than preeclampsia without chronic hypertension etiology.

Prevention and prediction of superimposed preeclampsia before it develops is a major task for obstetricians. None of the laboratory or ultrasonography findings has specified the prediction of superimposed preeclampsia occurring in patients with chronic hypertension. The only preventive choice, similar to de novo preeclampsia, is accepted as starting aspirin from 12 weeks onwards in patients with chronic hypertension and performing appropriate blood pressure control with appropriate medication. The termination of pregnancy is the only effective way of certain treatment.

This study hypothesized and evaluated whether the underlying gestational or chronic hypertension has a determining effect on pregnancy outcomes in pregnant women with preeclampsia who were followed up in the same tertiary center and managed in the same manner.

MATERIAL AND METHODS

The present retrospective case-control study was conducted on pregnant women with preeclampsia and low-risk pregnant women as the control group. Patient demographic information and neonatal-obstetric outcomes were taken from the hospital database. Patients with preeclampsia and delivered between January 2021 - June 2023, having a singleton pregnancy, maternal age between 18-45 years, and no chronic systemic diseases except for hypertension were included in the study. Patients were categorized according to having de novo preeclampsia or superimposed preeclampsia. The control group comprised 200 low-risk pregnant women consecutively delivered in the same timeline. Chronic hypertension diagnosed before mid-pregnancy with a new onset of proteinuria or worsening preexisting proteinuria, blood pressure control, and/or laboratory abnormalities was defined as superimposed preeclampsia. New-onset hypertension after mid-pregnancy with accompanying either proteinuria or end-organ failure was defined as de novo preeclampsia. Severe preeclampsia criteria were determined based on ACOG guidelines (6). Severe headache, visual disturbance and epigastric pain were defined as prodromal symptoms. All high-risk patients in the de novo group and those in the superimposed preeclampsia group were given acetylsalicylic acid prophylaxis. All severe preeclampsia-diagnosed patients were administered magnesium sulfate treatment for eclampsia prevention. Preeclampsia development before 34 weeks was accepted as early-onset preeclampsia as in the literature (7). This study was approved by the "Institutional Review Board of the University of Health Sciences Turkey, Ankara Bilkent City Hospital Ethics Committee" (approval number: E2-24-6138).

Hypertensive patients were followed closely and multidisciplinary by cardiology and perinatology departments with appropriate antihypertensive treatments for blood pressure, proteinuria, and laboratory abnormalities.

Preeclampsia and superimposed preeclampsia groups' demographic specialties and obstetric and neonatal outcomes were compared between groups. Parameters were then compared with the literature.

The statistical analyses used IBM Inc., Armonk, NY, USA's Statistical Package for the Social Sciences version 23. All descriptive statistics were presented as the mean and standard deviations (SD) due to the consistency with a normal distribution. The ANOVA test was used to compare the parameters between the groups. Categorical variables were presented as numbers and percentages. Statistical significance was a two-tailed P value of 0.05 with a 95% confidence interval.

RESULTS

The study was conducted on 150 patients with de novo preeclampsia, 100 patients with superimposed preeclampsia, and 200 low-risk pregnant women in the control group. Demographic parameters were similar between de novo preeclampsia and control groups. However, maternal age and gravida were higher in the superimposed preeclampsia group compared to the control group. Maternal demographic characteristics of groups are shown in Table 1.

Adverse neonatal outcomes were all found to be statistically higher both in de novo preeclampsia and in the superimposed preeclampsia groups compared to the control group. The only statistical difference observed between preeclampsia and superimposed preeclampsia was gestational age at birth. Neonatal outcomes characteristics of groups are shown in Table 2.

When the groups were evaluated according to the obstetric outcomes, neonatal invasive care unit admission and fetal growth retardation ratios were higher in both preeclampsia groups than in the control group. Early onset preeclampsia was higher in the superimposed preeclampsia group, and the presence of prodromal symptoms was lower than in the de novo preeclampsia group. Obstetric outcomes characteristics of groups are shown in Table 3.

Other obstetric complications seen in preeclampsia groups were placenta abruption, fetal demise, posterior reversible encephalopathy syndrome (PRESS), sinus vein thrombosis, and the need for re-laparotomy. The distribution of these complications in groups is presented below.

In the preeclampsia group, there were three placenta abruption cases in which two fetuses died intrauterine. Also, 1 PRESS, one pleural effusion, and one sinus vein thrombosis cases were observed, and two patients were gone to re-laparotomy because of post-operation intra-abdominal bleeding.

In the superimposed preeclampsia group, there was one PRESS syndrome, two patients with superficial infections and hematomas of incision, and two patients who went to re-laparotomy because of post-operation intra-abdominal bleeding.

Table 1. Maternal demographic characteristics and laboratory findings

Variable (Maternal indices)	Control group (n=200)	De novo Preeclampsia group (n=150)	Superimposed Preeclampsia group (n=100)	P value	P value[a]	P value[b]	P value[c]
Maternal age (years)	27.67 (5.33)	28.85 (5.96)	31.36 (5.99)	<0.001	0.134	<0.001	0.002
Gravidity	2.18 (1.26)	2.35 (1.70)	2.89 (1.81)	<0.001	0.537	0.001	0.021
Parity	1.00 (1.06)	0.89 (1.13)	1.30 (1.29)	0.018	0.627	0.081	0.014
Living Child	0.98 (1.05)	0.85 (1.12)	1.26 (1.25)	0.019	0.575	0.096	0.014

*All variables were presented as means and standard deviations (SD). P value[a], between control and De novo Preeclampsia groups; P value[b], between control and superimposed preeclampsia groups; P value[c], between superimposed preeclampsia and De novo Preeclampsia groups

Table 2. Neonatal Outcomes

Variable	Control group (n=200)	De novo Preeclampsia group (n=150)	Superimposed Preeclampsia group (n=100)	P value	P value[a]	P value[b]	P value[c]
Gestational age at birth. (weeks)	38.74 (1.23)	34.41 (4.06)	33.38 (3.77)	<0.001	<0.001	<0.001	0.026
Fetal birth weight. (g)	3281.58 (381.58)	2214.01 (950.60)	2085.35 (909.06)	<0.001	<0.001	<0.001	0.371
APGAR. first-minute	7.60 (0.59)	6.31 (1.99)	6.31 (1.48)	<0.001	<0.001	<0.001	1.00
APGAR. fifth-minute	8.95 (0.49)	7.97 (1.83)	8.07 (1.33)	<0.001	<0.001	<0.001	0.827

*All variables were presented as means and standard deviations (SD). P value[a], between control and De novo Preeclampsia groups; P value[b], between control and superimposed preeclampsia groups; P value[c], between superimposed preeclampsia and De novo Preeclampsia groups

Table 3. Obstetric Outcomes

Variable	Control group (n=200)	De novo Preeclampsia group (n=150)	Superimposed Preeclampsia group (n=100)	P value	P value[a]	P value[b]	P value[c]
NICU. %	14 (7.0)	82 (54.7)	52 (52.0)	<0.001	<0.001	<0.001	0.679
FGR. %	6 (3.0)	20 (13.3)	14 (14.0)	<0.001	<0.001	<0.001	0.880
Oligohydramnios. %	16 (8.0)	15 (10.0)	4 (4.0)	0.368	0.560	0.325	0.079
PPROM. %	3 (1.5)	6 (4.0)	3 (3.0)	0.347	0.144	0.382	0.678
Early preeclampsia. %	-	46 (30.7)	43 (43.0)	-	-	-	0.046
Severe preeclampsia. %	-	78 (52.0)	45 (45.0)	-	-	-	0.278
HELLP. %	-	15 (10.0)	10 (10.0)	-	-	-	1.000
Prodromal symptom	-	40 (26.7)	15 (15.0)	-	-	-	0.029
Eclampsia	-	4 (2.7)	3 (3.0)	-	-	-	0.876

* Categorical variables were presented as numbers (percentages). P value[a], between control and De novo Preeclampsia groups; P value[b], between control and superimposed preeclampsia groups; P value[c], between superimposed preeclampsia and De novo Preeclampsia groups. NICU, neonatal intensive care unit; FGR, fetal growth retardation; PPROM, preterm premature rupture of membranes; HELLP, hemolysis, elevated liver enzymes and low platelet.

DISCUSSION

The presented study showed in a single tertiary center experience that chronic hypertension etiology is an individual risk factor for early preeclampsia occurrence and preterm delivery. There are limited studies in the literature on the prevention of superimposed preeclampsia. In a systematic review, acetylsalicylic acid was found to be neither beneficial in preventing superimposed preeclampsia nor decreasing the early onset preeclampsia (8). In this study, all patients in the superimposed preeclampsia group and high-risk patients in the de novo preeclampsia group were used acetylsalicylic acid and managed with similar hospital manner for both delivery decision and control on hypertension but early preeclampsia and preterm delivery rates were higher in superimposed preeclampsia group, similar with the literature findings. In early onset preeclampsia, patients were followed by appropriate antihypertensive treatment and fetal ultrasound and Doppler findings. Delivery decisions were taken in uncontrolled hypertensive patients and fetal distress conditions in line with guidelines.

In the presented study, severe preeclampsia, HELLP, and eclampsia rates were similar in both preeclampsia groups. In contrast to the presented research, severe preeclampsia and eclampsia rates were found to be higher in the literature (9). This difference may occur from following all patients by the perinatology unit, managing them meticulously, and giving magnesium sulfate treatment as eclampsia prevention to all severe preeclampsia cases for 24 hours.

Prodromal symptoms like headache, visual disturbance, epigastric pain, etc., were seen significantly lower in the superimposed preeclampsia group than in the de novo group. This situation may be explained by the fact that the preeclampsia group is more sensitive to hypertension symptoms because of the no exposure to hypertension without pregnancy.

De novo preeclampsia was higher in nulliparous patients, and superimposed preeclampsia was higher in advance-aged pregnancies and multiparous patients as convenience with the literature (10,11).

Neonatal outcomes for APGAR scores, gestational weeks at birth, birth weights, and admission to the neonatal invasive care unit were similar and higher in both preeclampsia groups than in the control group in convenience with the literature (9, 12, 13).

Fetal growth retardation rates were higher in both preeclampsia groups than in the control group. However, oligohydramnios was not an accompanying condition of the same severity and were similar in all groups. In the literature, in many studies, fetal growth retardation and accompanying oligohydramnios was found as a result of preeclampsia (14, 15).

Other pregnancy complications like placenta abruption, intrauterine fetal demise, posterior reversible encephalopathy syndrome, or sinus vein thrombosis were not higher in the superimposed preeclampsia group. In the literature, superimposed preeclampsia patients were found to be at more risk than preeclampsia patients for per partum complications, such as placental abruption and cerebrovascular incidents (3). Conversely to the literature, all abruption cases, the sinus vein thrombosis case, and fetal demises were seen in the de novo preeclampsia group.

The presented study is one of the few studies that evaluate preeclampsia outcomes compared to de novo and superimposed preeclampsia. In the literature, many studies about preeclampsia etiology point out that the inflammatory processes occur before the clinical diagnosis of the disease. The literature demonstrated an increased inflammatory process for preeclampsia in the first trimester (16). It is known that placental insufficiency and hypertension secondary to defective trophoblastic invasion develop in preeclampsia (17). This study evaluated the effect of underlying chronic hypertension on preeclampsia outcomes when external variables were excluded as much as possible and where gestational hypertension was monitored and managed most appropriately in the tertiary center. It has been shown that early-onset preeclampsia is more common in patients with chronic hypertension. This finding indicates that the underlying chronic hypertension condition plays a determining and accelerating role in the process leading to preeclampsia. Further studies are needed for this purpose.

The present study's strengths were being a referral center for managing preeclampsia and having obstetric and neonatal outcomes for all preeclampsia patients. Its limitations were its single-center retrospective study design and limited patient numbers.

CONCLUSION

In light of this study's findings, chronic hypertension is an individual risk factor for early-onset preeclampsia. Because the prodromal symptoms are seen less in a superimposed preeclampsia group than in the de novo preeclampsia group, obstetricians must be careful with severe preeclampsia and the faster eclampsia process in such a valuable patient group.

Ethics Committee Approval

This study was approved by the "Institutional Review Board of the University of Health Sciences Turkey, Ankara Bilkent City Hospital Ethics Committee" (approval number: E2-24-6138).

Funding

No funding was received for the research.

Conflict of interests

The authors have no conflicts of interest.

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The Journal of Gynecology-Obstetrics and Neonatology

ÖZGÜN ARAŞTIRMA / ORIGINAL ARTICLE

DOI: 10.38136/jgon.1452700

Association of placental cysts with increased fetal anomalies and growth restriction: An observational cohort study

Plasental kistlerin artmış fetal anomalilerle ve büyüme kısıtlılığı ile ilişkisi: Gözlemsel kohort çalışması

Göksun İPEK[1], Esra Gülen YILDIZ[1], Ayşe Gülçin BAŞTEMUR[1], Salim ERKAYA[1]

[1]Department of Obstetrics and Gynecology, Ministry of Health, Ankara City Hospital, Ankara, Turkey

ABSTRACT

Aim: To investigate the placental cysts in every aspect and evaluate associations with fetal anomalies, fetal growth, accompanying maternal diseases, and obstetric outcomes.

Materials and Methods: The presented cohort study was conducted with twenty pregnant women diagnosed with placental cysts. Maternal age, obstetrical histories, maternal diseases, ultrasonographic characteristics of cysts, additional ultrasound findings, and fetal anomalies were recorded at the time of diagnosis and each examination. Pregnancy outcomes; birth weight, gestational age at birth, APGAR scores, neonatal intensive care unit (NICU) admissions, amniotic fluid disorders, and fetal growth restriction (FGR) were recorded for all participants. Data were evaluated according to diagnosis time, size of the cyst at diagnosis and at birth, fetal anomalies, and obstetric outcomes.

Results: All cysts were single. Five of them increased in size with follow-ups. The mean follow-up duration was 12 weeks. There were 9 FGR (64.3%). Six of the FGR patients had cyst sizes >5 cm. There were eight fetal anomalies; 5 were heart-associated, and 3 had a single umbilical artery. The frequency of C/S in delivered patients was 78%, and preterm delivery was 35.7%.

Conclusion: The presented study showed that placental cysts have clinical importance due to their potential risk for FGR and accompanying fetal anomalies. Appropriate patient follow-ups for cyst size enlargements and anomaly screening, especially for cardiac evaluation, might be important for placental cyst management. Also, uterine artery Doppler measurements and prophylactic acetylsalicylic acid use might be under consideration. However, the clinical utility of uterine Doppler examination and prophylactic use of acetylsalicylic acid needs further studies.

Keywords: Placental cyst; fetal anomalies; fetal growth restriction; adverse perinatal outcomes

ÖZ

Amaç: Plasental kistleri her yönüyle araştırmak ve fetal anomaliler, fetal büyüme, eşlik eden maternal hastalıklar ve obstetrik sonuçlarla ilişkisini değerlendirmek.

Gereçler ve Yöntem: Bu kohort çalışması plasental kist tanısı alan yirmi hamile kadınla yürütüldü. Tanı anında ve her muayene sırasında anne yaşı, doğum öyküsü, maternal hastalık, kistlerin ultrasonografik özellikleri, ek ultrason bulguları ve fetal anomaliler kaydedildi. Hamilelik sonuçları; doğum ağırlığı, doğumdaki gebelik haftası, APGAR skorları, yenidoğan yoğun bakım ünitesine (YYBÜ) yatış, amniyotik sıvı bozuklukları ve fetal büyüme geriliği (FBG) kaydedildi. Veriler tanı zamanına, tanı anındaki ve doğum zamanındaki kist boyutlarına, fetal anomalilere ve obstetrik sonuçlara göre değerlendirildi.

Bulgular: Kistlerin tamamı tekil idi. Takiplerinde beş tanesinin boyutu arttı. Ortalama takip süresi 12 haftaydı. 9 FBG (%64,3) vardı. FBG hastalarının altısında kist boyutları >5 cm idi. Sekiz fetal anomali mevcuttu; 5'i kalple ilişkiliydi ve 3'ünde tek umbilikal arter vardı. Doğum yapan hastalarda sezaryen sıklığı %78, erken doğum oranı ise %35,7 olarak belirlendi.

Sonuç: Sunulan çalışma, plasental kistlerin FBG ve eşlik eden fetal anomaliler açısından potansiyel risk taşımaları nedeniyle klinik öneme sahip olduğunu göstermiştir. Kist boyutunun büyümesinin takibi ve anomali taraması, özellikle kardiyak değerlendirme şeklinde uygun hasta takipleri plasental kist yönetimi açısından önemli olabilir. Ayrıca uterin arter Doppler ölçümleri ve profilaktik asetilsalisilik asit kullanımı da düşünülebilir. Ancak uterin arter Doppler incelemesinin klinik faydası ve asetilsalisilik asitin profilaktik kullanımı için daha fazla çalışmaya ihtiyaç vardır.

Anahtar Kelimeler: Plasental kist; fetal anomaliler; fetal büyüme geriliği; olumsuz perinatal sonuçlar

Cite as: İpek G, Yıldız EG, Baştemur AG, Erkaya S. Association of placental cysts with increased fetal anomalies and growth restriction: an observational cohort study. Jinekoloji-Obstetrik ve Neonatoloji Tıp Dergisi 2024;21(4):279–284.

Geliş/Received: 15.03.2024 • **Kabul/Accepted:** 26.03.2024

Sorumlu Yazar/Corresponding Author: Göksun İPEK, Üniversiteler Mahallesi 1604. Cadde, No: 9. Çankaya, Ankara, Türkiye
E-mail: drgoksunipek@gmail.com

Çevrimiçi Erişim/Available online at: https://dergipark.org.tr/tr/pub/jgon

INTRODUCTION

Identifying placental hypoechoic lesions is essential to determining patients at risk of subsequent complications in pregnancy and delivery. Hypoechoic lesions in the placenta surrounded by normal parenchyma are defined as lacunas and lakes based on vascular flows (1). However, placental cysts differ from lakes and lacunae and are identified as hypoechoic lesions protruding from the placental fetal surface to the amnion. Placental cysts are referred by different terms in the literature; including mostly 'membranous cysts', 'chorionic cysts' and 'sub-amniotic cysts' (2-5). The prevalence of placental cysts is 5-7% (6). Despite the high prevalence of cysts, the diagnosis is made mostly incidentally, and the clinical importance of cysts remains unknown.

The etiology of placental cysts has yet to be fully elucidated. The cyst wall microscopically consists of amniotic and chorionic membranes. Special cells called 'X-cells' surround cysts, but their function is unknown. Their possible secretory activity and contribution to cyst formation were reported in the literature (2, 4, 7).

In the literature, there are only a few studies about placental cyst outcomes, most of which are case reports. Controversial findings about accompanying diseases and adverse outcomes are reported in the literature. Fetal growth restriction (FGR) and preterm delivery are mostly reported adverse outcomes related to placental cysts (4, 5, 8).

We evaluated our experience with placental cysts for any association with fetal anomalies, fetal growth, accompanying maternal diseases, and obstetric outcomes to determine what clinical significance these cysts may have.

MATERIAL AND METHODS

The presented cohort study was conducted on 20 patients incidentally diagnosed and recorded with placental cysts. Patients whose cyst location, shape, structure and dimensions were not fully described were excluded from the study. Patients were obtained either by scanning the hospital patient database or outpatient follow-ups from January 2021 to January 2023. The study was approved by the Institutional Review Board of the Ankara Bilkent City Hospital Ethics Committee (approval number: E2-23-4716).

All patients were included in the study after giving written informed consent. Maternal age, obstetrical histories (gravity, parity, miscarriage, and living children), and maternal diseases were recorded at the time of diagnosis with ultrasonographic characteristics of cysts (location of cyst and size). All patients were numbered and followed up until delivery. Additional ultrasound findings, fetal anomalies, and cyst characteristics were recorded at each examination. Pregnancy outcomes; gestational age at birth, birth weight, APGAR scores in the first and fifth minutes, neonatal intensive care unit (NICU) admission, amniotic fluid disorders, delivery methods; either cesarean section (C/S) or vaginal birth (VB) and fetal growth restriction were also recorded for all participants. Obstetric and perinatal outcomes were evaluated and compared with the literature.

RESULTS

Maternal age ranged between 23 and 40 years. Ten patients did not have any maternal diseases. In the other patients, there were six cases of diabetes mellitus (3 type-2 DM and 3 GDM), four cases of hypertension (2 gestational hypertension (GHT) and 2 chronic hypertension (CHT)), four cases of goiter, and two other maternal diseases. There were two twin pregnancies and 18 singleton pregnancies. Maternal demographic characteristics are shown in Table 1.

All cysts were single. When the patients were grouped according to diagnosis weeks, there were 5 patients in the first-trimester group, 9 patients in the second-trimester group, and 6 patients in the third-trimester group. The mean diagnosis week was 22 (9 - 36) weeks. Cysts were grouped depending on their diagnosis time sizes. Group 1(<2 cm) included 3 patients, group 2 (2-5 cm) included 11 patients, and group 3 (>5 cm) included 6 patients. There were four cysts at the placental cord insertion site (PCIS). Examples for placental cyst images and measurement method are shown in Figures 1 a and b.

There were eight fetal anomalies, and the most accompanying were cardiac and cord anomalies. Five anomalies were heart-associated anomalies with 3 major cardiac anomalies and 2 cardiac echogenic focus with VSD, and 3 of the patients had a single umbilical artery. There were 2 patients who had non-cardiac anomalies; one had an amniotic band disruption sequence, and the second had multiple anomalies but did not have invasive genetic tests. Two patients terminated due to amniotic band distraction sequence and cystic hygroma with multiple anomalies (Table 2).

After the exclusion of 2 terminated patients, there were 18 patients. There were four patients whose pregnancy outcomes could not be obtained. Case 11 had a di-di twin pregnancy; one of the fetuses, which had a placental cyst with the hypoplastic right ventricle, was observed intrauterine exitus, and the case was delivered at 35 weeks. Patient number 11 and the remaining 13 pregnancies' outcomes are shown in Table 3.

Table 1. Demographic characteristics of patients

Patient Number	Age	Gravidity	Parity	Disease
1	24	1	0	None
2	29	2	1	Type-2 DM
3	36	3	2	None
4	36	4	3	Goiter, GDM
5-twin (Mono-di)	32	1	0	GDM
6	33	3	1	None
7	31	2	0	GHT-preeclampsia
8	23	2	0	None
9	28	1	0	None
10	33	1	0	None
11-twin (Di-di)	23	3	1	Asthma
12	35	7	1	None
13	24	1	0	None
14	38	4	3	GHT-preeclampsia
15	23	2	1	Epilepsy
16	28	6	4	Type-2 DM, CHT, Goiter
17	40	4	2	Type-2 DM, CHT, Goiter
18	24	2	0	None
19	37	4	2	None
20	40	3	2	GDM, Goiter

*DM, diabetes mellitus; GDM, gestational diabetes mellitus; GHT, gestational hypertension; CHT, chronic hypertension; Mono-di, monochoronic – diamniotic twin; Di-di, dichoronic-diamniotic twin

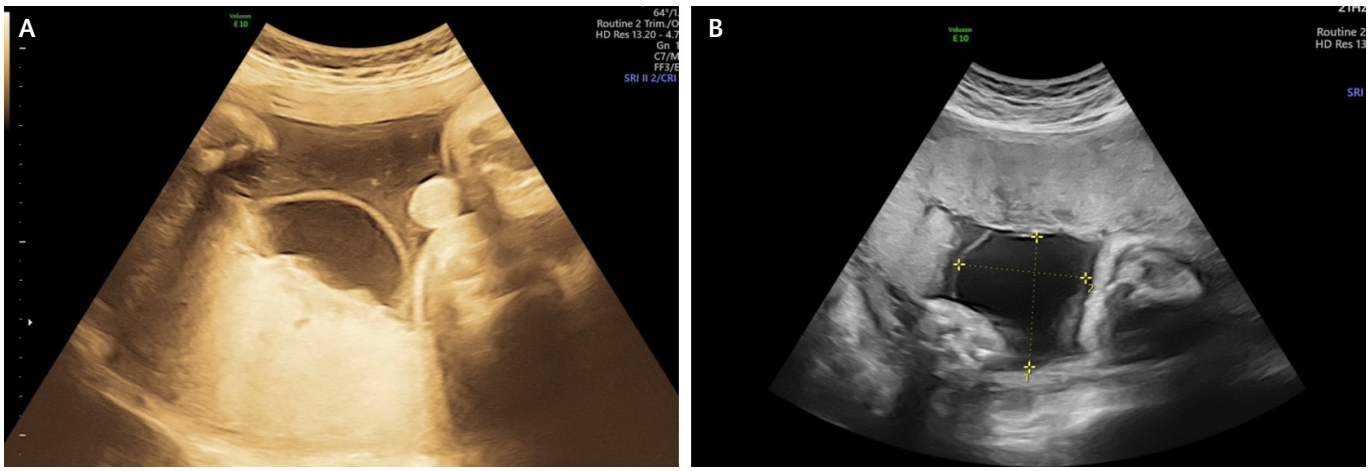

Figure 1. A and B. Images of a placental cyst and cyst measurement method

The frequency of C/S was 78.5%. There were five preterm deliveries (35.7%). Two who delivered before <34 weeks were diagnosed with severe preeclampsia. Two preterm deliveries had twin pregnancies. The fifth patient, who had a previous cesarean section, had severe uterine contractions and was delivered via c/s due to the risk of uterine rupture.

The mean follow-up duration was 12 weeks. No cyst was larger than >5 cm in the first trimester. The percentage of cysts larger than 5 cm was 33% in the second trimester and 50% in the third trimester. There were 9 FGR (64.3%). FGR patients were evaluated according to cyst's specialties, 5 had an increased cyst size with follow-ups. There were only 4 patients whose cyst size did not change during follow-up; cases 7 and 14 had severe preeclampsia and required emergency delivery only after 2 and 3 weeks of clinical follow-ups, case 19 was diagnosed at 36 weeks and delivered only after one week, and case 5 was mono-di twin pregnancy with possible confounder factor for FGR.

Table 2. Placental cyst characteristics and ultrasound findings

Case number	Diagnosis Week	Group	First Size (mm)	Last Size (mm)	PCIS	Growth pattern	Delivery Week	Additional Ultrasound Findings
Diagnosis in the first trimester								
1	13	1	15*12	-	No	-	MT	Cystic hygroma, encephalocele, AVSD, clenched hand, single umbilical artery
2	11	2	20*25	-	No	-	MT	Amniotic band distraction sequence, right lower extremity does not exist
3	12	2	21*27	ND	No	-	NR	Cardiac echogenic focus
4	9	2	26*23	ND	No	-	NR	None
5-twin (mono-di)	12	2	44*14	40*13	No	Same in 24w	36	None
Diagnosis in the second trimester								
6	20	1	18*20	ND	Yes		NR	Aorta hypoplasia
7	24	1	11*13	15*15	No	Same in 2w	26	None
8	18	2	35*20	40*45	No	Increase in19w	37	None
9	16	2	30*25	35*27	No	Same in 24w	40	Bilateral cleft lip and palate, hypertelorism, lobar holoprosencephaly
10	20	2	30*40	50*40	No	Increase in 19w	39	None
11-twin (di-di)	28	2	31*29	51*45	Yes	Increase in 7w	35	*Right ventricle hypoplasia and single umbilical artery
12	16	3	63*37	67*32	No	Same in 21w	39	None
13	23	3	34*58	58*42	No	Same in 16w	39	None
14	22	3	30*50	32*50	No	Same in 3w	25	None
Diagnosis in the third trimester								
15	31	2	24*35	32*38	No	Same in 8w	39	None
16	30	2	27*40	36*53	No	Increase in 8w	38	None
17	31	2	38*27	38*30	No	Same in 5w	36	None
18	29	3	59*46	NR	Yes		NR	None
19	36	3	52*40	50*44	No	Same in 1w	37	Cardiac echogenic focus
20	33	3	50*31	68*28	Yes	Increase in 4w	37	Single umbilical artery, bilateral choroid plexus cysts

*PCIS, placental cord insertion site; NR, not reached; MT, medical termination; AVSD, atrium-ventricle septal defect; w, week; Mono-di, monochoronic – diamniotic twin; Di-di, dichoronic-diamniotic twin

When the FGR outcomes were evaluated for the last sizes of cysts, six patients had >5 cm cysts, two patients had 2-5 cm cysts (case 8 had a 4.5 cm cyst which increased in size, and case 5 had twin pregnancy), and case 7 had <2 cm cyst and delivered at 26 weeks because of severe preeclampsia. FGR cases were also evaluated according to diagnosis time size groups. There were 1 FGR case in group 1, 5 cases in group 2, and 3 cases in group 3. There were 5 cases without FGR; in all cases, cyst size remained the same in follow-ups.

APGAR scores for all cases were above 7 at the first minute except for cases 7 and 14 (preterm birth with severe preeclampsia) and case 11 with multiple anomalies.

Table 3. Pregnancy outcomes

Patient number	Delivery week	Delivery method	C/S indication	Birth weight	APGAR	FGR	NICU
5-twin (mono-di)	36	C/S	Twin	2395/2445	7-8/7-9	Yes	Yes
7	26	C/S	Severe preeclampsia	550	4-6	Yes	Yes
8	37	C/S	Fetal distress	1885	7-8	Yes	Yes
9	40	VB		4000	5-7	No	Yes
10	39	C/S	CPD	2625	9-10	Yes	No
11-twin (di-di)	35	C/S	Twin preterm (right fetus IU-EX)	1650/1200*	7-8/0-0	Yes	Yes
12	39	C/S	Previous C/S	4000	8-9	No	No
13	39	VB		3700	8-9	No	No
14	25	C/S	Severe preeclampsia	410	2-4	Yes	Yes
15	39	C/S	Previous C/S	3840	8-9	No	No
16	38	VB		3065	7-9	Yes	No
17	36	C/S	Previous C/S	3285	7-9	No	No
19	37	C/S	CPD	2450	8-9	Yes	No
20	37	C/S	Previous C/S	2310	7-9	Yes	No

*FGR, fetal growth retardation; NICU, neonatal invasive care unit; C/S, cesarean section; VB, vaginal birth; CPD, cephalo-pelvic disportion, IUEX, intra uterine exitus; Mono-di, monochoronic – diamniotic twin; Di-di, dichoronic-diamniotic twin

In all cases, ultrasound diagnoses were confirmed histopathologically. Four placental cysts were at the umbilical cord insertion site; follow-up information for cases 6 and 18 could not be reached. Case 11 was a mono-di twin, and one of the fetuses with cyst and hypoplastic right ventricle died, and case 20 was growth restricted.

DISCUSSION

The present study found an increased FGR frequency associated with placental cysts. Preeclampsia, developing on the basis of gestational hypertension, and diabetes mellitus were mostly seen as maternal complications in the study group. There were also an increased number of fetal anomalies, and the cardiac and umbilical cord anomalies mostly accompanied ultrasound findings. To the best of our knowledge, this was the first study evaluating the association between placental cysts and fetal anomalies.

Placental cysts' etiology and clinical importance have remained controversial because of the limited studies that mostly report cases. Some authors found cysts associated with FGR and suggested clinical and ultrasound follow-up, whereas others considered them harmless and clinically not meaningful (3, 4).

FGR was described as a related outcome with placental cysts in the literature, and this study's findings were compatible with the literature. In the presented study, most of the FGR cases' cyst sizes were >5 cm, and increased growth patterns were seen. In the literature, in a retrospective evaluation, multiple cysts and cyst sizes larger than 4.5cm were found to be associated with FGR, similar to the presented study. In this research, researchers showed no relation with the cyst of the umbilical cord insertion site (5). In another study, researchers hypothesized that larger cysts and cysts at the PCIS had a higher risk for FGR because of interference with cord circulation. For this purpose, two case reports demonstrated an association between PCIS and FGR (3, 4). Our study did not have adequate case numbers for determining any relationship with FGR.

In a case report and review of the literature study, the FGR ratio was reported as 13%, and the preterm delivery ratio was reported as 37% (8). In another study, the preterm delivery ratio was reported as 20% (9). The preterm delivery ratio was similar to the literature in the presented study, whereas the FGR ratio was higher than in the literature. A possible reason for the increased FGR ratio could be hypoxia of the fetus due to the cyst.

The literature reported cysts mostly in women with diabetes mellitus and rhesus incompatibility (4). In our study, diabetes and

hypertension were mainly seen maternal diseases in concordance with the literature.

In the presented study, there were an increased number of fetal anomalies; the most accompanied were cardiac and cord anomalies. In the literature, there was no study in this context.

This study shows that placental cysts have clinical importance due to their potential risk for FGR and accompanying fetal anomalies. Placental cyst diagnosis can be made accurately and easily by ultrasound, even in the first trimester. Appropriate patient follow-ups for cyst size enlargements and anomaly screening, especially for cardiac evaluation, might be important for placental cyst management. Blood pressure measurements and oral glucose tests for gestational diabetes have increased importance for such patients. Also, uterine artery Doppler measurements and prophylactic acetylsalicylic acid use might be under consideration.

Strengths of the present study were its higher patient number than the literature, ultrasound follow-ups until delivery, and obstetric outcomes. The limitation of this study was that it involved mostly perinatology unit patients, and these group results may not reflect low-risk pregnant population outcomes.

CONCLUSION

The presented study showed that placental cysts have clinical importance due to their potential risk for FGR and accompanying fetal anomalies. Appropriate management for this special group necessitates ultrasound examinations for fetal well-being, cyst size and growth pattern, and anomaly screening, considering the increased risk for fetal anomalies and growth restriction. The clinical utility of uterine Doppler examination and prophylactic use of acetylsalicylic acid needs further studies.

Ethics Committee Approval

The study was approved by the Institutional Review Board of the Ankara Bilkent City Hospital Ethics Committee (approval number: E2-23-4716).

Funding

The authors declare that no funds, grants, or other support were received during the preparation of this manuscript.

Conflict of interest

The authors declare that there are no conflicts of interest.

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Jinekoloji - Obstetrik ve Neonatoloji Tıp Dergisi
The Journal of Gynecology-Obstetrics and Neonatology

ÖZGÜN ARAŞTIRMA / ORIGINAL ARTICLE

DOI: 10.38136/jgon.1438323

Severe vitamin D deficiency is associated with increased risk of first trimester miscarriage in the Eastern Black Sea region of Türkiye

Doğu Karadeniz Bölgesinde şiddetli D vitamini eksikliğinin ilk trimester düşük riski ile ilişkisi

Neslihan BEZİRGANOGLU ALTUNTAS[1], Sema BAKİ YILDIRIM[2], Yesim BAYOGLU TEKİN[1]

[1]Trabzon Kanuni Training and Research Hospital, Department of Obstetrics and Gynecology, Trabzon, Türkiye
[2]Giresun University, Obstetrics and Pediatrics Training and Research Hospital, Department of Obstetrics and Gynecology, Giresun, Türkiye

ABSTRACT

Aim: To measure 25-hydroxyvitamin D (25(OH)D) serum concentration among pregnant women in the first trimester and its association with first-trimester pregnancy loss in the Eastern Black Sea region of Türkiye.

Materials and Methods: In this retrospective, cross-sectional study, we collected health records of pregnant women attending prenatal care at our department between March 2020 and December 2020. Serum 25 (OH)D levels were measured in the first trimester, and the patient's characteristics and the course of the pregnancy were analyzed. We investigated the association between maternal vitamin D deficiency and the risk of subsequent miscarriage.

Results: The final analysis included 246 pregnant women, with 50 (20.3%) had a miscarriage in the first-timester. The prevalence of vitamin D deficiency was high in the group, with 78.5% of the study group having serum levels of 25(OH)D<20 ng/ml. The mean 25(OH)D concentration was 13.3±5.7 ng/ml in the miscarriage group, 15.5±6.4 ng/ml for control group. The miscarriage group had a statistically older maternal age, higher parity.and higher rate of severe vit D deficiency. Logistic regression showed that only severe vit D deficiency was associated with miscarriage.

Conclusion: We found high rates of vitamin D deficiency in this region among pregnant women in the first trimester. Severe Vitamin D deficiency was associated with an increased risk of first-trimester miscarriage. These findings suggest that a more aggressive approach for sufficient vitamin D supplementation may be considered in this region.

Keywords: 25-hydroxyvitamin D, miscarriage, pregnancy, spontaneous abortion, first trimester

ÖZ

Amaç: Türkiye'nin Doğu Karadeniz bölgesinde ilk trimesterda gebelerde 25-hidroksivitamin D (25(OH)D) serum konsantrasyonunu ve bunun ilk trimester gebelik kaybıyla ilişkisini değerlendirmek

Gereçler ve Yöntem: Bu retrospektif, kesitsel çalışmada, Mart -Aralık 2020 tarihleri arasında hastanemiz antenatal gebe takip polikliniğinde değerlendirilen gebe kadınların sağlık kayıtları toplandı. İlk trimesterda ölçülen serum 25 (OH)D düzeyleri, hastaların demografik özellikleri ve gebelik seyri not edildi. Maternal vit D eksikliği ile ilk trimester düşük riski arasındaki ilişki incelendi.

Bulgular: Çalışmaya 246 hamile hasta dahil edildi. Hastaların 50'si (%20,3) ilk trimesterda düşük yaptı. Tüm grupta vitamin D eksikliği prevalansı yüksekti; çalışma grubunun %78,5'inin serum düzeyleri 25(OH)D<20 ng/ml idi. Düşük yapan grupta ortalama 25(OH)D konsantrasyonu 13,3±5,7 ng/ml iken, kontrol grubunda 15,5±6,4 ng/ml idi. Düşük yapan grupta istatistiksel olarak anne yaşı daha yüksek, parite sayısı daha fazla, şiddetli D vitamini eksikliği insidansı daha yüksekti. Çok değişkenli analiz, şiddetli D vitamini eksikliğinin ilk trimester düşük riski ile ilişkili olduğunu gösterdi.

Sonuç: Bu bölgede ilk trimesterda gebelerde vitamin D eksikliğinin yüksek olduğu saptandı. Şiddetli D vitamini eksikliği, ilk trimesterde düşük yapma riskinin artmasıyla ilişkili idi. Bu bulgular, bu bölgede yeterli D vitamini takviyesi için daha agresif bir yaklaşımın düşünülebileceğini düşündürmektedir.

Anahtar Kelimeler: 25-hidroksivitamin D, gebelik, spontan düşük, ilk trimester, gebelik kaybı

Cite as: Bezirganoglu Altuntas N, Baki Yıldırım S, Bayoglu Tekin Y. Severe vitamin D deficiency is associated with increased risk of first trimester miscarriage in the Eastern Black Sea region of Türkiye. Jinekoloji-Obstetrik ve Neonatoloji Tıp Dergisi 2024;21(4):285–290.

Geliş/Received: 16.02.2024 • **Kabul/Accepted:** 29.03.2024

Sorumlu Yazar/Corresponding Author: Neslihan BEZIRGANOGLU ALTUNTAS, Trabzon Kanuni Training and Research Hospital, Department of Obstetrics and Gynecology, Maras Street, 61000 Ortahisar-Trabzon, Türkiye
E-mail: nel.bezirgan@yahoo.com.tr

Çevrimiçi Erişim/Available online at: https://dergipark.org.tr/tr/pub/jgon

INTRODUCTION

Miscarriage is one of the most common adverse outcomes of pregnancy, with significant pregnancy losses occurring within the first trimester. Several studies report that the prevalence of miscarriage ranges between 12% and 21% (1,2). While miscarriage is attributed to multiple factors, including maternal infections, uterine anomalies, thrombophilias, and chromosomal abnormalities, acquired or environmental factors are also believed to contribute significantly as preventable risk factors (3,4).

Vitamin D is crucial in regulating calcium and phosphorus levels and bone mineralization (5). Moreover, reproductive tissues, such as the human placenta, endometrium, and ovaries, also express vitamin D receptors and 1α-hydroxylase, which are involved in vitamin D metabolism (6). Studies have shown that vitamin D regulates implantation, cytokine production, and the immune response to infection during pregnancy (7,8). Considering its potential role in modulating human reproductive processes, vitamin D deficiency is a significant concern, particularly for pregnant women and those planning pregnancy who are at increased risk. Vitamin D deficiency is shown to be more prevalent among women experiencing major reproductive and obstetric complications like preeclampsia, gestational diabetes, and preterm birth (9,10). However, the impact of vitamin D deficiency and insufficiency on first-trimester pregnancy loss remains less clear.

Vitamin D deficiency may play a role in the pathophysiology of miscarriage due to its potential importance as a regulator of trophoblast invasion in early pregnancy (11). Moreover, vitamin D can directly regulate HOX10, which is crucial for embryo implantation (12). Low serum levels of 25(OH)D may lead to a concurrent decrease in placental 1,25(OH)2D and subsequent placental dysregulation (13). Several studies have found an association between low levels of vitamin D and an increased risk of miscarriage in various populations (13-15). However, studies examining the relationship between vitamin D levels and pregnancy loss in the Black Sea region of Türkiye are lacking.

The objective of this study is to assess the vitamin D levels of pregnant women in the first trimester and determine whether these levels are associated with an increased risk of miscarriage in the Black Sea region of Türkiye.

MATERIALS AND METHODS

This retrospective, cross-sectional study was conducted between March 2020 and December 2020 at the Department of Obstetrics and Gynecology of the Kanuni Training and Research Hospital, Trabzon, Türkiye. The study was conducted in accordance with the Declaration of Helsinki and approved by the ethics committee of the hospital (E1-20–602). All pregnant women attending the outpatient clinic of the hospital who were carrying singleton fetuses at 7-14 week gestation by first day of the last menstrual period were considered eligible for inclusion in the study. Patients with a history of previous miscarriage, diagnosed uterine anomalies, thyroid dysfunction, autoimmune disorders, preexisting chronic diseases, diabetes mellitus (type 1 or 2), severe hepatic and liver disease, positive serology for intrauterine infection, chromosomal abnormalities, congenital anomalies or those who had been prescribed hormonal and antiepilectic medication, that might effect vitamin D metabolism, within the last three months were excluded. Multiple pregnancies were also excluded. The geographical coordinates for Trabzon province, situated on the North coast of Türkiye, are latitude 41°0’ N, longitude 39°43’ E, and altitude 49 m/161 feet,respectively.

Miscarriage was defined as a missed miscarriage, a complete or incomplete miscarriage, or a blighted ovum before 14 completed weeks of gestation. All cases of miscarriage were confirmed through transvaginal ultrasound. Controls were women with healthy liveborn babies without birth defects. Data on maternal characteristics included age, parity, pre-pregnancy weight, date of last menstrual period, smoking habits, outfit clotting style, and the time of blood collection were recorded. The season for blood collection was dichotomized into either May to October or November to April, representing the seasons of high and low 25(OH)D concentrations, respectively. Clothing was categorized as; wearing full cover-out fit style clothing, covering the whole body but leaving the hand and face exposed and uncovered women with exposed heads, arms, and legs.

During the study period, 294 pregnant patients were initially recruited. However, 48 patients were subsequently excluded from the study for various reasons. Among the exclusions, 21 patients did not continue follow-up at our institution, seven were diagnosed with twin gestations, four were using anti-convulsant medication, eight had a history of previous pregnancy loss, three were diagnosed with diabetes mellitus, three were diagnosed with uterine anomalies, one tested positive for intrauterine infection, and one had significant thyroid dysfunction. The final analysis included 246 pregnant patients with 50 cases of first-trimester miscarriage and 196 controls.

For each participant a fasting venous blood samples were collected using EDTA tubes and rotated for 5 minutes at 2500 rotations per minute. Plasma samples were then analyzed using the Beckman

Coulter Unicel Dx1600 immune analyzer, with the same branded kits, to measure levels of 25(OH) D. Due to the discrepancies in the definition of optimal serum levels of 25(OH)D in the literature, although some data suggest potential benefits for higher thresholds, we opted to consider serum concentrations of 25(OH) D >50 nmol/L (20 ng/mL) as sufficient. Mild to moderate deficiency was characterized by values between 30-50 nmol/L (12-19 ng/mL), while severe vitamin D deficiency was identified when levels <30 nmol/L (12 ng/mL) (16).

Statistical analysis

Data were analyzed using SPSS, version 25.0 (SPSS, Chicago, IL). Continuous variables were presented as mean ± standard deviation (SD), and categorical variables were described median and as percentages. Continuous variables were compared between groups by independent samples t tests for normally distributed variables and the Mann–Whitney U test for non–normally distributed variables. We dichotomized 25(OH)D levels by cutoff values of 20 ng/mL and 12 ng/mL. Multivariate linear regression analysis was performed to determine independent effects of 25(OH)D levels and covariates on first-trimester miscarriage. Entry into the multivariate model was conditional on p value of 0.2 in univariate analysis. Pearson correlation test was used where appropriate. For all statistical analyses, a p value ≤0.05 was considered significant.

RESULTS

A total of 246 pregnant patients were included in the analysis, including 50 patients who experienced first-trimester miscarriage (cases) and 80 pregnant women who delivered healthy liveborn babies (controls). The characteristics of the study population are summarized in Table 1. The miscarriage group had a higher maternal age and a higher rate of parity compared to healthy controls (p=0.013 and 0.011, respectively). The overall serum 25(OH)D level for the entire cohort was 14.6±6.2 ng/mL. The control group demonstrated a borderline significantly higher level of 25(OH) D compared to the miscarriage group (p=0.056). Table 2 shows the variations in serum 25(OH)D levels within the cohort. Vitamin

Table 1. General characteristics of the participants.

	Total cohort (n= 246)	Miscarriage (n=50)	No miscarriage (n=196)	*p* value[a]
Maternal Age (years), (SD)	30.46 ±5.26	31.88±5.07	29.53±5.16	0.013
Maternal BMI, kg/m^2, median (IQR)	23 (22-25)	24 (22-25)	23 (22-25)	0.67
Smoking in pregnancy, n (%)	10 (4.1)	2 (4)	8 (4.1)	0.97
Season of blood sample, n (%) Summer (May to October) Winter (November to April)	 91 (36.9) 155 (63.1)	 17 (34) 33 (66)	 74 (37.8) 122 (62.2)	0.85
Dressing outfit style, n(%) Covered Uncovered	 84 (34.2) 162 (65.8)	 18 (36) 32 (64)	 66 (33.6) 130 (66.3)	0.81
Parity, n(%) Nulliparous Paraous	 125 (50.8) 66 (49.2)	 16 (32) 34 (68)	 109 (55.7) 87 (44.3)	***0.011***

Plus-minus values are mean±standard deviation, SD: standard deviation, IQR: interquartile range , BMI: body mass index
[a] p<0.05 values were considered as significan

Table 2. Association of vitamin D deficiency and occurrence of miscarriage

	Total cohort (n= 246)	Miscarriage (n=50)	No miscarriage (n=196)	*p* value[a]
25 (OH)D level, (ng/mL), (SD)[b]	14.62±6.20	13.32 ±5.68	15.47±6.40	0.056
25(OH)D status, n (%) Sufficient (>20 ng/mL) Deficient (≤ 20 ng/mL)	 53 (21.5) 193 (78.5)	 9 (18) 41 (82)	 44 (22.4) 152 (77.5)	0.65
Severe vit D deficiency (<12 ng/ml)	72 (29.3)	24 (48)	48 (24.4)	0.03

[a] p<0.05 values were considered as significant
[b] 25 (OH)D : 25-hydroxyvitamin D, Plus-minus values are mean±standard deviation, SD: standard deviation

Table 3. Multivariate analysis of parameters associated with miscarriage.

Variables	Multivariate analysis (95% CI)	p value[a]
Age	0.916 (.830-1.010)	0.08
BMI	0.102 (.956-1.650)	0.11
Parity	0.508 (0.185-1.393)	0.18
Vit D level (ng/mL)	1.001 (0.919-1.090)	0.98
Severe vit D deficiency	3.764 (1.225-11.566)	0.02

[a] p<0.05 values were considered as significant, CI, confidence interval; OR, Odds ratio, BMI: body mass index

D deficiency was prevalent in 78.5% of the entire cohort, with no significant difference observed between the two groups (p=0.65). However, severe vitamin D deficiency was significantly higher in the miscarriage group (p=0.03), with 48% of pregnant women having miscarriage presenting severe vitamin D deficiency. Multivariate analysis revealed that severe vit D deficiency was an independent risk factor for first-trimester miscarriage. (adjusted OR=3.76, 95 %CI 1.22-11.56; p=0.02) (Table 3). Moreover, the incidence of severe vit D was statistically associated with miscarriage (r = 0.267, p = 0.003).

DISCUSSION

This retrospective, cross-sectional study is one of the first to investigate the vitamin D levels of pregnant women during the first trimester of pregnancy and the potential association between 25(OH) D serum concentrations and the risk of first-trimester miscarriage in the Eastern Black Sea region of Türkiye. Our findings showed that the prevalence of vitamin D deficiency is very high among pregnant women in this region, with 78.5% of the pregnant women being vitamin D deficient and 29.3% severely vitamin D deficient. Furthermore, our study indicates that there is a correlation between severe vitamin D deficiency and first-trimester miscarriage.

A miscarriage is generally defined as the loss of a pregnancy that occurs before the fetus reaches viability. It is a common occurrence and can have significant physical and psychological consequences for women. A recent review, which included data from nine studies totaling 4,638,974 pregnancies, found that the overall risk of miscarriage was 15.3% (95% CI 12.5–18.7) of all recognized pregnancies (2). The rate of spontaneous miscarriage varies across different countries and regions. For instance, a large study conducted in Israel revealed that as many as 43% of women reported experiencing one or more spontaneous miscarriages during the first trimester of pregnancy (17). Our findings are in line with the literature, as 20.3% of the participants in our cohort had a first-trimester miscarriage. Maternal age is shown to be the most important factor for first-trimester miscarriages, as the risk significantly increases in older ages (18). In our study, we observed that the miscarriage group had a statistically older maternal age and higher parity.

The American College of Obstetricians and Gynecologists (ACOG) and the International Federation of Gynecology and Obstetrics recommend supplementing 250–600 IU/day vitamin D3 during pregnancy as a standard (19,20). However; the prevalence of vitamin D deficiency appears to be increasing globally among women of reproductive age. A study involving pregnant Swiss women revealed that only 26.8% of participants had sufficient serum 25(OH)D levels (≥30 ng/mL) during the first trimester (21). Previous studies from Türkiye have also reported elevated rates of vitamin D deficiency in pregnant women, even during the summer months (22). A study conducted in the Black Sea Region found an even higher prevalence of vitamin D deficiency in this region, with 94.2% of pregnant patients having deficiency (23). Our findings support these results, with the majority of our patients also were vitamin D deficient. We conducted the study in both the winter and summer time zones. The skin synthesis of vitamin D3 should be expected to be even lower during the winter period (5). The majority of blood samples were taken in the winter (63.1%), potentially contributing to the prevalence of deficiency in our cohort. Although the testing period did not differ between the two groups (p=0.85), the mean serum 25(OH)D level of the entire cohort during the summer was 19.32±6.36 ng/mL, which still fell below the recommended threshold for sufficiency. Latitude and season significantly affect vitamin D3 production, particularly in regions above 35 degrees latitude, where the angle of the sun during winter limits ultraviolet ray exposure necessary for vitamin D3 synthesis (24). As our study center is situated around 41 degrees latitude, this may also contribute to lower 25(OH)D levels in our region. In our study, we observed that 34.2% of pregnant women in the entire cohort were wearing covered clothing. This suggests that clothing style may play a role on severity of vitamin D deficiency.

The elucidation of the immunomodulatory effects of 1,25(OH)2D has led to interest in the potential role of vitamin D in protecting against spontaneous abortion (11). This hypothesis is supported by ex vivo analyses demonstrating that 1,25(OH)2D can suppress inflammatory cytokine production by endometrial cells from women with unexplained recurrent spontaneous abortions. (25). Moreover, Özkan et al. found that serum and follicular fluid 25(OH)D concentrations are highly correlated, women with higher vitamin D level in their serum and folicular fluid are significantly more likely to achieve clinical pregnancy following in vitro fertilization (26). Considering these observations, the influence of maternal vitamin D status on miscarriage risk has been investigated in several cohorts (13-15). While some studies have reported an increased risk of subsequent miscarriage with maternal vitamin D insufficiency or deficiency, others have not found such an association (14,15,27). In our study, although the miscarriage group exhibited a higher rate of vitamin D deficiency, only severe deficiency (<12 ng/mL) was significantly associated with first-trimester miscarriage. It is plausible that the overall high prevalence of vitamin D deficiency in our study population could potentially diminish the predictive performance of serum 25(OH)D levels for miscarriage risk in the recent study. Moreover, discrepancies in findings across studies could be attributed to differences in population characteristics, sample sizes, and methodologies used to measure 25(OH)D levels.

Our study has several limitations. Firstly, it was conducted in a single unit with a relatively small sample size, which may limit the generalizability of the findings to broader populations. Secondly, we did not account for potential confounding variables such as dietary habits, vitamin supplementation,and folic acid levels when assessing the association between 25(OH)D and miscarriage. Previous studies have demonstrated a significant association between vitamin D levels and the severity of COVID-19 in pregnant women (28). However, our study did not assess the role of previous COVID-19 history in miscarriage. Furthermore, evaluating the underlying factors contributing to vitamin D deficiency was beyond the scope of this study.

In conclusion, our study revealed high rates of vitamin D deficiency among healthy women in the first trimester of pregnancy in this region, without any prior history of miscarriage. Importantly, we observed a significant association between severe vitamin D deficiency and miscarriage in this study population. These findings may show the potential protective role of vitamin D against miscarriage. Developing novel, more agressive supplementation strategies specific to this region may lead to improved maternal health outcomes.

Ethics Committee Aproval

The study was conducted in accordance with the Declaration of Helsinki and approved by the ethics committee of the hospital (E1-20–602).

Authors' Contributions

NBA and SBY were primarily responsible for protocol development and the analytic framework of the study, outcome assessment, and manuscript preparation. NBA had primary responsibility for reviewing the files, patient screening, enrollment, and data entry, and prepared the manuscript. YBT contributed to preparation and revision of the manuscript.

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Jinekoloji - Obstetrik ve Neonatoloji Tıp Dergisi
The Journal of Gynecology-Obstetrics and Neonatology

ÖZGÜN ARAŞTIRMA / ORIGINAL ARTICLE

DOI: 10.38136/jgon.1322155

Preeklampside nötrofil lenfosit oranı ve platelet endeksleri; Şiddetli hastalık öngörülebilir mi ?

Neutrophil lymphocyte ratio and platelet indices in preeclampsia; Could we predict the severity of disease ?

Osman Onur ÖZKAVAK[1], Ezgi TURGUT[1], Hakkı ŞERBETÇİ[1], Refaettin ŞAHİN[1], Atakan TANAÇAN[1], Dilek ŞAHİN[1]

[1]T. C. Sağlık Bakanlığı Ankara Şehir Hastanesi Kadın Hastalıkları ve Doğum Kliniği, Perinatoloji Bölümü, Ankara, Türkiye

ÖZ

Amaç: Çalışmamızda; preeklampsi, şiddetli preeklampsi ve sağlıklı gebe grupları arasında; üçüncü trimester nötrofil-lenfosit oranı (NLR) ve platelet indekslerini karşılaştırdık. Ayrıca nötrofil-lenfosit oranının hastalığı öngörmedeki faydasını da inceledik.

Gereçler ve Yöntem: Retrospektif, kesitsel araştırma olarak dizayn edilen çalışmaya 40 preeklampsi, 59 şiddetli preeklampsi ve benzer yaş grubundan 66 sağlıklı gebe kontrol olmak üzere toplam 165 hasta dahil edildi. Gruplar arası demografik özellikler, kan basıncı verileri, yenidoğan sonuçları, maternal hemogram parametreleri ve NLR değerleri karşılaştırıldı.

Bulgular: Preeklampsi grubunun platelet-lenfosit oranı (PLR) kontrol grubundan düşük izlendi (p=0.027). Şiddetli preeklampsi grubunun nötrofil sayısı ve NLR değerleri hem kontrol grubundan (p<0.001 ve p=0.006) hem de preeklampsi grubundan (p=0.012 ve p=0.001) istatistiksel olarak anlamlı şekilde yüksek izlendi. Şiddetli preeklampsi grubunun platelet sayısı, MPV ve PLR değerleri kontrol grubundan anlamlı şekilde düşük izlendi (p=0.006, p=0.004 ve p=0.006). Nötrofil-lenfosit oranının şiddetli preeklampsi öngörüsündeki değerini incelemek için yapılan ROC eğrisi analizinde en iyi sensitivite-spesifite dengesi 3,8591 (%64.4 sensitivite, %62.5 spesifite, p=0.043) değerinde izlendi.

Sonuç: Şiddetli preeklampsi öngörüsü obstetrik takipte önemli bir konudur ve NLR değerleri hastalığın öngörüsünde faydalı olabilir. NLR ve benzeri prediktif belirteçlerin araştırılması daha iyi obstetrik ve neonatal sonuçlar için yararlı olacaktır.

Anahtar Kelimeler: Preeklampsi, nötrofil-lenfosit oranı

ABSTRACT

Aim: In our study we aimed to investigate the difference of the third trimester neutrophil to lymphocyte ratio (NLR) and platelet indices between preeclampsia, severe preeclampsia and healthy pregnant group. The predictive value of the third trimester NLR in severe preeclampsia was also evaluated.

Material and Methods: This retrospective cross sectional study, enrolled 165 pregnant women with 40 cases of preeclampsia, 59 cases of severe preeclampsia and 66 age-matched healthy pregnant women as control group. Demographic factors, blood pressure values, neonatal outcomes, maternal haemogram parameters (including platelet indices) and NLR values were compared between the control, preeclampsia and the severe preeclampsia groups.

Results: The platelet to lymphocyte ratio (PLR) value of the preeclampsia group was lower than the control group (p=0.027). Neutrophil count and NLR of the severe preeclampsia group was significantly higher than control (p<0.001 and p = 0.006) and preeclampsia (p=0.012 and p= 0.001) groups. Platelet count, MPV and PLR values of the severe preeclampsia group was significantly lower than the control group (p = 0.006, p=0.004, p=0.006). We made a Receiver Operating Characteristics (ROC) curve analysis to evaluate the value of the NLR for predicting severe preeclampsia. The values in the ROC curves with the best sensitivity - specificity balance was 3.8591 (64.4% sensitivity, 62.5% specificity, p = 0.043).

Conclusion: Using NLR could be useful for predicting severe preeclampsia. Predicting severe preeclampsia is an important issue and investigation of predictive markers like NLR will be beneficial for better outcomes.

Keywords: Preeclampsia, neutrophil to lymphocyte ratio

Cite as: Özkavak OO, Turgut E, Şerbetçi H, Şahin R, Tanaçan A, Şahin D. Preeklampside nötrofil lenfosit oranı ve platelet endeksleri; Şiddetli hastalık öngörülebilir mi ?. Jinekoloji-Obstetrik ve Neonatoloji Tıp Dergisi 2024;21(4):291–296.

Geliş/Received: 17.07.2023 • **Kabul/Accepted:** 20.08.2024

Sorumlu Yazar/Corresponding Author: Osman Onur ÖZKAVAK, Üniversiteler, 1604. Cd. No:9, 06800 Çankaya/Ankara, Türkiye
E-mail: onurozkavakdr@gmail.com

Çevrimiçi Erişim/Available online at: https://dergipark.org.tr/tr/pub/jgon

GİRİŞ

Preeklampsi, gebeliğin 20. haftasından sonra veya postpartum dönemde ortaya çıkan hipertansiyon ve buna eşlik eden proteinüri veya son organ hasarı ile karakterize bir hastalıktır. Şiddetli preeklapmsi ise hastalığın şiddetli hipertansiyon ve/veya önemli son organ hasarı görülen formu olarak tanımlanabilir (1).

Preeklampsi tüm gebeliklerin %2-8'lik kısmını etkileyen gebeliğin önemli bir komplikasyonudur (2). Dünya genelinde doğrudan anne ölümlerinin %10-15 kadarı preeklampsi ve eklampsiye bağlıdır ve birleşik devletlerde maternal ölümlerin en önemli dört nedeninden biridir (3,4).

Hastalığın patogenezi hala kesin olarak aydınlatılamamıştır. Bu konuda pek çok hipotez mevcuttur ve bu hipotezlerin önemli kısmında plasenta önemli rol oynamaktadır (5,6). Vasküler, immünolojik, genetik, endotelyal, çevresel faktörler ve inflamasyonun etiyolojide sorumlu oldukları düşünülmektedir (7).

Preeklampsi hastalarında sağlıklı gebelere kıyasla artmış bir inflamatuar süreç mevcuttur. Preeklampsi olgularında dolaşımdaki sinsisyotrofoblastik mikropartiküller, serbest fetal DNA, sFlt1 ve toksik sinsisyal protein düzeylerinin daha yüksek olduğu çeşitli çalışmalarla gösterilmiştir (8–10).

Nötrofil-lenfosit oranı (NLR) bir sistemik inflamasyon belirtecidir (11). Yüksek NLR değerleri ile sepsis hastalarında kötü prognoz, romatoid artrit gibi otoimün hastalıkların varlığı ve miyokardit hastalarında daha uzun hastanede kalış gibi istenmeyen durumlar arasında ilişki gösterilmiştir (11–13). Web of Science and Scopus, from inception to January 2018, were searched for studies reporting on NLR and PLR in RA in comparison with healthy subjects. Standardized mean difference (SMD. Preeklampsinin inflamatuar doğası nedeniyle NLR preeklampsi ilişkisi önemli bir araştırma sahası olmuştur.

Trombositopeni preeklampside en sık görülen hematolojik anomalidir (14). Artmış trombosit agregasyonu ve koagülasyon sistemindeki aktivasyon hastalığın patogenezinde önemli bir rol oynar (15). Trombosit aktivasyonunu gösteren indeksler trombosit sayısı, trombosit dağılım genişliği (PDW), ortalama trombosit hacmi (MPV), platelectrit (PCT) değerleridir (16). Çeşitli çalışmalarda preeklampsi hastalarında bu indekslerin değiştiği gösterilmiştir (17,18).

Biz çalışmamızda, sağlıklı gebeler, preeklampsi ve şiddetli preeklampsi olguları arasında üçüncü trimester rutin kontrolünde bakılan NLR ve platelet indeksleri açısından fark olup olmadığını ve nötrofil-lenfosit oranının prognostik değerini araştırmayı amaçladık.

GEREÇ VE YÖNTEM

Retrospektif, kesitsel çalışma olarak dizayn edilen çalışmamıza Kasım 2021 ve Nisan 2022 tarihleri arasında, üçüncü basamak bir eğitim araştırma hastanesi olan hastanemizin doğum ünitesine başvurmuş ve tedavi edilmiş benzer yaş grubundan 40 preeklampsi, 59 şiddetli preeklampsi ve 66 sağlıklı gebe olmak üzere toplam 165 hasta dahil edildi. Hastaların üçüncü trimester kontrol kan tahlillerinin sonuçları retrospektif olarak incelendi. Çalışmanın etik kurallara uygunluğu hastanemiz etik kurulu tarafından değerlendirilerek E2-22-1413 numarası ile onaylanmıştır.

Preeklampsi ve şiddetli preeklampsi tanıları Amerikan Kadın Hastalıkları ve Doğum Cemiyeti (ACOG) kriterlerine göre koyuldu(1). Kronik hipertansiyon, diyabet, renal hastalık, hematolojik bozukluk, kronik inflamatuar hastalık öyküsü bulunanlar ve çoğul gebeliği olan hastalar çalışmaya dahil edilmedi. Aile öyküsü, medikal, obstetrik ve sosyo-demografik öykü verileri laboratuvar sonuçları tıbbi kayıtlardan elde edildi.

Maternal yaş, gebelik sayısı, tanı anında gebelik haftası, sistolik ve diyastolik kan basıncı değerleri (mmHg), doğumda gebelik haftası, doğum ağırlığı (g), birinci ve beşinci dakika APGAR skorları, sezaryen oranları, yenidoğan yoğun bakım yatışı (YBÜ), maternal hemoglobin (g/dl), nötrofil sayısı ($x10^9$/L), lenfosit sayısı ($x10^9$/L), trombosit sayısı ($x10^9$/L), MPV (fL), PCT (%), PDW (%), NLR (nötrofil sayısı / lenfosit sayısı) ve trombosit-lenfosit oranı (PLR) (trombosit sayısı / lenfosit sayısı) değerleri üç grup arasında karşılaştırıldı.

Verilerin analizi için SPSS (version 21, SPSS Inc Company, USA) kullanıldı. Tanımlayıcı verilerden normal dağılıma uyanlar ortalama ± standart sapma şeklinde, normal dağılıma uymayanlar ortanca ve minimum-maksimum şeklinde verldi. Değişkenlerin normal dağılıma uyup uymadığının kontrolü için Shapiro – Wilk ve Kolmogorov – Smirnov testleri uygulandı. Kategorik olmayan veriler karşılaştırılırken Mann Whitney U ve Student's t test kullanıldı. Kategorik veriler Pearson ki-kare testi ve Fisher's exact test ile analiz edildi. NLR nin şiddetli preeklampsiyi öngörmedeki performansını değerlendirmek için ROC eğrisi kullanıldı. En uygun eşik değerin belirlenmesi için ise Youden indeksi eğriye uygulandı. p değeri 0,05'in altında olan farklar istatistiksel olarak anlamlı kabul edildi.

BULGULAR

Tüm grupların yaş, ortalama gebelik haftası ve nulliparite oranları benzerdi. Preeklampsi ve şiddetli bulgularının eşlik ettiği preeklampsi

Tablo 1. Katılımcıların demografik verileri

	Kontrol grubu (n=66)	Preeklampsi grubu (n=40)	Şiddetli preeklampsi grubu (n=59)	P değeri
Maternal yaş	28 ± 5	29 ± 5	29 ± 6	0,664
Nulliparite	34,8%	47,5%	44,1%	0,376
Ortalama gebelik haftası	34 ± 3	34,2 ± 4	33,9 ± 3	0,442
Sistolik kan basıncı	100 ± 8	146 ± 13	159±19	**<0,001** [a] **<0,001** [b] **<0,001** [c] **<0,001**
Diyastolik kan basıncı	71 ± 7	91 ± 9	98 ± 11	**<0,001** [a] **<0,001** [b] **<0,001** [c] **<0,001**
Doğumda gebelik haftası	38 ± 1	37,3 ± 1,3	33 ± 3	**<0,001** [a] 0,170 [b] **<0,001** [c] **<0,001**
Doğum ağırlığı (g)	3170 ± 446	2961 ± 558	2182 ± 916	**<0,001** [a] 0,124 [b] **<0,001** [c] **<0,001**
1. dakika APGAR	8 (1)	7 (1)	7 (2)	**<0,001** [a] 0,338 [b] **<0,001** [c] **0,001**
5. dakika APGAR	9 (1)	9 (1)	8 (1)	**<0,001** [a] 0,581 [b] **0,001** [c] **<0,001**
Sezaryen oranı	23 (20,5%)	32 (28,6%)	57 (50,9%)	**<0,001** [a] **<0,001** [b] **<0,001** [c] **0,007**
Yenidoğan YBÜ yatış	2 (6,5%)	5 (16,1%)	24 (77,4%)	**<0,001** [a] 0,068 [b] **<0,001** [c] **0,003**

Değerler ortalama ± SS, sayı, yüzde (n,%) şeklinde verilmiştir. YBÜ: yoğun bakım ünitesi. [a] Kontrol grubu ve preeklampsi grubunun karşılaştırılması, [b] Kontrol grubu ve şiddetli preeklampsi grubunun karşılarştırması, [c] Preeklampsi ve şiddetli preeklampsi gruplarının karşılaştırılması.

gruplarının kan basıncı değerleri kontrol grubundan anlamlı şekilde yüksek izlendi (p<0.001). Ayrıca şiddetli preeklampsi grubunun kan basıncı değerleri, preeklampsi grubununkinden de yüksekti (p<0.001). Doğumda gebelik haftası bakımından kontrol grubu ile preeklampsi grupları arasında anlamlı fark yoktu ancak şiddetli preeklampsi grubunda doğumda gebelik haftası ortalaması diğer iki gruptan da anlamlı şekilde düşük izlendi (p<0.001, p<0.001). Yenidoğan ağırlığı ve APGAR skorları da şiddetli preeklampsi grubunda diğer iki gruptan da istatistiksel olarak anlamlı şekilde düşük izlendi (p<0.001, p<0.001; p<0.001, p<0.001; p<0.001, p<0.001). Preeklampsi ve şiddetli preeklampsi gruplarının sezaryen oranları, kontrol grubundan yüksekti (p<0.001, p<0.001). Aynı zamanda şiddetli preeklampsi grubunun sezaryen oranı preeklampsi gruundan yüksek izlendi (p<0.001). Şiddetli preeklampsi grubunun yenidoğan YBÜ yatış oranı diğer iki gruptan anlamlı şekilde yüksekti (p<0.001 ve p=0.003). Grupların demografik, klinik özellikleri ve obstetrik sonuçları tablo 1'de gösterilmiştir.

Preeklampsi grubunun PLR değeri kontrol grubundan düşük izlendi (p=0.027). Hemogram parametreleri açısından preeklampsi ve kontrol grubu arasında başka anlamlı fark saptanmadı. Şiddetli preeklampsi grubunun nötrofil sayısı ve NLR değerleri hem kontrol hem de preeklampsi gruplanrından anlamlı şekilde yüksek izlendi (p<0.001, p = 0.006 ; p=0.012 and p= 0.001). Şiddetli preeklampsi

Tablo 2. Gruplar arası laboratuvar değerlerinin karşılaştırılması

	Kontrol Grubu	Preeklampsi	Şiddetli preeklampsi	P değeri
Hb (g/dl)	11,4 ± 1,4	11,8 ± 1,2	11,9 ± 1,4	0,069
Nötrofil sayısı (mm^3)	7 ± 2,1	7,5 ± 2,7	8,9 ± 3	**<0,001** [a] 0,377 [b] **<0,001** [c] **0,012**
Lenfosit sayısı (mm^3)	1,8 ± 0,5	1,9 ± 0,5	1,9 ± 0,7	0,119
Trombosit sayısı ($x10^9$)	239 ± 58	216 ± 70	207 ± 71	**0,019** [a] 0,075 [b] **0,006** [c] 0,505
MPV	10,5 ± 1,9	10,2 ± 1,9	9,6 ± 1,2	**0,013** [a] 0,384 [b] **0,004** [c] 0,085
PCT	0,27 ± 0,06	0,25 ± 0,06	0,24 ± 0,06	0,152
PDW	57,8 ± 9,8	58,6 ± 10	58,9 ± 8,3	0,775
NLR	3,9 ± 1,2	4,0 ± 1,9	5,3 ± 2,9	0,001 [a] 0,820 [b] **0,006** [c] **0,001**
PLR	1,4 ± 0,6	1,1 ± 0,5	1,1 ± 0,5	**0,012** [a] **0,027** [b] **0,006** [c] 0,793

Değerler ortalama ± SS, sayı, yüzde (n,%) şeklinde verilmiştir. Hb: hemoglobin, MPV: Ortalama platelet hacmi, PCT: Platelectrit, RDW: Red cell distribution width, NLR: nötrofil-lenfosit oranı, PLR: platelet lenfosit oranı [a] Kontrol grubu ve preeklampsi grubunun karşılaştırılması, [b] Kontrol grubu ve şiddetli preeklampsi grubunun karşılarştırması, [c] Preeklampsi ve şiddetli preeklampsi gruplarının karşılaştırılması.

Tablo 3. NLR değerinin şiddetli preeklampsiyi öngörmedeki değerine ilişkin ROC eğrisi analizi

	NLR için cut of değeri	Duyarlılık	Özgüllük	P değeri
Şiddetli preeklampsi öngörüsünde EAA:0,620 (95% CI: 0.509–0.732)	3,8591	64,4	62,5	0,043

EAA:eğrinin altındaki alan; CI: güven aralığı; ROC, receiver operating characteristic.

grubunda trombosit sayısı, MPV ve PLR düzeyleri kontrol grubuna göre anlamlı şekilde yüksek izlendi (p = 0.006, p=0.004, p=0.006). Bu parametreler açısından şiddetli ve preeklampsi grupları arasında anlamlı fark yoktu. Grupların hematolojik parametrelerinin karşılaştırılması tablo 2'de gösterilmiştir.

NLR düzeyinin şiddetli preeklampsi öngörüsündeki değerini incelemek için ROC eğrisi incelendi. Eğrinin altında kalan alan 0.620 (%95 CI: 0.509–0.732) olarak hesaplandı ve en iyi sensitivite-spesifite dengesi 3.8591 (%64.4 sensitivite, % 62.5spesifite, p = 0.043) olarak hesaplandı. NLR değerinin ROC eğrisi analizi tablo 3'te gösterilmiştir.

TARTIŞMA

Preeklampsi maternal immün sistemin kronik aktivasyonunun da rol aldığı önemli bir hastalıktır. Dolaşımda artmış proinflamatuar sitokin düzeyleri de bu durumun varlığını desteklemektedir(19). Bazı kompleman faktörlerinin preeklampside ileri derecede arttığı çalışmalarda gösterilmiştir (20). Bu kompleman aktivasyonu inflamatuar hücre göçünü ve nötrofil ve monosit aktivasyonunu uyarmaktadır (21). Bundan dolayı preeklampside nötrofil sayılarında artış görülmektedir (22).

NLR ve preeklampsi ilişkilini araştıran pek çok çalışma da mevcuttur. Gogoi ve ark. preeklampsi hastalarında kontrol grubuna göre daha yüksek NLR ve PLR değerleri saptamışlardır(23). Mannaerts ve ark. da benzer şekilde NLR ve PLR değerlerinin preeklampsi hastalarında daha yüksek izlendiğini ve buna ek olara 20. gebelik haftasından önceki MPV değerlerinin de preeklampsi hastalarında kontrol grubuna göre daha yüksek olduğunu raporlamışlardır(24). İlk trimesterda NLR, MPV ve PLR yüksekliğinin gebeliğin ilerleyen dönemlerinde preeklampsi gelişimi için bir belirteç olabileceği ile ilgili veriler mevcuttur(25). 3982 hastanın dahil edildiği bir meta-analizde özellikle şiddetli preeklampsi hastalarında kontrol grubuna göre daha yüksek NLR düzeyleri izlenmiştir(26).

Bizim çalışmamızda preeklampsi ve kontrol grupları arasında NLR düzeyleri açısından anlamlı bir fark saptanmadı, ancak şiddetli preeklampsi grubunun NLR düzeyleri diğer iki gruptan da yüksek izlendi. NLR açısından bulgularımız literatürle kısmen uyumludur. Preeklampsi ve şiddetli preeklampsi gruplarının PLR düzeyleri kontrol grubuna göre istatistiksel olarak anlamlı şekilde düşük olarak izlendi. Bu açıdan bulgularımız literatür ile uyuşmaktadır(23,24). Ek olarak preeklampsi ve şiddetli preeklampsi grupları arasında PLR düzeyleri açısından anlamlı fark izlenmedi.

NLR'nin preeklampsiyi öngörmede bir belirteç olarak kullanılabilirliği önemli bir araştırma konusu olmuştur. Bir meta-analizde NLR nin preeklampsi öngörüsünde %74 sensitivite ve %64 spesifite ile kullanılabileceği sonucuna varılmıştır (27). Başka bir araştırmada ise NLR düzeyinin tüm preeklampsi hastalarında şiddetli preeklampsiyi öngörmedeki değeri araştırılmış ancak yapılan incelemede eğrinin altındaki alan istatistiksel olarak anlamlı izlenmemiştir(28). Bu çalışmanın aksine, bizim çalışmamız üçüncü trimester NLR düzeylerinin %64.4 duyarlılık ve %62.5 özgüllükle tüm preeklampsi hastaları içerisinde şiddetli preeklampsi öngörüsünde kullanılabileceğini göstermiştir. Bu duyarlılık ve özgüllük değerleri başka belirteçlerle birlikte kullanımla daha da artırılabilir.

Preeklampsi hastalarında trombosit indeksleri önemli bir araştırma sahası olmuştur. Freitas ve ark. çalışmalarında şiddetli preeklampsi hastalarında daha düşük trombosit sayısı ve PCT değerleri; daha yüksek PDW ve MPV değerleri izlemişlerdir (29). Başka bir çalışmada ise preeklampsi ve kontrol grupları arasında PDW ve MPV düzeyleri açısından anlamlı fark saptanmamış ve aynı çalışmada preeklampsi ve şiddetli preeklampsi olguları arasında MPV, PDW ve trombosit sayısı açısından fark saptanmadığı belirtilmiştir (30).

Bizim çalışmamızda her üç grup arasında PCT ve PDW değerleri açısından anlamlı fark saptanmadı. Literatürde preeklampsi hastaları ile kontroller arasında PCT açısından istatistiksel olarak anlamlı fark olmadığını belirten ve preeklampsi hastalarında daha düşük PCT düzeyleri izlendiğini belirten çalışmalar mevcuttur(16,17,30). Benzer şekilde PDW düzeyleri ile preeklampsi arasında ilişki olduğunu belirten ve preeklampsi hastaları ve kontrol grupları arasında PDW açısından anlamlı fark saptamayan çalışmalar mevcuttur(16,17,30,31). Hem PCT hem de PDW açısından literatürdeki veriler çelişkilidir.

Preeklampsi hastalarında kontrol grubuna göre daha yüksek MPV değerleri olduğu ve MPV yüksekliğinin hastalığı şiddeti ile ilişkili olduğu çeşitli çalışmalarla gösterilmiştir(17,28,31,32). Biz de literatürle uyumlu şekilde, MPV düzeylerini, şiddetli preeklampsi grubunda, kontrol grubuna göre daha yüksek saptadık. Hastalığın şiddeti ve MPV yüksekliği arasındaki ilişki mevcut çalışma ile de desteklenmiştir.

Çalışmamızda literatüle uyumlu şekilde şiddetli preeklampsi, artmış sezaryen oranı, preterm doğum, düşük doğum ağırlığı, düşük APGAR skorları ve yenidoğan yoğun bakım ünitesine yatış oranlarında artış gibi kötü obstetrik ve neonatal sonuçlarla ilişkili bulundu. Bundan dolayı, şiddetli preeklampsi öngörüsü ve bunun için kullanılacak NLR gibi belirteçlerle ilgili araştırmaların bu sonuçları iyileştirmede faydalı olacağını düşünmekteyiz.

SONUÇ

Biz bu çalışmamızda hem şiddetli hem de preeklampsi gruplarında kontrol grubuna göre yüksek NLR ve düşük PLR düzeyleri saptadık. Ayrıca preeklmapsi hastalarında daha düşük MPV değerleri bulduk. Ve üçüncü trimester NLR düzeylerinin şiddetli preeklampsi öngörüsünde kullanılabilecek bir belirteç olduğunu gösterdik.

Şiddetli preeklmapsi öngörüsünde kullanılabilecek diğer belirteçlerin NLR ile kombine edildiği ve daha çok katılımcı içeren çalışmaların literatüre önemli katkıları olabilir. Preeklampsi hakkında artan bilgi düzeyinin kötü maternal ve neonatal sonuçların öngörülmesi ve önlenmesi için faydalı olacağını düşünmekteyiz.

Çıkar çatışması

Yazarlar mevcut çalışmada herhangi bir organizasyon ile finansal veya finansal olmayan bir ilişkileri olmadığını beyan etmektedirler. Verilerin sorumluluğu yazarlara aittir ve editörler tarafından talep edilirse veriler paylaşılabilir.

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Jinekoloji - Obstetrik ve Neonatoloji Tıp Dergisi
The Journal of Gynecology-Obstetrics and Neonatology

ÖZGÜN ARAŞTIRMA / ORIGINAL ARTICLE

DOI: 10.38136/jgon.1552961

Is it necessary to check β-hCG levels on day 4 after single-dose methotrexate treatment of ectopic pregnancy? A retrospective cohort study

Dış gebelikte tek doz metotreksat tedavisinden sonra 4. günde β-hCG düzeyine bakılması gerekir mi? Retrospektif bir kohort çalışması

Emre Erdem TAS

Ankara Yıldırım Beyazıt Üniversitesi Kadın Hastalıkları ve Doğum Ana Bilim Dalı, Ankara Bilkent Şehir Hastanesi Kadın Doğum Kulesi, Türkiye

ABSTRACT

Aim: This study aimed to investigate the usefulness of the percentage change in serum β-hCG levels from days 1 to 7 for predicting treatment success in patients treated with a single dose of methotrexate for tubal ectopic pregnancy.

Materials and Method: This retrospective observational study investigated 74 patients treated with a single-dose methotrexate regimen for tubal ectopic pregnancy at a tertiary hospital between January 2020 and December 2023. Patients were subdivided into two groups based on reduction in serum β-hCG levels between days 4 and 7: <15.0% - "successful treatment" or ≥15.0% - "need a second dose methotrexate". Then, the percentage change in serum β-hCG levels between days 1 and 7 and its usefulness in predicting "successful treatment" were analyzed.

Results: Treatment was considered successful in 66 of the 74 patients (86.5%). There was a negative linear correlation between treatment success and percentage change in serum β-hCG levels from day 1 to day 7 (p<0.001). ROC curve analyses revealed that the sensitivity of treatment success prediction decreased with increasing percentage change in serum β-hCG levels from days 1 to 7. The sensitivity and specificity of the-25.0%, 0.0%, and +25.0% changes in serum β-hCG levels from day 1 to day 7 for predicting treatment success were 100.0%-41.0%, 90.0%-93.7%, and 80.0%-96.9%, respectively.

Conclusion: Monitoring the percentage change in serum β-hCG levels from days 1 to 7 may effectively replace the traditional protocol, particularly when patient compliance is challenging or when day 4 measurements are impractical.

Keywords: Ectopic pregnancy, methotrexate, chorionic gonadotropin, treatment outcome

ÖZ

Amaç: Bu çalışma, tubal ektopik gebelik nedeniyle tek doz metotreksat ile tedavi edilen hastalarda tedavi başarısını öngörmek için serum β-hCG düzeylerinde 1. ve 7. günler arasındaki yüzde değişimin yararlılığını araştırmayı amaçladı.

Gereç ve Yöntemler: Bu retrospektif gözlemsel çalışmada, Ocak 2020 ile Aralık 2023 arasında üçüncü basamak bir hastanede tubal ektopik gebelik nedeniyle tek doz metotreksat tedavisi uygulanan 74 hasta araştırıldı. Hastalar, 4. ve 7. günler arasında serum β-hCG seviyelilerindeki azalmaya göre iki gruba ayrıldı: <%15,0 - "başarılı tedavi" veya ≥%15,0 - "ikinci doz metotreksata ihtiyaç var". Ardından, serum β-hCG düzeylerinde 1. ve 7. günler arasındaki yüzde değişim ve bunun «başarılı tedaviyi» öngörmedeki faydası analiz edildi.

Bulgular: Yetmiş dört hastanın 66'sında (%86,5) tedavi başarılı kabul edildi. Tedavi başarısı ile 1. günden 7. güne kadar serum β-hCG seviyelerindeki yüzde değişim arasında negatif doğrusal bir korelasyon vardı (p<0.001). ROC eğrisi analizleri, tedavi başarısı tahmininin duyarlılığının, 1. günden 7. güne kadar serum β-hCG düzeylerinde yüzdelik değişimin artmasıyla azaldığını ortaya çıkardı. Tedavi başarısını öngörmek için 1. ve 7. Günler arası serum β-hCG seviyelerindeki -%25,0, %0,0 ve +%25,0 değişikliklerin duyarlılığı ve özgüllüğü sırasıyla %100,0-%41,0, %90,0-%93,7 ve %80,0-%96,9'du.

Sonuç: Birinci ve 7. günler arası serum β-hCG seviyelerindeki değişimin yüzdesel olarak izlenmesi özellikle hasta uyumunun zor olduğu veya 4. gün ölçümlerinin pratik olmadığı durumlarda geleneksel protokolün yerini etkili bir şekilde alabilir.

Anahtar Kelimeler: Ektopik gebelik, metotreksat, koryonik gonodotropin, tedavi sonucu

Cite as: Tas EE. Is it necessary to check β-hCG levels on day 4 after single-dose methotrexate treatment of ectopic pregnancy? A retrospective cohort study. Jinekoloji-Obstetrik ve Neonatoloji Tıp Dergisi 2024;21(4):297–300.

Geliş/Received: 19.09.2024 • **Kabul/Accepted:** 18.10.2024

Sorumlu Yazar/Corresponding Author: Emre Erdem TAS , Mehmet Akif Eroy Mahallesi Yesilay Caddesi 5A/121 Yenimahalle/Ankara, Türkiye
E-mail: doctortas83@gmail.com

Çevrimiçi Erişim/Available online at: https://dergipark.org.tr/tr/pub/jgon

INTRODUCTION

Ectopic pregnancy (EP) is a potentially life-threatening condition that occurs when a blastocyst implants outside the uterine cavity, most commonly in the fallopian tubes (1). It affects approximately 1-2% of all pregnancies and remains a leading cause of maternal morbidity and mortality in the first trimester (2). Early diagnosis and prompt treatment are crucial to prevent complications, such as tubal rupture and internal bleeding. Management options for ectopic pregnancy include surgical intervention, medical treatment with methotrexate, or expectant management in select cases (3).

Single-dose methotrexate therapy has emerged as an effective non-invasive treatment option for hemodynamically stable patients with unruptured ectopic pregnancies (4). However, the optimal follow-up protocol for monitoring treatment success and potential complications remains debatable among healthcare providers (5, 6). Evaluation of treatment efficacy involves monitoring β-human chorionic gonadotropin (β-hCG) levels at specific intervals: days 1, 4, and 7 after methotrexate administration. A universally accepted indicator of successful treatment is a reduction in β-hCG concentration of ≥ 15% between days 4 and 7 post-injection (7). In recent years, the effectiveness of the current protocol has been questioned, which has led to the proposal of alternative approaches. One such suggestion involves eliminating the β-hCG measurement on day 4 and predicting treatment success based on any reduction between day 0/1 and day 7 (5, 6).

This study investigated the necessity of checking β-hCG levels on day 4 after single-dose methotrexate administration, as recommended by the current guidelines, to assess treatment efficacy in tubal ectopic pregnancy cases. To this end, the relationship between treatment success and the percentage change in serum β-hCG levels from days 1 to 7 was evaluated.

MATERIAL AND METHODS

This retrospective observational study was conducted at the Gynecology Department of Ankara Bilkent City Hospital between January 2020 and December 2023. This study was conducted in accordance with the principles outlined in the Declaration of Helsinki and approved by the Ethics Committee of the same institute (E.2.24.490). Oral informed consent was obtained from all participants prior to their participation in the study.

Eighty patients who were followed up and treated for tubal EP during the study period were assessed for eligibility using hospital records. The inclusion criteria were EP confirmed by ultrasound examination and insufficient β-hCG increase between two measurements 48 h apart, management with a single-dose methotrexate regimen, and thorough follow-up of β-hCG levels on days 4 and 7 of injection. The exclusion criteria were pregnancy of unknown location, multiple-dose methotrexate regimen, emergency surgery after methotrexate administration, pretreatment β-hCG level ≥ 10.000 IU/L, positive fetal cardiac activity, expectant management, and operation without methotrexate administration.

According to our clinical protocol, hemodynamically stable women with no evidence of rupture are managed with methotrexate therapy, particularly a single-dose regimen. The single dose of methotrexate was calculated according to the body surface area of each patient (50 mg/m^2). The day of methotrexate injection was defined as day 1. During the follow-up, β-hCG levels were measured on days 4 and 7. If levels decreased by ≥ 15% between days, the treatment was accepted as successful, and β-hCG levels were followed up weekly until a negative result was obtained. However, if the serum β-hCG levels decreased by < 15% between days 4 and 7, the treatment was considered unsuccessful, and a second dose of methotrexate was administered.

In this study, we first evaluated all the patients who were administered a single dose of methotrexate. After excluding patients who were undergone emergency surgery due to rupture of EP before day 7, the remains were subdivided into two groups: "successful treatment" and "need a second dose methotrexate". We then analyzed the percentage change in serum β-hCG levels between days 1 and 7 and its usefulness in predicting "successful treatment."

Statistical analysis

Normally distributed data are expressed as the mean ± standard deviation, whereas non-parametric data are presented as the median and interquartile range. The relationship between treatment success and percentage change in serum β-hCG levels from days 1 to 7 was determined using Spearman's correlation coefficient. The sensitivity and specificity of different percentage changes in serum β-hCG levels from days 1 to 7 for predicting treatment success were determined using receiver operating characteristic (ROC) curves. Statistical analyses were performed using the Statistical Package for the Social Sciences for Windows, version 21.0 (IBM, SPSS Corp.; Armonk, NY, USA). Statistical significance was set at $P<0.05$.

RESULTS

A single dose methotrexate administered to 80 patients on day 1. Six patients (7.5 %) underwent surgery for rupture before day 7 and were excluded from the study. Treatment was considered successful in 86.5% (64/74) of the remaining patients, whereas 13.5% (10/74) received a second dose of methotrexate. Figure 1 shows the flowchart of the study population. The demographic and clinical characteristics of the 74 patients are summarized in Table 1.

When the changes in serum β-hCG levels during the follow-up period were analyzed, the mean percentage change in serum β-hCG levels was -2.2±45.2% from days 1 to 4, -29.0±36.2% from days 4 to 7, and -26.6±53.8% from days 1 to 7. There was a negative linear correlation between treatment success and the percentage changes in serum β-hCG levels from day 1 to day 7 (P<0.001, Spearman's correlation coefficient =-0.54). ROC curve analyses revealed that the sensitivity of treatment success prediction decreased with increasing percentage changes in serum β-hCG levels from days 1 to 7 (Figure 2 and Table 2).

Table 1. Demographic and clinical characteristics of patients who were administered single-dose methotrexate for tubal ectopic pregnancy.

Age (years), mean±SD	32.2±4.8
Parity, median (IQR)	1 (1)
Gestational age (weeks), mean±SD	5.2±1.4
Day 1 serum β-hCG level (IU/L), mean±SD	1911.5±1710
Day 4 serum β-hCG level (IU/L), mean±SD	1960.0±2360.2
Day 7 serum β-hCG level (IU/L), mean±SD	1453.6±1977.0

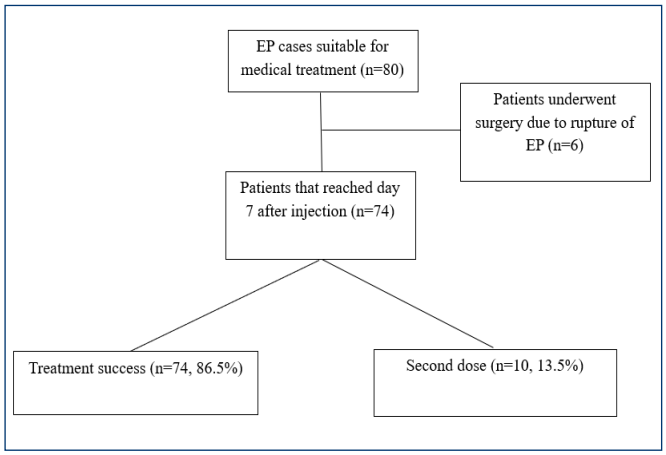

Figure 1. Flowchart of the study population.

Table 2. Sensitivity and specificity of treatment success predictions for different percentage changes in serum β-hCG levels from day 1 to day 7 (-50.0%, -25.0%, 0.0%, +25.0%, and +50.0%).

Percentage changes in serum β-hCG levels from day 1 to day 7	Sensitivity	Specificity
-50.0%	100.0%	41.0%
-25.0%	100.0%	77.6%
0.0%	90.0%	93.7%
+25.0%	80.0%	96.9%
+50.0%	60%	98.9%

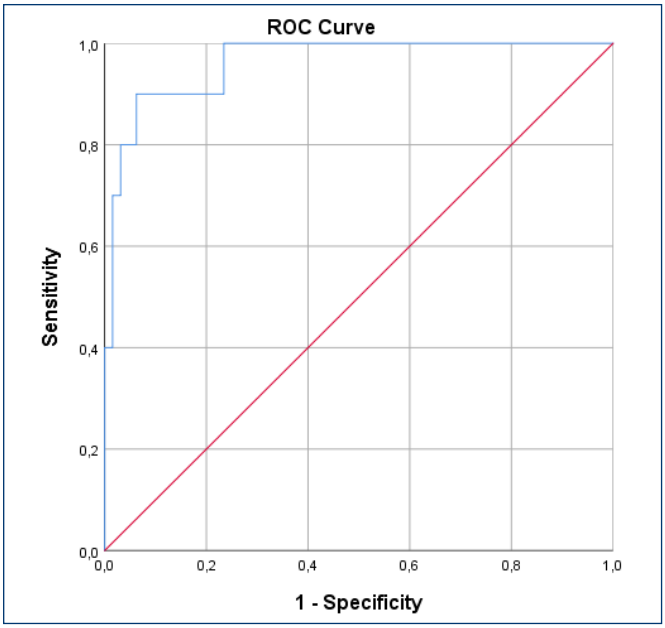

Figure 2. Receiver operating characteristic curve analysis of the percentage changes in serum β-hCG levels from days 1 to 7 for predicting single-dose methotrexate treatment in patients with tubal ectopic pregnancy (area under curve = 0.96).

DISCUSSION

Single-dose methotrexate is an effective treatment for ectopic pregnancy, with success rates influenced by the initial β-hCG levels and the rate of decrease in β-hCG post-treatment (8). These findings support the use of single-dose methotrexate as a viable alternative to surgical intervention in selected patients, potentially preserving future fertility and reducing the need for more invasive procedures (9).

The incidence of ectopic pregnancies varies with age and parity. Studies have shown that the incidence of disrupted ectopic pregnancy is most common in women aged 20-35 years and is more frequent in multigravida women, those who have been pregnant more than once (10). Our findings align with those in the literature, with a mean age of 32.2 years, median parity of 1. On the

other hand, EPs typically present clinically within the first trimester, with mean gestational ages reported at 7.2 weeks and 6.7 weeks (11,12). These figures suggest that the majority of ectopic pregnancies are identified relatively early in the pregnancy. In our study, the mean gestational age was 5.2 weeks and slightly lower than that reported in previous studies. Variations in study results may stem from patient demographics, clinical or socioeconomic factors, and differences in diagnostic tools, such as ultrasound quality.

The most widely adopted protocol for determining the success of single-dose methotrexate is based on a < 15% decrease in β-hCG levels between days 4 and 7 (7,13). Recently, alternative protocols have been introduced to establish a more economical and practical follow-up period after methotrexate administration (5,6,14,15). However, each of these new approaches has its own benefits and drawbacks. A prior investigation by Atkinson et al. examined various methods for forecasting treatment efficacy and suggested that the protocol measuring β-hCG reduction from days 0/1 to 7 was comparable in effectiveness to the currently employed approach (5). In their study, any reduction in serum β-hCG levels from days 1 to 7 had a 79% sensitivity and 86.0% specificity for predicting treatment success. Subsequently, Sukur et al. corroborated the findings of Atkinson et al., who concluded that any reduction in serum β-hCG levels on days 0/1–7 could replace the current method of determining treatment success in tubal EP management. In their study, Sukur et al. showed that any reduction in serum β-hCG levels from days 1 to 7 had 91.2% sensitivity and 80.0% specificity in predicting treatment success (6). Our findings were consistent with those of two previous studies. However, in the present study, we showed a negative linear correlation between treatment success and percentage changes in serum β-hCG levels from day 1 to day 7. Furthermore, our research indicates that treatment success can be reliably predicted not only by any decrease in serum β-hCG levels between days 1 and 7 but also by an increase of less than +25.0% in serum β-hCG levels.

In conclusion, this study provides valuable insights for predicting the success of single-dose methotrexate treatment in tubal ectopic pregnancies. These findings suggest that monitoring the percentage change in serum β-hCG levels from days 1 to 7 could be an effective alternative to the traditional protocol. This approach may prove particularly useful in cases where patient compliance is challenging or when day 4 measurements are not feasible owing to various constraints. Further research is warranted to validate these results and to potentially incorporate this method into clinical practice, ultimately improving the management of ectopic pregnancies and patient outcomes.

Ethics Committee Approval

This study was conducted in accordance with the principles outlined in the Declaration of Helsinki and approved by the Ethics Committee of the same institute (E.2.24.490)

Author Contributions

Data collection, analysis, interpretation, conception, design, and drafting of the manuscript were performed by Emre Erdem TAS.

Conflict of Interest

The author declares no conflict of interest.

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Jinekoloji - Obstetrik ve Neonatoloji Tıp Dergisi
The Journal of Gynecology-Obstetrics and Neonatology

ÖZGÜN ARAŞTIRMA / ORIGINAL ARTICLE

DOI: 10.38136/jgon.1491587

Gonadotropin+intrauterin inseminasyon uygulanan açıklanamayan infertilite hastalarında gebeliğe etki eden prediktif faktörler

Predictive factors affecting pregnancy in patients with unexplained infertility treated with gonadotropin+ intrauterine insemination

Aysegul ATALAY [1], Gonca YILDIRIM[2], Alev AYDIN[3]

[1]Van Bölge Eğitim ve Araştırma Hastanesi, Perinatoloji, Van, Türkiye
[2]Medipol Üniversitesi Tıp Fakültesi Kadın Hastalıkları ve Doğum Bölümü, İstanbul, Türkiye
[3]Hamidiye Etfal Eğitim ve Araştırma Hastanesi Kadın Hastalıkları ve Doğum Bölümü, Sağlık Bilimleri Üniversitesi, İstanbul, Türkiye

ÖZ

Amaç: Kontrollü ovaryen hiperstimulasyon ve intrauterin inseminasyon (KOH+IUI) uygulanan açıklanamayan infertilite hastalarında bazı prediktif faktörlerin gebelik oranlarına etkisini belirleyerek hastalarda tedavi şemasının yeniden düzenlenmesine katkıda bulunmak.

Gereç ve Yöntemler: Bu çalışmada, Ocak 2007-Temmuz 2014 tarihleri arasında Kanuni Sultan Süleyman Eğitim ve Araştırma Hastanesi infertilite polikliniğine başvurup açıklanamayan infertilite tanısı alan ve çalışmaya katılma kriterlerini karşılayan toplam 431 hasta ve toplam 874 siklus retrospektif olarak incelendi. Total ileri hareketli sperm sayısı (TMPSS) 10 milyon altında olan ve vücut kitle indeksi (BMI) ≥30kg/m2 olan hastalar çalışma dışı bırakıldı. Tüm hastalara gonadotropinlerle indüksiyon ve HCG ile ovulasyonun tetiklenmesinin ardından 36 saat sonra IUI uygulandı. Primer sonuç ölçütü gebelik oranı olarak kabul edildi. Prediktif faktörler olarak kadının yaşı, erkeğin yaşı, infertilite tipi, infertilite süresi, BMI, adetin 3.günü Folikül stimulan hormon (FSH) ve estradiol(E2) seviyesi ve antral folikül sayısı belirlendi.

Bulgular: 874 siklusta 431 çiftte toplam 88 gebelik elde edilmiştir (%20,4-%10,06/ siklus). Lojistik regresyon analizi yapılan prediktif faktörler içinde kadının yaşı (<35), antral folikül sayısı ve FSH düzeyi (<10 IU/L)'nin gebelik oranlarına anlamlı derecede katkıda bulunduğu tespit edildi.

Sonuç: 35 yaş altı FSH düzeyi <10 mIU/mL, BMI≤30kg/m2 ve TPMSS>10 milyon olan hastalarda KOH+IUI ilk tercih edilmesi gereken tedavi yöntemidir. Ayrıca FSH ve klomifen sitrat (CC) induksiyon açısından karşılaştırıldığında, gebelik oranları açısından anlamlı bir fark izlenmeyen birçok çalışma mevcuttur. Dolayısıyla maliyeti, OHSS riski ve çoğul gebelik riski yüksek olması nedeniyle FSH tedavisinin yerine CC tedavisi ile de aynı oranda başarılı sonuçlar elde edilebilir.

Anahtar Kelimeler: Açıklanamayan infertilite; gonadotropin; intrauterin inseminasyon; gebelik oranı

ABSTRACT

Aim: The aim of this study was to contribute to the reorganization of the treatment scheme in patients with unexplained infertility who underwent COH+IUI by determining the effect of some predictive factors on pregnancy rates.

Material and Methods: In our study, medical records of 431 patients and a total of 874 cycles who applied to the Infertility Clinic of Kanuni Sultan Süleyman Training and Research Hospital between January 2007 and July 2014 and were diagnosed with unexplained infertility and met the inclusion criteria were retrospectively analyzed. Males with a total progressive motile sperm count of less than 10 million and a body mass index of 30kg/m2 were excluded from the study. All patients underwent IUI 36 hours after induction with gonadotropins and assisted ovulation with HCG. The primary outcome measure was the pregnancy rate. The age of the females and males, infertility type , the duration of infertility, BMI, FSH and estradiol levels on the third day of menstruation, and antral follicle count were determined as predictive factors.

Results: A total of 88 pregnancies were achieved in 431 couples in 874 cycles (%20.4-%10.06 per cycles). Lojistik regresyon analizi yapılan prediktif faktörler içinde kadının yaşı (<35),antral folikül sayısı ve FSH düzeyi(<10 IU/L)'nin gebelik oranlarına anlamlı derecede katkıda bulunduğu tespit edildi. It was determined that the age of the woman (<35), antral follicle count and the FSH level (<10 IU/L) contributed significantly to pregnancy rates among the predictive factors for which logistic regression analysis was performed,

Conclusion: KOH+IUI should be the first treatment method of choice in patients under 35 years of age with FSH level <10 IU/L, BMI<30kg/m2 and TPMSS>10 million. In addition, there are many studies in which no significant difference was observed in pregnancy rates when FSH and clomiphene citrate were compared as induction methods. Therefore, similarly successful results could be obtained with CC treatment instead of FSH treatment, due to its high cost, OHSS risk and high risk of multiple pregnancy.

Keywords: Unexplained Infertility; gonadotropin; Intrauterine insemination; pregnancy rate

Cite as: Atalay A, Yıldırım G, Aydın A. Gonadotropin+ıntrauterin ınseminasyon uygulanan açıklanamayan infertilite hastalarında gebeliğe etki eden prediktif faktörler. Jinekoloji-Obstetrik ve Neonatoloji Tıp Dergisi 2024;21(4):301–308.

Geliş/Received: 28.05.2024 • **Kabul/Accepted:** 15.08.2024

Sorumlu Yazar/Corresponding Author: Aysegul ATALAY, Van Bölge Eğitim ve Araştırma Hastanesi, Perinatoloji, Süphan Mah. Havalimanı kavşağı, 65100, Edremit, Van, Türkiye
E-mail: draysegulatalay@gmail.com

Çevrimiçi Erişim/Available online at: https://dergipark.org.tr/tr/pub/jgon

GİRİŞ

Açıklanamayan infertilite (Aİ), sistematik değerlendirmede saptanabilir bir nedenin gösterilememesi sonucu ortaya konulan bir dışlama tanısı olmakla birlikte, insidansı tanı kriterine bağlı olarak infertil popülasyonda %10 ile 30 arasındadır (1-2). Normal popülasyonda ortalama siklus fekundabilitesi %20-25 iken, tedavi edilmemiş Aİ tanılı hastalarda siklus fekunditesi %2-4 olarak tespit edilmiştir (3). Tedavi siklus fekunditesini arttırmaya yöneliktir (4). Tanı için; semen kalitesi, ovulatuar fonksiyon ve uterin kavitenin normal olduğu ve bilateral tubal geçirgenlik gösterilmelidir. Açıklanamayan infertilite, her ne kadar bir dışlama tanısı olarak kabul edilse de iki açıklaması olabilir: İlki, var olan sebebin yapılan testlerle ortaya koyulamaması ya da araştırma için yapılan testlerin normal aralığın en alt seviyesinde veya en üst seviyesinde olmasına bağlı çiftin doğurganlığının azalmasıdır.

Açıklanamayan infertilite, çoğunlukla ileri yaşla birlikte fertilitedeki doğal azalmayla da ilişkilidir ve 35 yaş üzerindeki kadınlarda daha sıktır. Açıklanamayan infertilite tanısı olan tedavi edilmemiş çiftlerde, kadının yaşı ve infertilite süresi gebelik oranlarını olumsuz yönde etkileyen primer değişkenlerdir. En sık kullanılan tedavi yöntemleri; intrauterin inseminasyon (IUI), klomifen veya gonadotropinlerle overyan stimülasyon ve IUI, ve in-vitro fertilizasyon (IVF) olarak bilinmektedir.

Aİ, kontrollü ovaryen hiperstimulasyon sonrası IUI (KOH+IUI) uygulamaları için majör bir endikasyondur. NICE rehberlerine göre açıklanamayan infertilite grubuna yardımcı üreme teknikleri önerilmeden önce KOH+IUI seçeneğinin sunulması gerektiği ifade edilmektedir (5). Nedeni bilinmediği için tedavide kullanılan tüm yöntemler ampiriktir. Dolayısıyla bilinmeyen bozukluklar için kullanılan ampirik tedavilerden çarpıcı sonuçlar elde etmesi beklenmemektedir. Fakat bu hastalarda demografik bilgilerin, laboratuar ve radyoloji sonuçlarının, ve kullanılan tedavi rejimlerinin tedavi başarısına olan etkisi ile ilgili literatürde yeterli çalışma mevcut değildir.

Bu çalışmanın amacı, Gonadotropin ile KOH+IUI tedavisi uygulanan açıklanmayan infertilite hastalarında bağımlı ve bağımsız değişkenlerin birbirleri arasındaki ve gebelik sonuçlarıyla olan ilişkisi, ayrıca normal referans aralığında artmış basal FSH düzeylerinin gebelik sonuçlarına etkisini araştırmak, ve bu sonuçlar üzerinden hastalara uygulanacak tedavi seçiminde klinisyene yardımcı olmaktır.

GEREÇ VE YÖNTEM

Bu çalışma, Kasım 2014 tarihinde tamamladığımız tıpta uzmanlık tezi esas alınarak üretilmiştir. Çalışmamızda, Ocak 2007-Temmuz 2014 tarihleri arasında Kanuni Sultan Süleyman Eğitim ve Araştırma Hastanesi (eski adıyla Bakırköy Kadın Doğum ve Çocuk Hastalıkları Eğitim Araştırma Hastanesi) Kadın Hastalıkları ve Doğum Kliniği İnfertilite polikliniğine başvuran, korunmasız düzenli cinsel ilişkiye rağmen en az bir yıl boyunca gebe kalamayan, yapılan tetkiklerle açıklanamayan infertilite tanısı alan ve çalışmaya katılma kriterlerini karşılayan toplam 431 hasta ve toplam 874 siklus retrospektif olarak incelendi. Hastalarda infertilite etyolojisini araştırmaya yönelik yapılan öykü (yaş, infertilite suresi, ilave medikal faktörler, koitus alışkanlıkları, gecirilmiş pelvik operasyonlar, geçirilmiş hastalıklar, alışkanlıkları), fizik muayene, jinekolojik muayene, adetin 3. günü bakılan estradiol (E2), folikül stimule edici hormon (FSH), tiroid stimulan hormon (TSH), luteinizan hormon (LH), prolaktin ve adetin 21. günü bakılan progesteron seviyeleri, histerosalpingografi (HSG), yaşadığı il, vücut kitle indeksi (BMI), endikasyonu olan hastalara yapılan laparotomi, laparoskopi ve histeroskopi sonuçları, erkek yaşı, yapılan spermiogram, mesleği ve geçirdiği hastalık ve ameliyatlar incelendi. Çalışmaya dahil edilen hastaların kriterleri: BMI 30 kg/m^2 ve altı, düzenli menstrüel siklus ile birlikte normal PRL, TSH ve siklusun 21. günü bakılan normal progesteron değeri, normal sperm parametreleri (Total ileri hareketli sperm sayısı (TPMSS) >10 milyon), HSG'de normal uterin kavite ve bilateral tubalardan abdomene geçiş olan hastalar olarak belirlendi.

Tüm hastalar aynı hekimler tarafından tedavi edilmiş, aynı kontrollü ovarian stimulasyon ve intrauterin inseminasyon prosedürü uygulanmıştır. Çalışma grubuna alınan hastalar sadece açıklanamayan infertilite tanısı almış olan hastalardan oluşmaktaydı. Açıklanamayan infertilite tanısı almış olup, total ileri hareketli sperm sayısı 10 milyon altında olan hastalar ve vücut kitle indeksi 30 kg/m^2 olan hastalar çalışma dışı bırakıldı. Tüm sikluslarda ekzojen gonodotropin stimulasyonu rekombinant FSH (Gonal F; Serono®, Puregon; Organon®) veya üriner FSH (Fostimon; IBSA®, Menogon; Fering®) ile uygulanmıştır. İlk siklusta tedavi başlangıç dozu 37,5 IU olarak menstrüel siklusun 3.günü başlanmış, ovarian cevap folikuler büyüme ile takip edilmiş olup FSH ve human menopozal gonadotropin (hMG) dozu her 1-3 günde bir foliküler büyümedeki takibe göre ayarlanmıştır. Human koryonik gonadotropin (hCG) uygulanmasının zamanı >17 mm dominant folikül varlığına göre ayarlanmıştır. Eğer her iki overde >14mm üzerinde 3 veya daha fazla folikül gelişirse hCG uygulanmamıştır. Hastalar 5.000 IU uriner hCG (Chorigon:Teva, Petah Tigva, Israel® veya Pregnyl ;Organon, Oss, The Netherlands®) veya 250 µg rekombinant hCG (ovitrelle; Serono®) almıştır. hCG uygulanmasından 36 saat sonra intrauterin inseminasyon yapılmıştır. Sperm hazırlamada swim-up yöntemi kullanılmıştır. Serum gebelik testi hCG uygulamasından 15 gün sonra yapılmış olup, gebelik varlığında ultrason kontrolleri fetal kalp atışı görülene kadar aralıklarla takip edilmiştir. Araştırmada hiçbir hasta kaybı izlenmemiştir.

İstatistiksel Yöntem

Verilerin tanımlayıcı istatistiklerinde ortalama, standart sapma en düşük, en yüksek, medyan, oran ve frekans değerleri kullanılmıştır. Değişkenlerin dağılımı kolmogorov simirnov testi ile kontrol edilmiştir. Nicel verilerin analizinde Mann-Whitney u test ve niteliksel verilerin analizinde ki-kare test, test koşulları sağlanmadığında fischer test kullanılmıştır. Korelasyon analizinde Spearman korelasyon analizi kullanılmıştır. Analizlerde SPSS 22.0 programı kullanılmıştır.

BULGULAR

Çalışmamızda, açıklanamayan infertilite tanısı alarak KOH+IUI uygulanan 431 olgu toplam 874 siklus üzerinde analiz yapıldı. Çalışmaya katılan hastaların öncelikle klinik, demografik ve endokrinolojik özellikleri ve sonuçları incelendi. Hastaların yaşları 19-43 arasında değişmekte olup yaş ortalaması 29,7 ve infertiltite süresi ortalaması 4,1 yıl, FSH ortalaması 7,7 IU/L, gebelik oranı %20,4, siklus fekundabilitesi %10,06 olarak izlenmiş olup diğer tanımlayıcı istatistik bulguları ayrıntılı olarak Tablo 1'de gösterilmiştir.

Gebelik olmayan ve olan olgulardaki yaş ortalaması (29,0/29,9) anlamlı (p>0,05) farklılık göstermemiştir. Hastalar yaş <30 ve ≥30 olarak iki gruba ayrıldığında gebelik oranı (19,6 / 21,2) anlamlı (p>0,05) farklılık göstermemiştir. Hastaların yaşı <35 ve ≥ 35 olarak iki gruba ayrıldığında ise gebelik oranı (23,3 / 3,2) anlamlı (p<0,05) olarak daha düşük izlenmiştir. Gebelik olmayan ve olan

Tablo 1. Tanımlayıcı İstatistik

Değişkenler	Medyan (min-max)	Ortalama±SD	n (%)
Yaş (yıl)			
<30 yaş	30 (19-43)	29,7 ± 4,4	219 (%50,8)
30-34 yaş			150 (%34,8)
≥35 yaş			62 (%14,4)
İnfertilite süresi (yıl)			
<3 yıl	3 (1-25)	4,1 ± 3,0	249 (%58)
≥3 yıl			182 (%42)
BMI (kg/m²)			
<25 kg/m²	24 (16-30)	24,3 ± 3,3	269 (%62,5)
≥25 kg/m²			182 (%37,5)
Sigara kullanımı			
Yok	24 (16-30)	24,3 ± 3,3	327 (%75,9)
Var			104 (%24,1)
İnfertilite tipi (hasta sayısı)			
Primer			314 (%72,9)
Sekonder			117 (%27,1)
Erkek yaşı	32 (21-52)	32,3 ± 4,7	
TMPSS (mn/ml)	46 (10-600)	67,1 ± 65,4	
Antral folikül sayısı	8 (1-17)	7,9 ± 3,5	
FSH (mIU/ml)			
<10 mIU/ml	7 (2-15)	7,7 ± 2,3	339 (%78,7)
≥10 mIU/ml			92 (%21,3)
E2 (pg/ml)			
<80 pg/ml	49 (7-218)	54,3 ± 30,9	369 (%85,6)
≥80 pg/ml			62 (%14,4)
KOH+IUI uygulanan toplam siklus sayısı			874
1 siklus (hasta başı)			108 (%25,1)
2 siklus			203 (%47,1)
3 siklus			120 (%27,8)
Tedavide kullanılan ilaç			
Rekombinant FSH			333 (%77,3)
Üriner FSH			98 (%22,7)
Gebelik oranı			88 /431 (%20,4)
1. siklusta			43 (%48,9)
2. siklusta			31 (%35,2)
3. siklusta			14 (%15,9)

BMI: Vücut kitle indeksi, TMPSS: Total ileri hareketli sperm sayısı, FSH: Follikül Stimülan Hormon, E2: Estradiol, KOH+IUI: Kontrollü ovaryen hiperstimulasyon ve intrauterin inseminasyon

Tablo 2. Yaş ve Gebelik ilişkisi

Değişkenler	Gebelik pozitif n=88	Gebelik negatif n=343	p
Tüm hastalar (mean±SD) (median) (min-max)	 29,2 ± 4,3 30 (28-38)	 29,9 ± 4,4 30 (19-43)	0.318
<35 yaş (n, %) **≥35 yaş** (n, %)	79 (%89,8) 9 (%10,2)	283 (%82,5) 60 (%17,5)	0.097
<30 yaş (n, %) **≥30 yaş** (n, %)	43 (%48,3) 45 (%51,7)	176 (%51,3) 167 (%48,7)	0,613
Erkek yaşı (mean±SD) (median) (min-max)	 32,5 ± 4,5 32 (21-52)	 31,8 ± 5,2 31 (24-48)	0.114

Tablo 3. Gebelik/ FSH ve gebelik/E2 ilişkisi

	Gebelik pozitif n=88	Gebelik negatif n=343	p
FSH (mIU/ml) (mean±SD)	7,2 ± 2,2	7,9 ± 2,3	**0,007**
FSH<10 (n, %) FSH≥10 (n, %)	79 (%23,3) 9 (%9,8)	260 (%76,7) 83 (%90,2)	**0,004**
E2 (pg/ml) (mean±SD)	56,9 ± 35,1	53,7 ± 29,7	0,637
E2<80 (n, %) E2≥80 (n, %)	76 (%20,6) 12 (%19,4)	293 (%79,4) 50 (%80,6)	0,822

FSH: Follikül Stimülan Hormon, E2: Estradiol

vakalardaki erkek yaşı ortalaması (32,5/31,8) anlamlı (p>0,05) farklılık göstermemiştir (Tablo 2).

Gebelik olan ve olmayan vakalarda hastaların infertilite süresi ortalaması (3,9/4,2) anlamlı (p>0,05) farklılık göstermemiştir. İnfertilite süresi <3 yıl ve ≥ 3 yıl olan grupta gebelik oranı (20,9/20,0) anlamlı (p>0,05) farklılık göstermemiştir. İnfertilite süresi <5 yıl ve ≥5 yıl olan grupta da gebelik oranı(21,3/18,8) yine anlamlı (p>0,05) farklılık göstermemiştir.

Gebelik olan ve olmayan vakalarda hastaların BMI ortalaması (24,3/24,1) anlamlı (p>0,05) farklılık göstermemiştir. Hastalar BMI <25 kg/m2 ve ≥25 kg/m2 olarak iki gruba ayrıldığında gebelik oranı (21,3 /19,4) anlamlı (p>0,05) farklılık göstermemiştir. Sigara içen ve içmeyen grupta gebelik oranı (20,5 /20,2) anlamlı (p>0,05) farklılık göstermemiştir.

Gebelik olan grupta adetin 2-4. günleri arasında bakılan FSH değeri ortalaması gebelik olmayan gruptan anlamlı (p<0,05) olarak daha düşüktü. FSH ≥10 olan grupta gebelik oranı (9,8) FSH<10 olan gruptaki gebelik oranından (%23,3) anlamlı (p <0,05) olarak daha düşüktü (Tablo 3). Gebelik olan ve olmayan olgularda hastaların E2 değeri ortalaması anlamlı (p>0,05) farklılık göstermemiştir. E2 <80 ve E2 ≥80 olan grupta gebelik oranı anlamlı (p>0,05) farklılık göstermemiştir (Tablo 3).

Primer ve sekonder infertilite tanısı alan hastalar arasında gebelik oranı anlamlı (p>0,05) farklılık göstermemiştir. Rekombinan FSH ve üriner FSH kullanan hastalarda da gebelik oranı anlamlı (p>0,05) farklılık göstermemiştir.

Yaş ile antral folikül sayısı arasında anlamlı (p <0,05) negatif korelasyon mevcuttu. FSH değeri ile antral folikül sayısı arasında da anlamlı (p <0,05) negatif korelasyon mevcuttu (Tablo 4, Şekil 1).

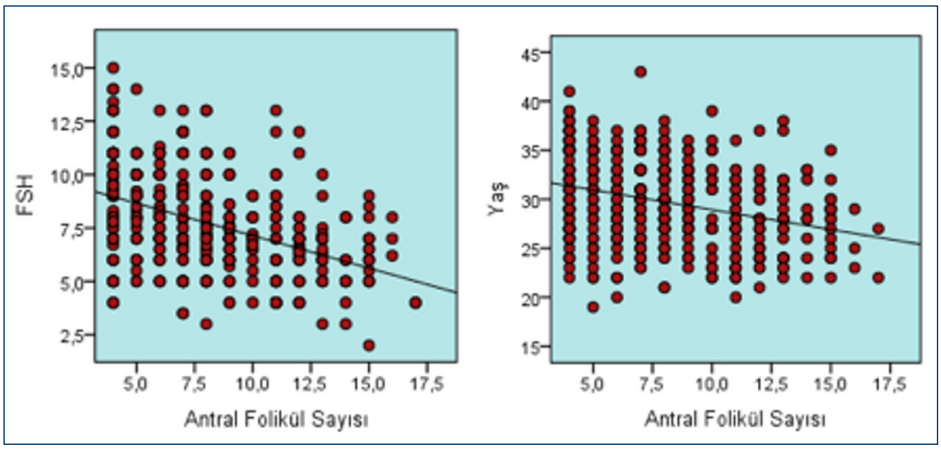
35 yaş altı kadınlarda FSH ≥ 10 olan grupta gebelik oranı FSH <10 olan gruptan anlamlı (p<0,05) olarak daha düşüktü. 35 yaş ve üstü kadınlarda FSH<10 olan 41 hastada 2 gebe izlenmiş (%4,7), FSH≥10 olan grupta hiç gebe hasta izlenmemiştir (Tablo 5). FSH ≥ 10 olan kadınlarda E2 değeri 80 altı ve üstü olarak gruplandırıldığında gebelik oranlarında anlamlı (p>0,05) olarak farklılık gözlenmemiştir.FSH ≥ 10 olan kadınlarda E2 değeri 80 altı ve üstü olarak gruplandırıldığında antral folikül sayısı anlamlı (p>0,05) olarak farklılık göstermemiştir. FSH ≥ 10 olan kadınlarda E2 değeri 60 altında ve üstünde olan gruplandırıldığında da antral folikül sayısı anlamlı (p>0,05) olarak farklılık göstermemiştir.

Gebelik olan ve olmayan vakalarda koit sıklığı, LH değeri, TSH değeri, PRL değeri, TPMSS değeri, anlamlı (p>0,05) farklılık göstermemiştir. Gebelik olan grupta antral folikül sayısı gebelik olmayan gruptan anlamlı (p <0,05) olarak daha yüksekti (Tablo 6).

Tablo 4. Yaş ve FSH değerinin antral folikül sayısı ile ilişkisi

Korelasyon*		Yaş	FSH
Antral folikül sayısı	r	-0,304	-0,439
	p	**0,000**	**0,000**

* Spearman Korelasyon, FSH: Follikül Stimülan Hormon



Şekil 1. Yaş ve FSH değerinin antral folikül sayısı ile ilişkisini gösteren korelasyon analizi

Tablo 5. FSH değeri ve yaş arasındaki ilişkinin gebelik oranlarına etkisi

	Gebelik pozitif n=88	Gebelik negatif n=343	P
Yaş <35			
FSH<10 (n, %)	77 (%26)	219 (%74)	**0.013**
FSH≥10 (n, %)	9 (%12,3)	64 (%87,7)	
Yaş ≥35			
FSH<10 (n, %)	2 (%4,7)	41 (%95,3)	0.339
FSH≥10 (n, %)	0 (%0)	19 (%100)	

FSH: Follikül Stimülan Hormon

Tablo 6. Gebeliğin Koit sıklığı, TPMSS ve Antral Folikül sayısı ile ilişkisi

Değişkenler	Gebelik pozitif n=88	Gebelik negatif n=343	P
Antral folikül sayısı (mean±SD)	9,8 ± 3,5	7,4 ± 3,4	0,000
Koit sıklığı (hafta) (median) (min-max)	3 (1-6)	3 (1-8)	0,338
TPMSS (mn/ml) (mean±SD)	73,2 ± 80,6	65,5 ± 61	0,630

TPMSS: Total ileri hareketli sperm sayısı

TARTIŞMA

Açıklanmayan infertilite, üreme alanında tanı yöntemlerinin gelişmesine rağmen halen infertil populasyonda %10 ile %30 arasında değişen yüksek bir orana sahiptir (6). Açıklanamayan infertilitede, IUI öncesi tedaviye KOH eklendiğinde siklus fekundabilitesi ortalama %10 civarındadır, IVF'den sonra en etkin tedavi olarak kabul edilmektedir (7).

Çalışmamızda, kliniğimizde son 8 yıl içinde KOH+IUI ile tedavi edilen açıklanmayan infertilite hastalarında, yaş ve bazı testlerin normal değerlerin üst ve alt aralığında olmasının, tedavide kullanılan ilacın gebelik sonuçlarına olan etkisini retrospektif olarak inceledik ve lojistik regresyon analizi yaptık. Karşılaştıracağımız diğer parametrelere etki etmemesi için ek olarak obezitesi olan (BMI>30) hastaları çalışma dışında tuttuk. Ayrıca yapılan çalışmalarda en iyi sonuçların TMPSS sayısının >10 milyon olması durumunda

sağlandığı ve 10 milyon üstü herhangi bir değerin IUI başarısına ek yarar sağlamadığının görülmesi nedeniyle TPMSS<10 milyon olan hastaları da çalışma dışında bıraktık (8-11). Erkek yaşının, TPMSS 10 milyon üstünde olması halinde gebelik oranlarına herhangi bir etkisi olmadığını gördük (p=0,114). Fakat artan kadın yaşı birlikte gebelik oranlarının azaldığını gösteren literatürde hem geçmiş hem de yakın zamanda yapılmış birçok çalışma mevcuttur. Birçok çalışmada yaş, IUI'da gebelik sonuçlarını etkileyen major faktör olarak kabul edilmiştir (12-16). Literatürü incelediğimizde, yaş ve FSH değerlerinin tek başına olduğu gibi, bir arada da gebelik oranlarına etkisini inceleyen birçok çalışma mevcuttur. Meenakshi ve arkadaşları, 2013 yılında IVF/ICSI uygulanan 135 hastada, yüksek FSH değerinin gebelik sonuçlarına etkisini retrospektif olarak değerlendirmişler. Geçirilmiş pelvik cerrahi öyküsü olan, TV-US'de >2cm endometrioma tespit edilen ve laparoskopide ciddi endometriosis görülen hastaları çalışma dışı bırakmışlar. Hastaları bizim çalışmamızda olduğu gibi <35 yaş ve ≥35 yaş olmak üzere iki ana gruba ve her grubu da FSH<10 ve ≥10 olarak iki subgruba ayırmışlar. En yüksek gebelik oranlarını <35 yaş FSH<10 olan grupta (%40,6) en düşük gebelik oranını yaş ≥35 ve FSH ≥10 olan grupta (%11,1) elde etmişler (17). Biz de çalışmamızda bu çalışma ile orantılı (%26-%0,0) fakat KOH+IUI nedeniyle daha düşük gebelik oranları elde ettik. Ayrıca Meenaksski ve arkadaşlarının çalışmasında 35 yaş ve üzerinde FSH <10 iken gebelik oranı %25,9 iken, bizim çalışmamızda benzer grupta gebelik ciddi anlamda düşük çıkarak oranı %4,7 olarak bulunmuştur.

Sabatini L ve arkadaşları, 2008 yılında 1589 IVF hastasının yaş ve FSH değerlerinin, canlı doğum oranına etkisini lojistik regresyon analizi ile değerlendirmiş. <30-45 yaş aralığındaki hastalarda her 10 yıllık yaş artışının ve FSH'daki her 5 mIU/ml yükselişin canlı doğum oranındaki odds değerlerini düşürdüğünü gözlemlemiş, fakat FSH ve yaş analizlerinde, 35 yaş altında FSH değerlerinin gebelik oranlarını belirgin bir şekilde değiştirmediğini belirtmişler. Ayrıca FSH>10 olan genç hastalarda ve FSH<5 olan yaşlı hastalarda kabul edilebilir düzeyde gebelik oranları olduğunu tespit etmişler ve basal serum FSH değerinin gebelik sonuçlarına etkisinin yaşla birlikte değiştiği sonucuna varmışlar (18). Biz çalışmamızda bu çalışmadan farklı olarak KOH+IUI uygulanan ve sadece açıklanmayan infertil hastaları değerlendirdik ve 35 yaş altında da FSH düzeyinin gebelik oranlarına anlamlı derecede etki ettiğini saptadık. <35 yaş grupta FSH<10 iken gebelik oranı %26, FSH>10 iken gebelik oranı ise %12,3 (p=0,013). ≥ 35 yaş toplam 72 hastamız mevcuttu ve sadece 2 gebelik elde edebildik ve gebe hastaların ikisinin de FSH değerleri <10 idi. Bu sonuçlar ışığında yaşla birlikte artan FSH düzeyinin gebeliğe olumsuz etkisi daha fazla olduğu bulgusu bizim çalışmamızda da örtüşmektedir, fakat biz 35 yaş altı grupta da FSH değerinin önemli bir etkisi olduğunu görmekteyiz.

Schorsch ve arkadaşları da 2013 yılında, KOH+IUI uygulanan 1612 hasta ve 4246 siklusta maternal yaş ve gebelik oranı ilişkisini inceleyen lojistik regresyon çalışması yapmış. 19-45 yaş aralığındaki hastaların dahil edildiği, yaş ortalamasının 33.9 olduğu çalışmada artan yaşla birlikte gebelik oranlarının düştüğü tespit edilmiş (p=0,000). Bu çalışmaya göre 35 yaş altında elde edilen hasta başı gebelik oranı %37,5-26 arasında değişmekte iken 35 yaş ve sonrasında %22 'den %8 lere kadar düşmektedir (19). Bu çalışma sonuçları gebelik oranları daha yüksek çıksa da bizim çalışmamız ile korreledir. Çalışmamızda gebelik oranı <30 yaş %19,6, 30-34 yaş arası %28 iken 35 yaş ve üzerinde ciddi bir şekilde düşerek %3,2'lere gerilemektedir.

Yavuz A. ve arkadaşları 2013 yılında yayınlanan, KOH+IUI uygulanan 569 hasta 980 siklusu retrospektif olarak incelemişler. Siklus başı gebelik oranları %4,7 (bizim çalışmamıza (%10,06) ve benzer birçok çalışmaya (19, 20) göre çok düşük olarak bulunmuş ve bu nedenle gebeliğe etki eden prediktif faktörleri belirlemek amacıyla lojistik regresyon çalışması yapmışlar. BMI>25 iken IUI başarı şansında azalma, FSH>9,4 olduğunda ve E2 >80 olduğunda gebelik oranlarında anlamlı olarak düşme kaydetmişler. Ayrıca infertilite süresinin 6 yıl üstünde ve altında olmasının gebelik sonuçlarına etkisi olmadığını göstermişler (21). Biz çalışmamızda BMI 30 ve üstünde olan hastaları, gebelik sonuçlarını olumsuz etkilediğine dair literatürde birçok çalışma mevcut olduğundan çalışma dışı tuttuk ve normal kilolu ve fazla kilolu (BMI: 25-30) olan hastaları değerlendirdiğimizde ise, gebelik oranları arasında anlamlı bir fark izlemedik. Çalışma sonuçlarımızın da desteklediği gibi obesite (BMI>30) dışında BMI değerlerinin gebelik sonuçlarına etkisi olduğunu düşünmemekteyiz. Yine Yavuz A ve arkadaşlarının yaptığı çalışmaya baktığımızda FSH ve E2 artışının gebelik sonucunu olumsuz etkilediği görülmüş. Biz de FSH açısından yukarıda da belirtildiği gibi uyumlu sonuçlar tespit ettik fakat E2 sonuçlarının hem 60ng/ml hem de 80ng/ml altı ve üstü olarak incelediğimizde tek başına da , FSH ile birlikte olduğunda da gebelik sonuçlarına ve antral folikül sayısına etki etmediğini saptadık.

Çalışmamızda hastaların infertilite süresinin gebelik sonuçlarına etkisini de inceledik. Hastaları infertilite süresi hem 3 yıl altı ve üstü, hem de 5 yıl altı ve üstü olarak gruplandırarak analiz ettik ve gebelik oranlarına etkisi olmadığını gördük. Benzer şekilde Merviel ve arkadaşları, Yavuz A ve arkadaşları da infertilite süresinin gebelik oranlarına etki etmediğini saptamışlar (10, 22). Fakat literatürde aksini iddia eden yayınlar da mevcuttur (13, 21, 23).

Üriner ve rekombinant FSH ile ovulasyon indüksiyonunun gebelik sonuçlarına etkisi, bugüne kadar birçok çalışma, review hatta metaanalizlerle irdelenmiş bir konudur. IUI yapılacak hastalarda ve IVF sikluslarındaki etkinlikleri detaylıca irdelenmiştir. Literatür verileri genellikle bizim çalışmamızın sonuçlarıyla da uygun bir

şekilde uFSH ile rFSH`ın gebelik sonuçlarına etkisinin benzer olduğunu göstermektedir.

Demirol A. ve arkadaşları Eylül 2006`da açıklanamayan infertil 241 hastayı randomize etmişler ve üç gruba bölmüşler.Birinci gruba rFSH,ikinci gruba uFSH ve üçüncü gruba hMG ile ovulasyon indüksiyonu ve IUI yapmışlar.Klinik gebelik oranlarını rFSH grubunda (% 25,9) diğer gruplara göre (% 13,8 uFSH, % 12,5 hMG) istatistiksel olarak anlamlı şekilde daha yüksek bulmuşlar (P=0,04). Bu sonuçlar açıklanamayan infertilitede rFSH seçilebileceği şeklinde yorumlanmış (24). Biz 431 hastadan oluşan çalışmamızda rFSH ve uFSH gruplarının gebelik oranları (%20,1 vs %21,4 P=0,778) arasında istatistiksel olarak anlamlı bir farklılık saptamadık.

Ali E. ve arkadaşlarının 2013 yılında yaptığı çalışmada uFSH / rFSH ile indüksiyon ve IUI uygulanan hastalarda gruplardaki gebelik sonuçları arasında (%16,7 rFSH, %14,4 uFSH p=0,837) anlamlı fark saptanmamıştır (25). Bulgular bizim çalışmamızla örtüşmektedir fakat, bu çalışmanın bizim çalışmamızdan farkı sadece açıklanamayan infertil değil, tubal faktör, ovulatuar disfonksiyon, hafif düzeyde erkek faktörü olan hastaları da kapsamasıdır.

Berker B. ve arkadaşlarının 2011 yılında yaptığı çalışmada açıklanamayan infertil hastalarda IUI öncesi ovulasyon indüksiyonu için rFSH ve CC tedavisi karşılaştırılmış ve gelişen folikül sayısı açısından rFSH uygulanan grupta anlamlı bir üstünlük sağlansa da gebelik oranlarında anlamlı bir farklılık saptanmamıştır. rFSH grubunda siklus başına gebelik oranı %9,6 ve CC grubunda gebelik oranı %15,6 (p=0,31) olarak bulunmuş (26). Benzer bir çalışma da, 2006 yılında Dankert ve arkadaşları tarafından yapılmıştır.Bu çalışmada da yine açıklanamayan infertil hastalarda IUI öncesi rFSH ve CC ile indüksiyon karşılaştırılmış ve siklus başına canlı doğum oranları açısından rFSH (%8,7) ve CC (siklus başına gebelik oranı %10) arasında anlamlı fark gösterilememiştir (27). Biz de çalışmamızda, uFSH ve rFSH ile ovulasyon indüksiyonu uygulanan hastalarımızda siklus başına %10,06 gebelik oranı elde ettik. Sonuç olarak gebelik oranlarımız, literatürde CC ile yapılmış olan indüksiyonlardaki gebelik oranları ile benzer çıkmıştır.

SONUÇ

FSH, kadınlarda üreme ile ilgili yaşlanmanın en erken belirteçlerinden biridir ve hala en sık kullanılan over reserv testidir. Uygulama kolaylığı, düşük maliyeti ve her kurumda kolay ulaşılabilir olması nedeni ile infertilite değerlendirilmesinde popülerliğini korumalıdır.

Açıklanmayan infertlitede, KOH+IUI tedavisi IVF/ICSI ile karşılaştırıldığında,maliyet- etkinlik açısından 35 yaş altında FSH değeri <10 olan hastalarda yüksek özgüllüğe sahip olması nedeniyle mutlaka ilk tedavi seçeneği olmalıdır. Fakat 35 yaş altı olup FSH değeri ≥10 mIU/ml olan kadınlarda ise KOH+IUI ile gebelik oranları %26'dan %12'ye gerilemekte olduğu için ilk planda düşünülmesi tartışmalıdır. 35 yaş üstünde ise FSH düzeyine bakılmaksızın ve maddi kaygıları düşünmeksizin vakit kaybettirmeden hastaları IVF'e yönlendirmeliyiz.

KOH tedavisinde uFSH/rFSH seçimi üzerine literatürde henüz bir fikir birliği oluşmamış gibi gözükmektedir ancak biz uFSH'nın rFSH kadar etkili olduğu ve daha düşük maliyetle ovulasyon indüksiyonunda başarlı sonuçlar elde edilebileceği kanısındayız. Ayrıca FSH ve klomifen sitrat induksiyon açısından karşılaştırıldığında, gebelik oranları açısından anlamlı bir fark izlenmeyen bir çok çalışma mevcuttur. FSH tedavisinin yerine CC tedavisi ile de aynı oranda başarılı sonuçlar elde edilebilirken, düşük maliyeti, FSH'ya göre OHSS ve çoğul gebelik riskinin daha düşük olması da ekstra avantajlarındandır. Sonuç olarak çalışmamız göstermektedir ki; açıklanamayan infertil hastalara KOH+IUI tedavisi uygulamaya karar verme aşamasında bazı prediktif faktörlerle anlamlı yararlar sağlanabilir. Bu tedavi için en uygun hasta grubu, 35 yaş altında FSH seviyesi <10 mIU/mL olanlardır. Açıklanamayan grupta hastaların infertilite süresinin, adetin 3. günü bakılan estradiol seviyesinin, primer veya sekonder infertil olmasının, 30 kg/m2 altındaki herhangi bir BMI değerinin, kullanılan gonadotropin tipinin gebelik oranlarına olumlu veya olumsuz herhangi bir katkısı yoktur.

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Jinekoloji - Obstetrik ve Neonatoloji Tıp Dergisi
The Journal of Gynecology-Obstetrics and Neonatology

ÖZGÜN ARAŞTIRMA / ORIGINAL ARTICLE

DOI: 10.38136/jgon.1457845

Assessment of the fibrinogen-to-albumin ratio in predicting the severity of hyperemesis gravidarum

Hiperemezis gravidarum şiddetinin tahmininde fibrinojen-albumin oranının etkinliğinin incelenmesi

Zahid AGAOGLU[1], Atakan TANACAN[2], Betul AKGUN AKTAS[1], Esra KARATAS[1], Gulcan OKUTUCU[1], Hakkı SERBETCI[1], Ozgur KARA[1], Dilek SAHIN[2]

[1]Department of Obstetrics and Gynecology, Ministry of Health, Ankara City Hospital, Ankara, Turkey
[2]Department of Obstetrics and Gynecology, Ministry of Health, Ankara City Hospital, University of Health Sciences, Ankara, Turkey

ABSTRACT

Aim: To investigate whether the fibrinogen-to-albumin ratio (FAR) could predict the severity of disease in hyperemesis gravidarum (HG).

Materials and Methods: This study was designed prospectively at a single tertiary center and included a total of 283 patients with HG. The patients were divided into the following groups based on the severity of the disease evaluated using the Pregnancy-Unique Quantification of Emesis scoring system: mild HG (n=144) (score≤6), moderate HG (n=80) (score: 7-12), and severe HG (n=59) (score≥13). FAR was calculated by dividing fibrinogen by albumin.

Results: There was a significant difference between the HG groups in terms of the gestational week at disease onset (p<0.001). In the severe HG group, the rate of weight loss due to nausea and vomiting and the rate of hospitalization were significantly higher (p<0.001 for both). The FAR value was 0.075 ± 0.015, 0.089 ± 0.019, 0.12 ± 0.023 for the mild, moderate and severe HEG groups, respectively. The FAR value increased as the disease severity increased and was found to be significantly higher in the severe HG group (p<0.001). Using the receiver operating characteristic analysis, the optimal cut-off value of FAR in predicting severe HG was determined to be 0.09 with 88% sensitivity and 85% specificity (area under the curve=0.931; p<0.001).

Conclusion: As the severity of HG increased, the FAR value increased and predicted disease severity with high sensitivity. This novel marker has the potential to reduce the adverse maternal and perinatal consequences of HG by facilitating the detection of severe disease, and it may also offer a pathway for promptly initiating individual treatment for severe HG.

Keywords: Albumin, fibrinogen, fibrinogen-to-albumin ratio, hyperemesis gravidarum

ÖZ

Amaç: Bu çalışmanın amacı hiperemezis garavidarum (HG) hastalarında fibrinojen-albumin oranının (FAR) hastalığın şiddetini predikte edip etmediğini araştırmaktı.

Gereç ve Yöntemler: Bu çalışma tek merkezli, üçüncü basamak bir merkezde prospektif olarak tasarlandı. Çalışmaya toplamda 283 HG hastası dahil edildi. Hastalar, hastalığın şiddeti Pregnancy-Unique Quantification of Emesis 24 skorlama sistemi ile değerlendirilerek, gruplara ayrıldı. Grup 1 de hafif HG'lu 144 hasta (skor≤6), grup 2 de orta HG'lu 80 hasta (skor 7-12) ve grup 3 de ise şiddetli HG'lu 59 hasta (skor≥13) dahil edildi. FAR, fibrinojen/albümin şeklinde hesaplandı.

Bulgular: HG grupları arasında, hastalığın başlama haftası açısından anlamlı fark vardı (p<0.001). Şiddetli HG grubunda (grup 3) bulantı ve kusmalara bağlı kilo kaybı daha fazlaydı (p<0.001). Grup 3 de hospitalizasyon oranları daha fazlaydı (p<0.001). FAR değeri hafif, orta ve şiddetli HEG grupları için sırasıyla 0,075 ± 0,015, 0,089 ± 0,019, 0,12 ± 0,023 idi. FAR değerinin, hastalık şiddeti arttıkça arttığı görüldü ve grup 3'de anlamlı yüksek bulundu (p<0.001). Yapılan ROC analiz sonucunda şiddetli HG'u tahmin etmede FAR değerinin optimal kesme noktası %88 sensivite ve %85 spesifite ile 0.09 olarak tespit edilmiştir (AUC=0.931; p<0.001).

Sonuç: HG şiddeti arttıkça FAR değeri artmaktadır ve FAR hastalık şiddetini yüksek sensivite ile predikte edebilmektedir. Bu yeni markerın uygulanması, şiddetli hastalığın kolay tespitini sağlayarak, HG'un olumsuz maternal ve perinatal sonuçlarını minimalize edebilir ve şiddetli HG'un bireysel tedavisinin gecikmeden uygulanması için yön belirleyici olabilir.

Anahtar Kelimeler: Albümin, fibrinojen, fibrinojen/albümin oranı, hiperemezis gravidarum

Cite as: Agaoglu Z, Tanacan A, Akgun Aktas B, Karatas E, Okutucu G, Serbetci H et al. Assessment of the fibrinogen-to-albumin ratio in predicting the severity of hyperemesis gravidarum. Jinekoloji-Obstetrik ve Neonatoloji Tıp Dergisi 2024;21(4):309–315.

Geliş/Received: 23.03.2024 • **Kabul/Accepted:** 07.06.2024

Sorumlu Yazar/Corresponding Author: Zahid AGAOGLU, Universiteler Mahallesi Bilkent Cad. No: 1, Çankaya, Ankara, Türkiye
E-mail: zahidagaoglu04@hotmail.com

Çevrimiçi Erişim/Available online at: https://dergipark.org.tr/tr/pub/jgon

INTRODUCTION

Approximately 65-80% of patients experience nausea and vomiting during the early stages of pregnancy, which are the primary cause of hospitalization during the first trimester (1, 2). Hyperemesis gravidarum (HG) is defined as prolonged and severe vomiting during pregnancy accompanied by weight loss, electrolyte imbalance, and the presence of ketone bodies in the urine (2). It complicates 0.3-3.5% of all pregnancies (3) and can seriously threaten maternal health and lead to adverse pregnancy outcomes (4). According to various studies, the documented obstetric complications of HG encompass a range of adverse maternal outcomes, including preeclampsia, eclampsia, and venous thromboembolism, as well as adverse pregnancy outcomes, such as delivering a very-low-birth-weight infant or an infant with low birth weight for gestational age, premature birth, and neonatal intensive care requirements (4).

The pathogenesis of HG is attributed to multifactorial causes (5). Elevated maternal hormones, the presence of a female fetus, abnormal placental growth, pre-existing *Helicobacter pylori* infection, hyperthyroidism, and angiogenesis-stimulating factors have been identified among the causes of HG (5, 6). To date, methods such as the evaluation of serum electrolyte levels, the measurement of maternal weight loss, and the determination of ketone bodies in urine have been used to predict the severity of HG (7, 8). Although these methods have been shown to have relative success in predicting disease severity, there is ongoing debate on the definitively superior method (8).

Predicting the severity of HG is important for determining individual treatment strategies for patients with a severe disease course and planning targeted studies for those with a poor prognosis. The severity of HG is assessed using the modified Pregnancy-Unique Quantification of Emesis (PUQE-24) system (9). Traditional guidelines have advocated using the ketonuria mechanism to determine the severity of HG (2). However, in a recent review involving the analysis of five studies, it was concluded that the measurement of ketonuria was not recommended to determine the severity of HG (10).

Studies have demonstrated changes in serum electrolytes, liver and kidney functions, coagulation systems, and thyroid function tests in patients with HG (11, 12). In the normal physiology of pregnancy, the level of fibrinogen, known as factor I in the coagulation system, increases by at least 50% (13). In addition, in a study conducted by Katarey and Westbrook, it was reported that the fibrinogen level might increase in pregnancy-specific liver diseases, including HG (14). It is well-established that as the severity of HG increases, the serum albumin level decreases due to nutritional deficiency (12).

The fibrinogen-to-albumin ratio (15) has been previously utilized as a predictive tool for the diagnosis and severity assessment of several diseases, including cancer, sepsis, ischemic heart diseases, ischemic diseases of the brain, and obstetric complications, such as preeclampsia and placental abruption (16-20). However, to the best of our knowledge, no study in the literature has investigated FAR in predicting the severity of HG. Therefore, the current study aimed to evaluate whether the FAR mechanism could predict disease severity in patients with HG.

MATERIAL AND METHOD

Study Population

This study was designed retrospectively at a single tertiary hospital and included patients at 6 to 14 weeks of gestation who were treated with a diagnosis of HG at the High-Risk Pregnancies Department of Ankara City Hospital between April 2019 and December 2023. Approval for the study was received from the ethics committee of the hospital (E2-23-5176). The principles of the Declaration of Helsinki were followed at every stage of the study.

The gestational age of the patients was determined based on the crown–rump length measured in the first trimester. Pregnancy was confirmed by the presence of an intrauterine viable pregnancy product on transvaginal ultrasound. For each patient included in the study, clinicodemographic and obstetric data, including age, parity, gravida, body mass index, gestational week at the onset

Table 1. Pregnancy-Unique Quantification of Emesis Scoring System

In the last 24 hours, for how long have you felt nauseated or sick to your stomach?	Not at all (1)	1 hour or less (2)	2-3 hours (3)	4–6 hours (4)	More than 6 hours (5)
In the last 24 hours, have you vomited or thrown up?	I did not throw up (1)	1–2 times (2)	3–4 times (3)	5–6 times (4)	7 or more times (5)
in the last 24 hours, how many times have you had retching or dry heaves without bringing anything up?	No time (1)	1–2 times (2)	3–4 times (3)	5–6 times (4)	7 or more times (5)

Mild = ≤6; Moderate = 7–12; Severe = 13–15.

of HG, gestational week at the time of study, weekly weight loss during hospital stay, results of routine liver function tests performed at diagnosis, ketone level in spot urine, thyroid function test results, and fibrinogen and albumin values, were retrospectively recorded from the hospital database. FAR was calculated by dividing the fibrinogen value by the albumin value.

The diagnosis of HG was made by the presence of severe vomiting in the early weeks of pregnancy, accompanied by weight loss of more than 5% accompanied by urine ketonuria or maternal serum electrolyte imbalance, after excluding other possible causes. The inpatient management of HEG involved administering intravenous fluids to ensure proper hydration, along with the adequate supply of electrolytes. Antihistamines such as doxylamine combined with pyridoxine, meclizine, dimenhydrinate, and diphenhydramine were used to treat HEG. The severity of HG was assessed over anamnesis information using the modified PUQE-24 system (9). The PUQE-24 scores were determined by evaluating the responses of each patient to three questions either at the time of their outpatient clinic presentation or during their hospital stays. The PUQE-24 system provides a score between 3 and 15 points. A score of 3-6 was accepted to indicate mild HG, a score of 7-12 to indicate moderate HG, and a score of 13-15 to indicate severe HG (Table 1). According to their PUQE-24 scores, the patients with HG were divided into three groups: mild, moderate, and severe.

The sample included both outpatients and hospitalized patients. Excluded from the study were multiple pregnancies, molar pregnancies, hypertensive patients, diabetic patients, pregnant women with active or chronic viral hepatitis and autoimmune hepatitis, those with known major fetal chromosomal and structural anomalies, and those with missing or unavailable data.

Statistical Analysis

SPSS v. 22.0 (SPSS Inc., Chicago, IL, USA) statistical program was used for data analysis. The Kolmogorov–Smirnov and Shapiro–Wilk tests were used to analyze the suitability of the data for a normal distribution. Student's t-test was conducted to compare normally and non-normally distributed variables. Means and standard deviations were used for normally distributed variables. The box represents the interquartile range, where the median is shown by the center line intersecting the box. The chi-square test was employed to compare categorical variables. A receiver operating characteristic (ROC) curve analysis was used to determine the cut-off value of FAR in predicting severe HG. A P value of less than 0.05 was considered statistically significant.

RESULTS

A total of 283 patients with HG were included in the study. The patients were divided into three groups according to the severity of HG. There were 144 patients in the mild HG group, 80 in the moderate HG group, and 59 in the severe HG group. Table 2 presents the patients' clinicodemographic and obstetric data, body mass index, biochemistry results, gestational age at diagnosis, gestational age at presentation, FAR values, and PUQE-24 scores. There was no significant difference between the three groups in terms of gravida, parity, miscarriage rates, or body mass index. The patient age was higher in the mild HG group. While gestational week at the onset of HG was lower, gestational week at the time of study, hospitalization rate, length of hospital stay, weekly weight loss during hospital stay, and the PUQE-24 score were statistically significantly higher in the severe HG group.

Table 2. Clinicodemographic and obstetric data, length of hospital stay, and PUQE-24 scores of the patients with HG

Variables	Mild HG (n = 144)	Moderate HG (n = 80)	Severe HG (n = 59)	p-value
Age (year)	27.9 ± 5.1	26.6 ± 5.1	24.9 ± 6.06	0.018
Gravida	2.32 ± 1.45	2.09 ± 1.53	2.09 ± 1.24	0.808
Parity	0.93 ± 1.16	0.65 ± 0.88	0.83 ± 1.09	0.892
BMI (kg/m²)	22.37 ± 5.95	20.53 ± 7.08	19.33 ± 5.16	0.958
Miscarriage	0.40 ± 0.88	0.44 ± 1.05	0.26 ± 0.61	0.192
Gestational week	9.79 ± 2.24	9.23 ± 1.90	7.91 ± 1.09	<0.001
Length of hospital stay	2.49 ± 0.94	3.09 ± 1.40	5.05 ± 2.27	<0.001
Gestational week at disease onset	8.75 ± 1.29	7.24 ± 1.56	5.51 ± 0.9	<0.001
Hospitalization	43 (29.8%)	35 (43.75%)	59 (100%)	<0.001
Weight loss (kg)	0.12 ± 0.03	0.19 ± 0.08	0.3 ± 0.12	<0.001
PUQE-24 score	3.98 ± 0.74	8.65 ± 1.17	15.85 ± 1.35	<0.001

HG: hyperemesis gravidarum, PUQE: Pregnancy-Unique Quantification of Emesis
Statistically significant at p < 0.05

Table 3. Laboratory parameters and FAR values of the patients with HG

Variables	Mild HG (n = 144)	Moderate HG (n = 80)	Severe HG (n = 59)	p-value
ALT (IU/L)	28.87 ± 29.34	32.90 ± 46.18	38.74 ± 53.49	0.711
AST (IU/L)	19.91 ± 17.81	23.81 ± 20.58	29.68 ± 37.58	0.130
Creatinine (mg/dL)	0.52 ± 0.86	0.50 ± 0.12	0.55 ± 0.27	0.701
Sodium (mEq/L)	136.70 ± 1.82	136.30 ± 2.41	133.80 ± 2.52	<0.001
Potassium (mEq/L)	3.88 ± 0.21	3.76 ± 0.30	3.69 ± 0.23	<0.001
Chloride (mEq/L)	105.64 ± 2.68	105.32 ± 3.05	103.14 ± 2.55	<0.001
T4 (ng/dl)	1.25 ± 0.42	1.33 ± 0.40	1.34 ± 0.44	0.973
TSH (mU/ml)	0.73 ± 0.60	0.41 ± 1.29	0.03 ± 1.40	0.011
Fibrinogen (gr)	3.23 ± 0.50	3.81 ± 0.75	4.44 ± 0.69	<0.001
Albumin (g/dL)	43.24 ± 4.31	41.40 ± 5.21	35.68 ± 3.11	<0.001
FAR	0.075 ± 0.015	0.089 ± 0.019	0.12 ± 0.023	<0.001

FAR: fibrinogen-to-albumin ratio, HG: hyperemesis gravidarum, ALT: alanine aminotransferase, AST: aspartate aminotransferase, TSH: thyroid-stimulating hormone
Statistically significant at p < 0.05

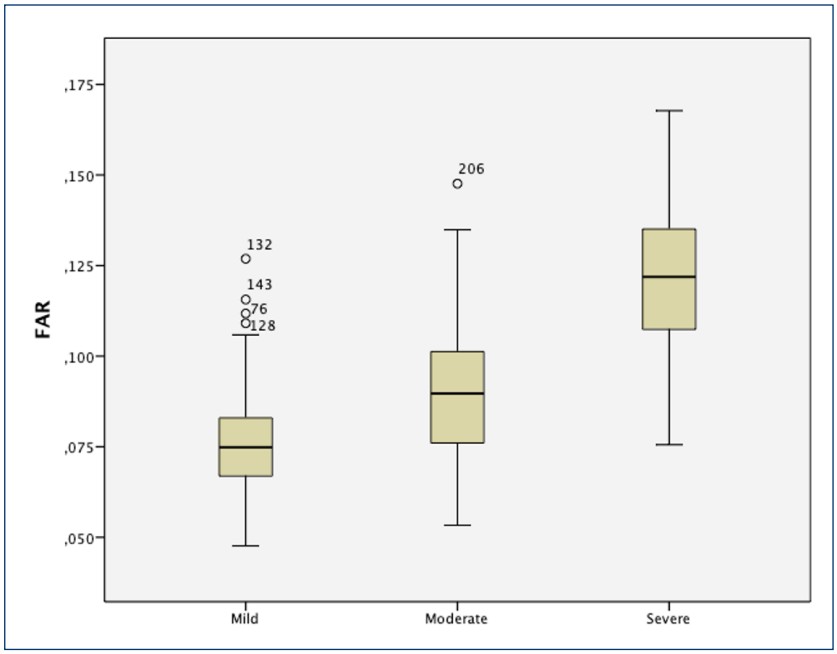

Figure 1. The fibrinogen-to-albumin ratio between the groups

Table 3 shows the comparison of the results of the laboratory analysis and FAR values between mild, moderate and severe HEG groups (0.075 ± 0.015, 0.089 ± 0.019, 0.12 ± 0.023 respectively, p<0.001). Accordingly, there were no differences among the three groups in relation to alanine aminotransferase, aspartate aminotransferase, creatinine, or free T4 values. However, sodium, potassium, chloride, thyroid-stimulating hormone (TSH), fibrinogen, and albumin values significantly differ according to the severity of HG. There were also statistically significant differences in the FAR results between the groups; FAR was found to be higher in the severe HG group (p < 0.001) (Figure 1).

The spot urine ketone levels of the HG groups are given in Table 4. There was no significant difference between the three groups in terms of the ketone levels measured in spot urine.

In the ROC analysis, the optimal cut-off value of FAR in predicting severe HG was determined to be 0.09 with 88% sensitivity and 85% specificity (area under the curve=0.931; p<0.001) (Table 5) (Figure 2).

Table 4. Results of ketonuria analysis in the spot urine of the patients with HG

	Ketonuria in spot urine					p-value
	Ketonuria (-)	Ketonuria (+)	Ketonuria (++)	Ketonuria (+++)	Ketonuria (++++)	
HG severity						
Mild	5 (3.5%)	39 (27.0%)	15 (10.4%)	27 (18.8%)	58 (40.3%)	
Moderate	2 (2.5%)	16 (20.0%)	14 (17.5%)	17 (21.3%)	31 (38.8%)	0.494
Severe	1 (1.7%)	13 (22.0%)	11 (18.6%)	14 (23.7%)	20 (33.9%)	
Total	8 (2.9%)	68 (24.0%)	40 (14.1%)	58 %20.5	109 (38.5%)	

HG: hyperemesis gravidarum
Statistically significant at $p < 0.05$

Table 5. Predictive performance of FAR in predicting severe hyperemesis gravidarum

Variable	Area under curve	Standard error	p-value	Cut-off	Asymptotic 95% confidence interval	
					Lower bound	Upper bound
FAR	0.931	0.018	<0.001	0.09	0.896	0.965

FAR: fibrinogen-to-albumin ratio
Statistically significant at $p < 0.05$

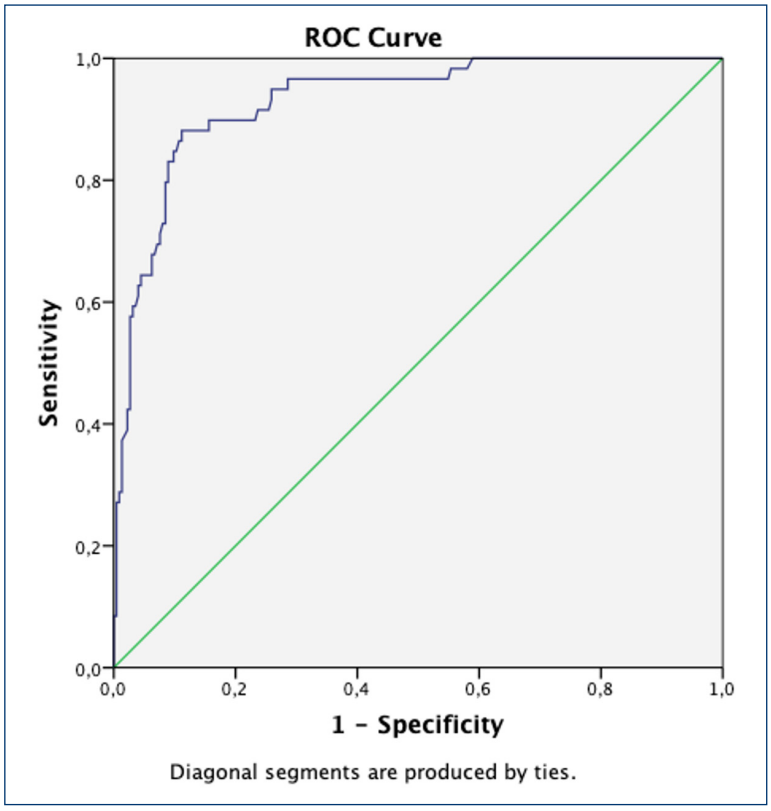

Figure 2. The ROC curve for the fibrinogen-to-albumin ratio to predict severe hyperemesis gravidarum

DISCUSSION

In this study, we examined the role of FAR in predicting disease severity in patients with HG. We found that as the severity of HG increased, the FAR values also increased. We determined that FAR predicted the severity of HG with a sensitivity of 88% and a specificity of 85%. In the severe HG group, the disease onset was earlier, and the hospitalization rate, length of hospital stay, and weight loss were higher. We also detected more profound electrolyte disturbance and more transient hyperthyroidism in the severe HG group than to the remaining groups.

HG is the primary cause of hospitalization during the early weeks of gestation and is an obstetric complication known for its adverse maternal and perinatal outcomes (21). HG is also considered a social and economic problem, as it increases health problems, is more common in first pregnancies and early stages of pregnancy and causes symptoms of anxiety and depression in less experienced pregnant women (22, 23). As the severity of HG increases, maternal and perinatal outcomes become more complicated (24). Therefore, predicting the severity of the disease and implementing personalized treatment approaches for patients are crucial for improving maternal and perinatal outcomes.

To date, many biomarkers and markers have been used to predict the severity of HG. However, the usefulness of these methods remains controversial, and their superiority over each other has faced criticism (10, 25). While fibrinogen is a part of the blood coagulation cascade (factor I), it is also a biomarker that plays a role in the systemic inflammation process (13). Pregnancy is a process in which blood coagulation system factors increase. In addition, it has been determined that fibrinogen remains elevated due to HG, which falls under the category of pregnancy-related liver diseases (14). It is also known that fibrinogen is cumulatively much higher in pregnant women with HG compared to healthy pregnancies (26). Consequently, the levels of fibrinogen are significantly higher in pregnancies with hypertensive disorders than in healthy pregnancies. Since the serum level of albumin is seriously affected by nutrition, as the severity of HG increases, nutrition deteriorates, and the maternal serum albumin level decreases in direct proportion (12).

The hypothesis of the current study was that FAR could predict the severity of HG more precisely due to the aforementioned reasons. To our knowledge, no study has previously examined the FAR mechanism for the prediction of the severity of HG. FAR has previously been successfully used in predicting the course and severity of various cancers, sepsis, and ischemic vascular diseases of the heart and brain (18, 19, 27). FAR has also been utilized in obstetric practice to predict the severity and course of important complications, such as placental abruption and preeclampsia, and this parameter has been reported to have high values in these conditions (16, 17). In the current study, FAR increased as the severity of HG increased. We also determined that FAR successfully predicted the severity of HG with high sensitivity (88% sensitivity; 95% CI 0.896-0.965).

Ketonuria is a common condition in HG (25). Extended episodes of vomiting and malnutrition accelerate lipolysis in maternal tissues, leading to an increase in the urinary excretion of its product, ketone. Ketonuria is included in widely adopted guidelines for the diagnosis of HG and the prediction of its severity. However, a systematic review reported that ketonuria was not a valuable marker for the prediction of the severity of HG (10). In a recent study by Koot et al., no relationship was detected between ketonuria and disease severity (7). Consistent with the literature, we found no significant difference between the HG severity groups in our study.

Electrolyte imbalance frequently occurs in HG due to excessive vomiting and nutritional deficiency and potentiates maternal morbidity. It can result in the development of conditions such as hypokalemia, hypomagnesemia, hyponatremia, and hypochloremia. Kondo et al. and Corona et al. demonstrated electrolyte imbalance in severe hyperemesis cases (28, 29). Similarly, in our study, we observed that the rates of hypokalemia, hyponatremia, and hypochloremia increased as the severity of HG increased. In a recent study, blood urea nitrogen (30), fibrinogen/albumin ratio (15), blood urea nitrogen/creatinine ratio (BUN/Cr), and blood urea nitrogen/albumin ratio (BUN/ ALB) were used to predict gestational diabetes (31). Further studies can be conducted including similar parameters in predicting HEG.

Elevated hormone levels in the early weeks of pregnancy have been implicated in the pathophysiology of HG. Studies have shown that elevated beta human chorionic gonadotropin creates transient hyperthyroidism, in addition to its role in the pathophysiology of HG (32). It is considered that transient hypothyroidism, presenting with low TSH and high free T4 values, contributes to the development of HG manifestations (11, 33). In a recent systematic review, Farshbaf-Khalili et al. analyzed 28 studies and reported that low TSH and high free T3 and T4 values were common in HG and that there was a relationship between HG and transient hyperthyroidism (34). The current study also revealed statistically significant deterioration in thyroid function tests in the severe HG group.

The limitations of this study include its retrospective and single-center nature and the limited number of cases included in the sample. In addition, the perinatal outcomes of the HG groups were not included in the study, which can be considered a limitation.

In conclusion, as the severity of HG increased, the FAR value increased. FAR was found to predict disease severity with high sensitivity. By utilizing this new, easily accessible marker, individual treatment methods can be identified for the severe HG patient group to minimize adverse maternal and perinatal outcomes. For clinicians managing severe cases of HG, the calculation of FAR based on maternal blood values evaluated at the onset of the disease can serve as a guide in treatment, follow-up, and prospective outcome prediction.

Ethics Committee Approval
Approval for the study was received from the ethics committee of the hospital (E2-23-5176). The principles of the Declaration of Helsinki were followed at every stage of the study.

Author contribution
ZA: methodology, data collection, writing, editing, AT: methodology, writing, editing, analysis, BAA: technical assistance, data collection, correction, analysis, EK: technical assistance, writing, editing, analysis, GO: methodology, design, correction, analysis, HS: technical assistance, data collection, correction, analysis, OK: technical assistance, data collection, correction, analysis, DS: methodology, design, correction, analysis.

Conflict of interest statement
None

Funding
None

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Jinekoloji - Obstetrik ve Neonatoloji Tıp Dergisi
The Journal of Gynecology-Obstetrics and Neonatology

ÖZGÜN ARAŞTIRMA / ORIGINAL ARTICLE

DOI: 10.38136/jgon.1315367

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

İsa KAPLAN

Department of Obstetrics and Gynecology, Faculty of Medicine, Uşak University, Uşak, Turkey

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

Cite as: Kaplan İ. Investigation of the relationship between genitourinary system infection in pregnancy and preterm delivery-retrospective case control study. Jinekoloji-Obstetrik ve Neonatoloji Tıp Dergisi 2024;21(4):316–322.

Geliş/Received: 15.06.2023 • **Kabul/Accepted:** 12.05.2024

Sorumlu Yazar/Corresponding Author: İsa KAPLAN, Department of Obstetrics and Gynecology, Faculty of Medicine, Uşak University, Uşak, Türkiye
E-mail: isakaplan_48@hotmail.com

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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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Jinekoloji - Obstetrik ve Neonatoloji Tıp Dergisi
The Journal of Gynecology-Obstetrics and Neonatology

ÖZGÜN ARAŞTIRMA / ORIGINAL ARTICLE

DOI: 10.38136/jgon.1362074

Prediction of gestational diabetes by second trimester complete blood count derived inflammatory markers

İkinci trimester tam kan sayımından elde edilen inflamatuar belirteçler ile gestasyonel diyabetin öngörülmesi

Şebnem KARAGÜN[1], Yusuf DAL[1], Sadık KÜKRER[2], Ayhan COŞKUN[1]

[1]Department of Obstetrics and Gynecology, Perinatology Department, Mersin University Faculty of Medicine, Mersin, Turkey
[2]University of Health Sciences Turkey, Adana City Training and Research Hospital, Clinic of Obstetrics and Gynecology, Adana, Turkey

ABSTRACT

Aim: To investigate the predictive ability of routine complete blood count (CBC) derived inflammatory markers on gestational diabetes mellitus (GDM) in the second trimester.

Materials and Methods: A total of 181 patients whose routine CBC was measured between 14 and 24 weeks of gestation were divided into two groups according to a 75 g oral glucose tolerance test (OGTT) results. The first group consisted of 99 women with GDM, while the second group included 82 women with normal glucose tolerance (NGT). The groups were compared with regard to mean platelet volume (MPV), platelet distribution width (PDW), plateletcrit (PCT), immature granulocyte count, delta neutrophil index (DNI), neutrophil/lymphocyte ratio (NLR), platelet/lymphocyte ratio (PLR) and Systemic Immune-Inflammation Index (SII).

Results: PDW, immature granulocyte count, NLR, PLR and SII were higher in the GDM group. However, no statistically significant difference was identified. Mean values of DNI were lower in women with GDM compared to those with NGT, although not statistically significant (0.84 versus 0.99, p =0.742).

Conclusion: Our findings revealed that utilizing inflammatory CBC markers during the second trimester as a pre-screening test is not a reliable approach for predicting GDM.

Keywords: Complete blood count; Delta Neutrophil Index; gestational diabetes mellitus; inflammatory markers; prediction.

ÖZ

Amaç: Rutin tam kan sayımından (CBC) elde edilen inflamatuar belirteçlerin ikinci trimesterde gestasyonel diabetes mellitus (GDM) üzerindeki prediktif yeteneğini araştırmak.

Gereç ve Yöntem: Rutin tam kan sayımı (CBC) 14 ila 24. gebelik haftaları arasında ölçülen toplam 181 hasta, 75 g OGTT sonuçlarına göre iki gruba ayrıldı. 99 kadın GDM ve 82 kadın normal glukoz toleransına (NGT) sahipti. Gruplar ortalama trombosit hacmi (MPV), trombosit dağılım genişliği (PDW), trombositokrit (PCT), olgunlaşmamış granülosit sayısı, delta nötrofil indeksi (DNI), nötrofil/lenfosit oranı (NLR), trombosit/lenfosit oranı (PLR) ve Sistemik İmmün-İnflamasyon İndeksi (SII) açısından karşılaştırıldı.

Bulgular: GDM grubunda PDW, immatür granülosit sayısı, NLR, PLR ve SII daha yüksekti, ancak istatistiksel olarak anlamlı bir fark gözlenmedi. Ortalama DNI değerleri GDM'li kadınlarda NGT'ye göre daha düşüktü, ancak istatistiksel olarak anlamlı değildi (0,84›e karşı 0,99, p =0,742).

Sonuç: Bulgularımız, tarama testi öncesinde ikinci trimester inflamatuar CBC parametrelerinin kullanılmasının GDM'yi öngörmede doğru bir yöntem olmadığını ortaya koymuştur.

Anahtar Kelimeler: Tam kan sayımı, delta nötrofil index, gestasyonel diyabet öngörüsü

Cite as: Karagün Ş, Dal Y, Kükrer S, Coşkun A. Prediction of gestational diabetes by second trimester complete blood count derived inflammatory markers. Jinekoloji-Obstetrik ve Neonatoloji Tıp Dergisi 2024;21(4):323–328.

Geliş/Received: 20.09.2023 • **Kabul/Accepted:** 20.08.2024

Sorumlu Yazar/Corresponding Author: Şebnem KARAGÜN, Department of Obstetrics and Gynecology, Perinatology Department, Mersin University Faculty of Medicine, TR-33110, Mersin, Türkiye
E-mail: karagunsebnem@gmail.com

Çevrimiçi Erişim/Available online at: https://dergipark.org.tr/tr/pub/jgon

INTRODUCTION

Any degree of glucose intolerance that begins or is first noticed during pregnancy is described as gestational diabetes mellitus (GDM) (1) . GDM affects approximately 7% of all pregnancies worldwide, and the diagnosis of type 2 diabetes mellitus increases by up to 70% during follow-up (2, 3). Long-term complications of diabetes load a serious financial burden and require multidisciplinary teamwork (4). Positive linear associations have been found between glucose exposure and short-term adverse consequences of gestational diabetes, such as cesarean section, induction of labour, macrosomia, and shoulder dystocia (5). Once the diagnosis is confirmed, there is limited time to prevent and manage the complications. Predicting GDM prior to the diagnostic tests will extend this limited time and allow patients with risk factors to modify their lifestyle.

Hyperglycemic and insulin-resistant conditions have been shown to cause the release of a number of maternal inflammatory markers (6). This increase in pro-inflammatory cytokines has been demonstrated even low-intensity hyperglycaemic conditions not qualified as GDM (7). The effect of inflammation on complete blood count (CBC) parameters in the 2nd trimester were also studied (8, 9). Although the platelet/lymphocyte and neutrophil/lymphocyte ratios (PLR and NLR, respectively) are considered indicators of subclinical inflammation and predictive markers in prediabetes and diabetes mellitus, investigations on their predictive value in GDM have yielded conflicting results (10-14). Most researchers have investigated platetalet related markers such as platelet count, mean platelet volume (MPV), platelet distribution width (PDW), plateletcrit (PCT) for early detection of GDM (9, 15, 16). The Systemic Immune-Inflammation Index (SII) as a new inflammatory marker, has been studied in the first trimester in GDM (17). The Delta Neutrophil Index (DNI), which reflects the ratio of circulating immature granulocytes to the total neutrophil count, was observed to be elevated at 37 weeks of gestation (18).

The primary goal of this retrospective study is to determine whether routine CBC derived inflammatory markers measured in the second trimester could predict GDM.

METHODS

This is a retrospective case–control study. Pregnant women who attended the obstetrics outpatient clinic at Mersin University Faculty of Medicine between January 2021 and June 2022 were included in the study. The study protocol was approved by the Ethics Committee of Mersin University (no:2023/41), and was carried out in accordance with the Helsinki Declaration. Informed consent was not obtained as data were analyzed anonymously. Data were collected from 181 pregnancies in women attending for gestational diabetes screening between 24-28 weeks of pregnancy, with 99 women having GDM (54.7%) and 82 women with normal glucose tolerance (NGT, 45.3%). The inclusion criteria were (1) age between 18 and 43 years; (2) singleton pregnancy; (3) having a CBC for routine control in our clinic between the 14th and 24th weeks of pregnancy; (4) basic demographic and clinical data were complete; (5) the embryo size was consistent with the gestational age. Exclusion criteria were as follows: (1) multiple pregnancy; (2) known fetal malformations; (3) preexisting diabetes, thyroid or other endocrine diseases; (4) cardiovascular diseases; (5) acute and chronic inflammatory diseases in pregnancy.

We perform one-step approach for universal screening after overnight fast in all women not previously found to have overt diabetes or GDM during testing earlier in this pregnancy. GDM was diagnosed in according with the International Association of Diabetes and Pregnancy Study Groups (IADPSG) by performing a 75-g oral glucose tolerance test (OGTT) (19). Women were diagnosed with GDM if one of the following was abnormal, including fasting plasma glucose level ≥92 mg/dL, 1-hour value ≥180 mg/dL, or 2-h value ≥153 mg/dL.

In this study, venous blood samples were collected from all pregnant women from 14 weeks to 24 weeks of pregnancy for routine monitoring. Patients with local or active systemic infection were not included in the study. Venous blood samples were drawn into 3-mL EDTA tubes (Samplix®, Greiner Bio One, Austria). Complete blood count was analyzed using an automated haematology analyser (Beckman Coulter Gen-S system device). DNI (%) (the sub-fraction of leukocytes tested by cytochemical reaction in the MPO channel) was calculated by a flow cytometry-based hematological analyzer.

Medical records were retrospectively analysed for clinical data such as maternal age, weight, height, gestational age at diagnosis, neonatal outcomes, maternal white blood cell (WBC) count, neutrophil, lymphocyte, and platelet counts, MPV, PCT, immature granulocytes, and delta neutrophil index (DNI). Neutrophil to lymphocyte ratio, platelet to lymphocyte ratio, SII index [(Platelet counts x Absolute Neutrophil Counts (ANC)/Absolute Lymphocyte Counts (ALC))/1000], Body mass index (BMI) [weight (kg)/height $(m)^2$] were calculated.

SPSS (Statistical Package for the Social Sciences) 25.0 program was used for statistical analysis of the data. Categorical measures were summarised as numbers and percentages, and continuous measurements as mean and standard deviation (median and minimum-maximum where appropriate). The Shapiro-Wilk test

was used to determine whether the variables in the study showed a normal distribution. The Independent Student's t-test was used for normally distributed variables, and the Mann-Whitney U test was used for pairwise group analyzes for non-normally distributed variables. The Pearson correlation test was used to determine the relationship between continuous measurements. A p-value ≤ 0.05 with confidence intervals at 95% was considered as statistically significant in all analyses.

RESULTS

A total of 181 pregnant women (82 with NGT and 99 with GDM) who gave blood for a routine CBC test between 14 and 24 weeks of gestation met the inclusion criteria for this study. There was no statistically significant difference between the two groups in terms of maternal demographics and neonatal outcomes, except for the BMI, which was higher in the GDM group (Table 1).

Hematological parameters are depicted in Table 2. No statistically significant differences were found between the two groups in WBC, neutrophil, lymphocyte, RBC, and platelet counts, hemoglobin concentration, hematocrit and MPV values. PDW, immature granulocyte count, NLR, PLR and SII were higher in the GDM group, but no statistically significant difference was observed. Mean values of DNI were lower in women with GDM than in those with NGT, although not statistically significant (0.84 versus 0.99, p =0.742).

The correlations between DNI and SII values and immature granulocyte count were evaluated in GDM group (Table 3). There was no correlation between DNI, SII and immature granulocytes (p>0.05).

Table 1. Patient characteristics and neonatal results (mean ± SD)

	GDM group (n=99)	NGT group (n=82)	*p* value
Age (years)	33.3 ± 5.6	30.7 ± 5.1	**0.002****,a
Gravida	2.97 ± 1.6	2.79 ± 1.7	0.343[b]
Parity	1.40 ± 1.2	1.21 ± 1.2	0.251[b]
BMI (kg/m^2)	30.8 ± 5.3	23.6 ± 2.9	**<0.001****,b
Gestational age at delivery (weeks)	38.1 ± 1.5	38.4 ± 1.3	0,192[a]
Birthweight of neonate (g)	3294.9 ± 535.4	3240.5 ± 444.7	0.566[a]
1-minute Apgar score	7.81 ± 1.6	7.56 ± 1.5	0.246[b]
5-minute Apgar score	9.19 ± 1.1	9.06 ± 1.1	0.403[b]
Cord blood pH	7.30 ± 0.08	7.32 ± 0.06	0.067[b]

* p<0.,05, **p<0.001, a: Independent student T-test, b: Mann-Whitney U test

Table 2. Comparison of hematological parameters between groups (mean ± SD)

Routine CBC parmeters	GDM group (n=99)	NGT group (n=82)	*p* value
White blood cell count (WBC) (x10^9/L)	9.89 ± 2.4	9.83 ± 2.2	0.860[a]
Neutrophil count (NEUT) (x10^9/L)	7.21 ± 2.1	7.00 ± 1.9	0.487[a]
Lymphocyte count (LYMPH) (x10^9/L)	1.88 ± 0.5	1.99 ± 0.5	0.199[b]
Monocyte count (MONO) (x10^9/L)	0.62 ± 0.2	0.65 ± 0.2	0.210[a]
Red blood cell count (RBC) (x10^{12}/L)	4.07 ± 0.4	3.98 ± 0.4	0.117[a]
Hemoglobin (HGB) g/dL	11.7 ± 1.1	11.5 ± 1.1	0.219[a]
Hematocrit (HCT), %	34.4 ± 2.6	33.9 ± 2.9	0.214[a]
Platelet count (PLT) (x10^9/L)	233.5 ± 67.5	249.3 ± 64.7	0.071[b]
Platelet distribution width (PDW), fL	12.8 ± 2.5	12.3 ± 2.3	0.105[b]
Mean platelet volume (MPV), fL	10.7 ± 0.9	10.7 ± 1.0	0.714[a]
Plateletocrit (PCT), %	0.25 ± 0.07	0.26 ± 0.06	0.503[a]
Immature granulocyte count	0.10 ± 0.12	0.096 ± 0.088	0.906[b]
DNI (%)	0.84 ± 0.51	0.99 ± 0.92	0,742[b]
NLR	4.14 ± 1.9	3.63 ± 1.2	0.071[b]
PLR	131.8 ± 47.4	129.4 ± 38.6	0.991[b]
SII	966.8 ± 572.9	913.3 ± 385.3	0.966[b]

p<0.05 a: Independent t-test b: Mann-Whitney U test

Table 3. Correlation analysis between DNI ,SII and immature granulocytes in the GDM group

GDM (n=99)	DNI		SII	
	r	p	r	p
SII	-0.032	0.750		
Immature granulocyte count	-0.138	0.174	0.166	0.100

Table 4. Effects on SII and DNI on age, BMI and GDM variables: Regression Analysis.

Dependent Variable SII		**Standardized Coefficients**	**p value**	**95.0% Confidence Interval for B**	
		Beta		Lower Bound	Upper Bound
	Age (years)	0,180	**0,019**	-29,697	-2,692
	BMI (kg/m²)	0,034	0,718	-13,542	19,621
	GDM	0,069	0,477	-121,137	257,979
Dependent Variable DNI		**Standardized Coefficients**	**p value**	**95.0% Confidence Interval for B**	
		Beta			B
	Age (years)	0,067	0,396	-,012	,029
	BMI (kg/m²)	0,101	0,303	-,038	,012
	GDM	0,102	0,303	-,136	,435

Significant at the p<0.05 level. Bold p values indicate statistically significant.

Table 4 shows the results of a regression analysis using SII and DNI as dependent variables and age and BMI as independent variables in the GDM group. SII dependent variable only the coefficient of the age variable is significant (p<0.05). The coefficient of age is -16,195, indicating that with an increase in age by one year, SII decreases by an average of 16,195 units. The coefficients of the other variables are not significant (p>0.05).

DISCUSSION

The major findings of the present study demonstrated that routine CBC-derived inflammatory markers measured between 14th and 24th weeks of pregnancy are not effective to predict future development of GDM. To the best of our knowledge, this study is the first to demonstrate that predicting GDM using the CBC inflammatory markers PLR, NLR, and SII is not a reliable strategy.

The results of this study confirm previous reports that raised maternal BMI is a risk factor for the onset of GDM (20). In a meta-analysis with 120 million participants, the risk of GDM increased linearly with advanced maternal age (21). This result was consistent with our findings.

Based on the literature showing that insulin resistance is the main determinant of platelet activation in female obesity (22), platelet indices in the prediction of GDM has received much attention in recent years (23, 24). A meta-analysis from China demonstrated that MPV was significantly increased in GDM (15), but in subgroup analysis, significantly increased MPV was observed in the third trimester, while the difference did not reach statistical significance during the second trimester. In our study, second trimester MPV values were not increased, either. In a study investigating the relationship between maternal age and MPV value in the prediction of GDM, no significant difference was found in the MPV value in pregnant women younger than 28 years old (24). Huang et al. showed that the diagnostic accuracy of PCT in prediction of GDM is low (23). Similar to our findings, Gorar et al. found no significant difference in PDW levels and platelet counts (25). The results of platelet parameters in GDM are inconsistent depending on the gestational week, maternal age and pre-pregnancy inflammatory status.

In a study evaluating the number of immature granulocytes in GDM, no significant difference was found at the time of OGTT (26), while Uysal et al. found significant difference in DNI at the delivery stage (18) DNI and immature granulocyte counts in the second trimester

were not significant in our study. Sargın et al. claimed that NLR and PLR from the CBC results done on the same day as OGTT can not be used to screen for GDM (p=0.911, p=0.416) (12). However, in a relatively small cohort from China, PLR, NLR, and MPV were found to be independent predictors of GDM development (11). In first trimester studies SII value has been shown to be statistically significant in predicting GDM (17, 27). A subclinical inflammation that existed prior to pregnancy may be the cause of first trimester high SII levels. In a larger study, no significant difference was observed in MPV, PLR, NLR and SII values measured simultaneously with OGTT (28).

As demonstrated by the discordant results reported by the studies described above, the results of our study showed that none of the CBC-derived inflammatory parameters made a significant prediction of GDM. GDM is a state of transient hyperglycemia during pregnancy. Soon after delivery, the majority of GDM patients' blood glucose levels return to normal. While GDM and DM share several inflammatory pathways, the intensity of the inflammatory processes in GDM differ. In GDM, the severity of chronic low-grade inflammation is related to advanced maternal age, obesity, and the presence of underlying PCOS (polycystic ovary syndrome). As a result, in low-risk populations, CBC inflammatory markers might have no reliable predictive value for the development of GDM.

There are several limitations in the present study worthy of mention. First, the study was retrospective and included only tertiary center experience. Another limitation was the small number of participants. This might have precluded to discern subtle differences in terms of inflammatory markers in GDM patients. Larger prospective studies are needed for early prediction of GDM. The fact that we did not include patients with impaired pre-pregnancy glucose metabolism by following strict criteria in patient selection, screening with only one-step 75-gr OGTT, and the ethnic composition of the population may be some of the reasons why we found different results in the literature on this topic.

In conclusion, our main objective was to investigate the predictive value of inflammatory markers in routine CBC for the early detection of GDM. According to our study, CBC-derived inflammatory parameters were not sufficiently reliable to predict the future development of GDM.

Ethics Committee Aproval

The study protocol was approved by the Ethics Committee of Mersin University (no:2023/41), and was carried out in accordance with the Helsinki Declaration.

Disclosure Statement

No potential conflict of interest was reported by the authors.

Funding

The authors have not disclosed any funding.

Data Availability

Data availability is supplied up on request.

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Jinekoloji - Obstetrik ve Neonatoloji Tıp Dergisi
The Journal of Gynecology-Obstetrics and Neonatology

ÖZGÜN ARAŞTIRMA / ORIGINAL ARTICLE

DOI: 10.38136/jgon.1476370

Risk factors in pregnancy-related carpal tunnel syndrome

Gebeliğe bağlı karpal tünel sendromunda risk faktörleri

Ufuk ATLIHAN[1], Meltem DURAKLI ULUKÖK[2], Onur YAVUZ[3], Hüseyin Aytuğ AVŞAR[4], Can ATA[5]
Tevfik Berk BİLDACI[6], Selçuk ERKILINÇ[7]

[1]Private Karataş Hospital
[2]Private Cankaya Medical center
[3]Dokuz Eylul University School of Medicine
[4]Torbalı State Hospital
[5]Buca Seyfi Demirsoy Training and Research Hospital
[6]Izmir Democracy University Faculty of Medicine, OB/GYN Department
[7]Izmir Democracy University Faculty of Medicine, Oncology Department

ABSTRACT

Aim: The purpose of our study was to highlight carpal tunnel syndrome (CTS), which is generally overlooked by physicians in pregnant women, resulting in inadequate diagnosis and treatment, and to investigate the related risk factors in pregnant women, who are diagnosed with CTS.

Materials and Methods: In our study, the demographic, clinical, and laboratory data of 82 pregnant women, who were diagnosed with CTS, who were in the 3rd trimester, and whose pregnancy follow-ups were performed by us between March 2018-2023, and 82 pregnant women in the control group were assessed retrospectively.

Results: Body mass index (BMI) values were observed to be significantly higher in the group with CTS compared to the group without CTS(p:0.036). The HbA1c level was 5.4±0.2 in the group with CTS, and 5.1±0.3 in the group without CTS, and it was significantly higher in the group with CTS(p:0.038). The TSH level was 2.9±0.6(mIU/L) in the group with CTS, and 2.4±0.5(mIU/L) in the group without CTS, and it was significantly higher in the group with CTS(p:0.042). A positive, statistically significant, and moderate correlation was detected between the CTS-6 value and BMI (p:0.006, r=0.438). Another statistically significant, positive, and weak correlation was detected between the CTS-6 score and HbA1c level(p:0.028, r=0.234).

Conclusion: It is especially important to pay attention to many risk factors because subclinical CTS during pregnancy can lead to permanent complications. We think the present study's findings are important for healthcare providers and will contribute significantly to the understanding of the relationship between CTS and pregnancy by shedding light on the relationship between relevant variables and the prevalence of CTS.

Keywords: Carpalitunnel syndrome, CTS-6, Pregnancy

ÖZ

Amaç: Bu çalışmanın amacı gebelerde genellikle hekimler tarafından gözden kaçırılan, tanı ve tedavide yetersizliğe neden olan karpal tünel sendromunu (KTS) vurgulamak ve KTS tanısı alan gebelerde ilişkili risk faktörlerini araştırmaktır.

Gereç ve Yöntemler: Bu çalışmada Mart 2018 - Mart 2023 tarihleri arasında hastanemizde gebelik takipleri yapılan, 3. trimesterde KTS tanısı alan 82 gebe ile kontrol grubundaki 82 gebenin demografik, klinik ve laboratuvar verileri retrospektif olarak değerlendirildi.

Bulgular: KTS saptanan grupta beden kitle indeksi (BMI) saptanmayan gruba göre anlamlı derecede yüksek saptandı (p:0.036). HbA1c düzeyi KTS saptanan grupta 5.4±0.2, saptanmayan grupta ise 5.1±0.3 olup KTS grubunda anlamlı olarak yüksek saptandı (p:0.038). TSH düzeyi KTS saptanan grupta 2.9±0.6 (mIU/L), saptanmayan grupta ise 2.4±0.5 (mIU/L) olup, KTS grubunda anlamlı olarak yüksek saptandı (p:0.042). KTS-6 değeri ile BMI skoru arasında pozitif, istatistiksel olarak anlamlı ve orta düzeyde bir korelasyon tespit edildi (p:0.006, r=0.438). KTS-6 skoru ile HbA1c düzeyi arasında istatistiksel olarak anlamlı, pozitif ve zayıf bir korelasyon daha tespit edildi (p:0.028, r=0.234).

Sonuç: Gebelikte subklinik KTS kalıcı komplikasyonlara neden olabileceğinden birçok risk faktörüne dikkat etmek özellikle önemlidir. Bu çalışmanın bulgularının sağlık çalışanları açısından önemli olduğunu ve ilgili değişkenler ile KTS prevalansı arasındaki ilişkiye ışık tutarak KTS ile gebelik arasındaki ilişkinin anlaşılmasına önemli katkı sağlayacağını düşünüyoruz.

Anahtar Kelimeler: Karpal tünel sendromu, KTS-6, Gebelik

Cite as: Atlıhan U, Ulukök Duraklı M, Yavuz O, Avşar HA, Ata BC, Bildacı TB et al. Risk factors in pregnancy-related carpalitunnel syndrome. Jinekoloji-Obstetrik ve Neonatoloji Tıp Dergisi 2024;21(4):329–334.

Geliş/Received: 01.05.2024 • **Kabul/Accepted:** 21.08.2024

Sorumlu Yazar/Corresponding Author: Ufuk ATLIHAN, Private Karataş Hospital
E-mail: cfl.ufuk@gmail.com

Çevrimiçi Erişim/Available online at: https://dergipark.org.tr/tr/pub/jgon

INTRODUCTION

A group of symptoms known as carpal tunnel syndrome (CTS) result from by pressing of the median nerve inside the carpal tunnel. The carpal tunnel is a tunnel that has no elasticity and cannot adapt to different pressure situations (1). However, it's not entirely inflexible since the carpal bones make sliding movements on each other during wrist movements and, therefore, they can stretch the canal slightly. In anatomical terms, the carpal tunnel gets narrow in sections towards 2.0-2.5 cm distally (1). Patients with CTS suffer High Intra-Carpal tunnel pressure which spikes at that point. Mechanical pressure on the nerve sheath or interruption of blood circulation may block the conduction of the median nerve, which may cause CTS (1). The general population is estimated to have a 4% prevalence of CTS (2). It has been proposed that the morphology of women may make them more susceptible to CTS (3). The most prevalent entrapment neuropathy is thought to be CTS (4). CTS symptoms include intense pain in the hand and wrist and paresthesia (sensation of numb, buzzing and burn) in the median nerve distribution (the first three fingers and the middle half of the fourth digit) (4). Often, symptoms appear gradually and at nights, and the pain may radiate to the arm. Grip strength may be quite weak in these patients (5). Over time, the thenar eminence muscles might weaken, and in over 50% of instances, the condition affects both sides (5). Tinel's, Phalen's, and Median Nerve Compression are standard tests that are used in clinical examinations to diagnose CTS and can either produce or exacerbate symptoms (6). With a sensitivity of 49–84% and a specificity of 95%, electrodiagnostic testing carried out by a qualified electromyographer is the most accurate diagnostic technique (6). With a high degree of sensitivity and specificity, electrodiagnostic investigations are an essential electrophysiological follow-up to the history and examinations in the diagnosis of CTS (4, 6). The existence and severity of wrist median neuropathy can be assessed by nerve conduction tests and electromyography (EMG) (4, 6). CTS usually develops idiopathically (7). However, it is also considered that CTS is associated with some pathological (thyroid disease, colles fracture, polyneuropathies, etc.) and physiological (pregnancy, menopause) conditions (7). One of the most prevalent physiological factors linked to CTS is thought to be pregnancy (7). However, the data on its incidence in the literature are quite contradictory (7). Physiological evidence suggests that elevated pressure in the carpal tunnel causes the deterioration of the median nerve functions (8). Studies regarding the CTS dominance at pregnancy reported a wide spectrum because different methods were used in diagnosis (9, 10). The pathophysiology of CTS during pregnancy is shown as fluid accumulation under the influence of hormonal fluctuations during pregnancy (11). The kidneys increase blood volume in the third trimester of pregnancy by increasing fluid retention and the simultaneous increase in estrogen, progesterone, and aldosterone levels plays roles in the development of CTS (12). Predisposing factors supporting the onset of symptoms in this period were shown to be the changes in glucose levels, edema, and hypersensitivity of the relevant nerve (13). As the pregnancy progresses, the incidence of CTS also increases (14). Most pregnant women show symptoms that are sufficiently painful to interfere with their ability to sleep and use their hands. The quality of life of these individuals appears to be significantly affected (14). The purpose of the present study was to highlight CTS, which is often overlooked by physicians in pregnant women, resulting in inadequate diagnosis and treatment, and to examine the related risk factors in pregnant women diagnosed with CTS.

MATERIALS AND METHODS

The research had a retrospective case-control design in line with the Helsinki Declaration. Informed consent forms were taken from the participants. The research was started after receiving ethics committee approval number 2024/250 from our hospital. The study was conducted in the 3rd trimester of pregnancy follow-up in the clinic between March 2018 and 2023, who described upper extremity complaints (numbness in the hands or arms, tingling, pain, pain coming from the neck to the arms, etc.) and therefore were consulted to the neurology department. A total of 82 pregnant women who were diagnosed with CTS during pregnancy and 82 pregnant women in the control group were included in the research. Being diagnosed previously with CTS, having a history of treatment, chronic hypertension, diabetes mellitus, and known connective tissue disease were considered as exclusion criteria. The age, gravidity, parity, birth weight, gestational age, body mass index (BMI) values, first and fifth minute Apgar values, glycated hemoglobin (HbA1C), HOMA-IR, fasting glucose, Thyroid stimulating hormone (TSH), FreeT3 (fT3), FreeT4 (fT4), Anti-thyroglobulin (Anti-tg), Anti-thyroid peroxidase (Anti-TPO) values, systolic and diastolic blood pressure values of the patients were evaluated retrospectively. Blood results of insulin resistance and thyroid function parameters of all patients included in the study, performed at 24-28 weeks, were evaluated retrospectively. Weakness, numbness, night numbness, thenar atrophy, and Tinel and Phalen Tests were performed with the CTS-6 evaluation method modified by Graham (15). The CTS-6 scale evaluates six basic criteria out of 26 points, according to history, symptoms, and physical examination results. It is possible to diagnose CTS with a probability of >12=0.80 and > 5=0.25 according to the CTS-6 scoring results (15). In this scale, patients who scored 12 points or more were evaluated as CTS-6 positive, and patients who scored less than 12 points were evaluated as CTS-6 negative (15). The correlation between CTS-6 values and risk factors was also evaluated in the present study. The Nihon

Kohden Neuropack S3 MEB-9600 Device was used at our hospital's EMG laboratory to conduct nerve conduction tests. Median motor and sensory nerve conductions and ulnar motor and sensory nerve conductions were studied in the upper extremity under normal room temperature and by ensuring that the skin temperature was at least 31-32 degrees. The data analysis was conducted with the SPSS 26.0 (IBM Inc. Chicago, IL, USA). The Kolmogorov-Smirnov Test was employed to make an evaluation regarding the normality distribution of the data. Normally distributed data were given as Mean±SD. The Student's t-test was employed to make a comparison on normally distributed data and the Chi-Square Test and Fisher's Exact Test were used to make an evaluation regarding the categorical variables. The degree of correlation between two variables and their link to one another was assessed using the Pearson Correlation Test. In every test, a p-value of less than 0.05 was deemed statistically significant.

RESULTS

The average age of the 164 participants was 30.6±9.7 years and the average BMI score was 26.8±4.8 kg/m^2 in this research. The mean gravidity of the patients was 2.1±0.8, mean parity was 1.8±0.7, week of birth was 37±2.4, birth weight was 2990±860 g, first-minute Apgar score was 7.9±0.9, and fifth-minute Apgar score was 8.5±0.6. No significant differences were detected with regard to age and parity averages between the group with CTS and the group without CTS (p:0.810, p:0.840, respectively). There were no significant differences between the group with CTS and the group without CTS with regard to week of birth and birth weight (p:0.770, and p:0.830, respectively). The first and fifth-minute Apgar scores (p:0.760, p:0.740, respectively) did not significantly vary between the CTS group and the non-CTS group. The CTS group had considerably higher BMI ratings than the non-CTS group (p: 0.036) (Table 1).

Among the patients who participated in the study, the glucose level in the CTS group was 90.1±9.9 (mg/dl), and 82.5±9.7 in the non-CTS group (mg/dl), and no significant difference was seen between the groups (p:0.270). The HbA1c level was found to be 5.4±0.2 in the CTS group, and 5.1±0.3 in the non-CTS group, and it was significantly higher in the CTS group (p:0.038). HOMA-IR level was 2.1±0.3 in the CTS group, and 2.1±0.1 in the non-CTS group, and no significant difference was observed between the groups (p:0.870). The TSH level was found to be 2.9±0.6 (mIU/L) in the CTS group, and 2.4±0.5 (mIU/L) in the non-CTS group, and it was significantly higher in the CTS group (p:0.042). No significant differences were detected in fT3 and fT4 values between the CTS group and the non-CTS group (p:0.790, p:0.820, respectively). No significant difference was found in Anti-Thyroid peroxidase and Anti-Thyroglobulin values between the CTS group and the non-CTS group (p:0.220, p:0.420, respectively). The systolic blood pressure level was 128±10 (mmHg) in the CTS group, and 122±10 (mmHg) in the non-CTS group, and no significant differences were found between the groups (p:0.640). The diastolic blood pressure level was 85±11 (mmHg) in the CTS group, and 81±10 (mmHg) in the non-CTS group, and no significant differences were found between the groups (p:0.550) (Table 2).

A positive, statistically significant, and moderate correlation was observed between the CTS-6 value and BMI (p:0.006, r=0.438). Another positive, statistically significant, and weak correlation was detected between the CTS-6 score and HbA1c level (p:0.028, r=0.234). There was a positive, statistically significant, and weak correlation between CTS-6 score and TSH level (p:0.018, r=0.208) (Table 3).

Table1. Demographic and clinical characteristics of the participants

	CTS (+) n:84	CTS (-) n:84	Total n:168	
	Mean±SD			p
Age (year)	30.8±9.4	30.5±9.8	30.6±9.7	0.810
BMI (kg/m^2)	28.8±3.7	25.7±4.7	26.8±4.8	**0.036**
Gravidity	2.2±0.7	2.1±0.8	2.1±0.8	0.890
Parity	1.8±0.6	1.7±0.8	1.8±0.7	0.840
Birth week	37±2.2	37±2.6	37±2.4	0.770
Birth weight (g)	3020±820	2950±870	2990±860	0.830
1st minute Apgar score	8±0.8	7.8±0.9	7.9±0.9	0.760
5th minute Apgar score	8.4±0.5	8.5±0.7	8.5±0.6	0.740

*CTS: Carpal tunnel syndrome, BMI: Body mass index

Table 2. The comparison of clinical and laboratory data according to the presence of CTS

	CTS (+) n:84	CTS (-) n:84	Total n:168	
	Mean±SD			p
Glucose (mg/dl)	90.1±9.9	82.5±9.7	87.7±9.7	0.270
HbA1c (%)	5.4±0.2	5.1±0.3	5.3±0.2	**0.038**
HOMA-IR	2.1±0.3	2.1±0.1	2.1±0.2	0.870
TSH (mIU/L)	2.9±0.6	2.4±0.5	2.6±0.5	0.042
fT3 (pg/ml)	2.7±0.2	2.6±0.4	2.6±0.3	0.790
fT4(ng/dl)	1.4±0.1	1.3±0.2	1.3±0.2	0.820
Anti-Thyroid peroxidase (IU/ml)	68.40±20.1	62.40±18.50	64±25.20	0.220
Anti-Thyroglobulin (IU/ml)	40.4±8.6	42±6.8	40.9±7.8	0.420
Systolic Pressure (mmHg)	128±10	122±10	124±13	0.640
Diastolic Pressure (mmHg)	85±11	81±10	82±13	0.550

*CTS: Carpal tunnel syndrome, HbA1c: Glycosized hemoglobin, TSH: Thyroid stimulating hormone, fT3: Free T3, fT4: Free T4

Table 3. The relationship between CTS-6 score and clinical and laboratory data

	Grade 1-2	Grade 3-4	Grade 5	Grade 6
1. CTS-6 score	1			
2. BMI (kg/m²)	.438 **	1		
3. HbA1c (%)	.234 *	.317 **	1	
4. TSH (mIU/L)	.208 *	.292 **	.301	1

* CTS: Carpal tunnel syndrome, BMI: Body mass index, HbA1c: Glycosized hemoglobin, TSH: Thyroid stimulating hormone, **r: Spearman correlation coefficient

DISCUSSION

Although the relationship between pregnancy and CTS is already known, untreated CTS symptoms in pregnant women are a common occurrence in the gynecology practice. There is no agreement about the results of the several research that looked at the risk factors of CTS. In the present study, the extent of CTS was evaluated in pregnant women, taking into account various demographic data and characteristics of possible risk factors. It was reported in previous studies that advanced maternal age is a risk factor for CTS during pregnancy (9). In the present study, no significant difference was found with regard to age between the CTS group and the non-CTS group. In their study, Hanif et al. reported no relationship between age and CTS, similar to our results (14). No significant difference is reported in the literature in the nerve conduction study parameters for CTS in studies conducted with pregnant women with primigravida and multigravida history (15-17). Similarly, no significant differences were seen in our study between the two groups with regard to gravidity averages. Contradictory results were reported in studies evaluating the relationship between parity and CTS in the literature. Meems et al. reported in their study that they detected no relationships between parity and CTS (10). Wright et al. reported that there may be a relationship between increasing parity and CTS (9). No significant difference was found in our study with regard to parity averages between the groups with and without CTS. Research indicates that BMI, as for the general population, is a separate risk factor for CTS related to pregnancy (9). It was also reported that the difference in weight increase at pregnancy is correlated with the prognosis of CTS (17). Many studies report significant relationships between obesity and the risk of CTS development on a global scale (18-20). Weimer et al. showed that when compared to slim people, the risk of CTS increased 2.5 times among those who were categorized as obese (BMI < 20) (21). In our study, the group with CTS had a considerably higher BMI than the group without it. In our investigation, we also found a somewhat strong, positive, statistically significant link between the BMI and the CTS-6 score. Maternal physiology and behavior, such as increased blood volume, uterine mass, interstitial fluid volume, growing fetus, and belly fat cause weight gain during pregnancy (22). It is considered that in the transverse carpal ligament, the decreased blood flow to the median nerve because of the increased edema and adipose tissue developing during pregnancy causes

CTS (22). Gestational Hypertension, which may develop secondarily to weight gain, and diabetes-related systemic pregnancy problems can also result in reduced blood supply to the median nerve and an elevated CTS risk (22). Although its exact origin is not clear, increased Vascular Endothelial Growth Factor (VEGF) and advanced glycation end products (consistent with median nerve edema caused by hyperglycemia, increased sensitivity to external stress, nerve myelin ischemia, and axonal degeneration) seem to play roles in the development of CTS (23). In their study, after dividing patients into three groups as severe, moderate, and mild based on the severity of CTS, Demirel et al. showed that individuals with CTS had substantially higher fasting blood sugar and HbA1c values than those without CTS (24). Rydberg et al. showed that high plasma glucose and HbA1c levels were linked with an increased risk of CTS and that the presence of diabetes was an important risk factor in this regard (25). In our study, glucose and HOMA-IR levels did not have significant differences between the groups, and the HbA1c level was significantly higher in the group with CTS. Also, a positive, statistically significant, and weak correlation was detected between the CTS-6 value and HbA1c level in our study. The relationship between hypothyroidism and the development of CTS was shown in multiple studies in the literature (26-28). Excessive amounts of mucopolysaccharides, hyaluronic acid, and glycosaminoglycans may accumulate in the subcutaneous tissues in the presence of hypothyroidism (26). A narrow space exists in the carpal tunnel where pseudomucinous substances accumulate and this causes the median nerve compression and causes CTS (26). In an investigation to find out how common CTS is in hypothyroidism-affected women, 20 of 300 hypothyroidism patients were examined because hypothyroidism is more common in women with CTS. It was reported that there were 160 individuals with mild CTS and 160 with moderate CTS (26). These numbers showed that a significant portion of women diagnosed with hypothyroidism were diagnosed with CTS (27). In a meta-analysis of Shiri et al., the results of 10 studies were summarized and it was concluded that CTS was strongly associated with hypothyroidism (28). TSH levels were considerably higher in the CTS group in our investigation, which is consistent with results from the literature. We also found a small but statistically significant positive association between the TSH level and the CTS-6 score. In the literature, some studies report that hypertension is generally associated with edema during pregnancy because of fluid retention, which will elevate the pressure within the tunnel and increase the CTS development risk (29, 30). However, it is already known that long-term hypertension is generally associated with different types of neuropathies (31). Unlike the literature data, no significant relationships were found in our study between diastolic and systolic blood pressure levels and the presence of CTS. The difference between this relationship in the literature and the results of our study may be because patients diagnosed with chronic hypertension were excluded from our research. Voitk et al. showed in their study that only 46% of symptomatic pregnant women consulted a doctor because of hand symptoms and only 35% of them received treatment (32). It is considered that the most important reason for this is that patients do not explain their symptoms or physicians do not question patients about their symptoms. When the studies conducted using the electrodiagnostic method in the diagnosis of CTS are reviewed, the results show that the prevalence of CTS is high during pregnancy, but the prevalence is reported to be low in studies where only clinical tests were used (33). Padua et al. reported the prevalence of CTS in pregnant women as 7-43% according to electrodiagnostic findings and 31-62% according to clinical findings (33). Graham et al. reported that the correlation between the pretest probability determined by CTS-6 and the posttest probability calculated based on EMG results was quite high (34). For this reason, we think that the CTS-6 Test is a useful noninvasive scale for making a preliminary diagnosis and it was applied to our patients during the first examination. The most important limitation of the study was that it was designed retrospectively. Also, the limited number of participants in the study restricted the adequate evaluation of risk factors in pregnant women diagnosed with CTS. Confirmation of each patient evaluated with CTS-6 scoring by electrodiagnostic method, and in this way, confirming the presence of CTS can be shown as the strength of the study.

CONCLUSION

It is important to pay special attention to the risk factors that may lead to the development of CTS because subclinical CTS during pregnancy can lead to permanent complications. Diagnosis and management of such risk factors to be modified may prevent disease progression. We believe that the results of the present research are important for healthcare providers and will contribute significantly to the understanding of the relationship between CTS and pregnancy in the literature by shedding light on the relationship between the relevant variables and the prevalence of CTS.

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Jinekoloji - Obstetrik ve Neonatoloji Tıp Dergisi
The Journal of Gynecology-Obstetrics and Neonatology

ÖZGÜN ARAŞTIRMA / ORIGINAL ARTICLE

DOI: 10.38136/jgon.1587956

Relationship between bone mineral density and inflammatory markers in postmenopausal patients

Postmenopozal hastalarda kemik mineral yoğunluğu ile inflamatuar belirteçler arasındaki ilişki

Mohammad İbrahim HALİLZADE[1], Emre Erdem TAŞ[2]

[1]University of Health Sciences Ankara City Hospital, Gynecology and Obstetrics Department, Ankara, Turkey
[2]University of Ankara Yıldırım Beyazıt, Gynecology and Obstetrics Department, Ankara, Turkey

ABSTRACT

Aim: This study aimed to determine the effects of acute-phase reactants and other factors on osteoporosis in postmenopausal women and to investigate inflammation markers that can be used in early diagnosis.

Materials and Methods: This study included 200 postmenopausal patients aged 40-65. Patients were divided into two groups: those with a bone mineral densitometry T-score below -2.5 (osteoporosis-positive) and above -2.5 (osteoporosis-negative). Patient demographics (age, parity, height, weight, body mass index (BMI - kg/m^2), duration of menopause, education level [<University vs. ≥University], and occupation status [Working vs. Housewife/ Pensioner]), complete blood count (hematocrit, white blood cell (WBC) count, neutrophil-to-lymphocyte (NLR) ratio), and serum biochemistry (low-density protein (LDL), vitamin D, and C-reactive protein (CRP)) levels were compared between the two groups.

Results: The mean lumbar T-score in the osteoporosis-positive group was significantly lower than in the osteoporosis-negative group (-2.9±0.4 vs. -0.8±1.0, p<0.01). Age, height, duration of menopause, and occupation status did not differ between the groups. However, mean parity, weight, and BMI were significantly higher in the osteoporosis-negative group (p<0.01). Blood Htc, WBC, NLR, and serum CRP and vitamin D levels showed no significant differences, but serum LDL levels were significantly lower in the osteoporosis-positive group (p=0.03). Binary logistic regression indicated low parity (OR: 0.65; p=0.02) and high educational level (OR: 0.42, p=0.01) were independently associated with a reduced risk of osteoporosis.

Conclusion: In our study, postmenopausal osteoporosis was not associated with serum inflammatory markers, and inflammatory markers were not valuable in predicting osteoporosis. However, postmenopausal osteoporosis was found to be closely related to parity, education level, weight and BMI.

Keywords: Acute-Phase Proteins, osteoporosis, postmenopausal, body mass index, parity

ÖZ

Amaç: Bu çalışmanın amacı, postmenopozal kadınlarda akut faz reaktanlarının ve diğer faktörlerin osteoporoz üzerindeki etkilerini belirlemek ve erken tanıda kullanılabilecek inflamasyon belirteçlerini araştırmaktır.

Gereç ve Yöntemler: Bu çalışmaya 40-65 yaş aralığında 200 postmenopozal hasta dahil edildi. Hastalar iki gruba ayrıldı: Kemik mineral dansitometrisi T skoru -2,5'in altında ve -2,5'in üzerinde olanlar. Hastaların yaşı, vücut kitle indeksi (VKİ (kg/m^2)), parite, doğum şekli (sezaryen veya vajinal doğum), demografik özellikleri, tam kan sayımı sonuçları (hematokrit (Htc), beyaz kan hücresi (WBC), nötrofil/lenfosit oranı (NLR)), düşük yoğunluklu protein (LDL), D vitamini düzeyleri ve CRP düzeyleri iki grup arasında karşılaştırıldı.

Bulgular: Ortalama parite, kilo ve VKİ, osteoporoz negatif grupta osteoporoz pozitif gruba göre anlamlı derecede daha yüksekti (P <0,01). Gruplar, kan Htc, WBC sayısı, NLR ve serum CRP ve D vitamini seviyelerine göre farklılık göstermedi. Ancak, serum LDL seviyeleri osteoporoz pozitif grupta osteoporoz negatif gruba göre anlamlı derecede düşüktü (P = 0,03). İkili lojistik regresyon analizi, düşük paritenin (OR: 0,65; P = 0,02) ve yüksek eğitim düzeyinin (OR: 0,42, P = 0,01) bağımsız olarak düşük osteoporoz riski ile ilişkili olduğunu ortaya koydu.

Sonuç: Çalışmamızda, postmenopozal osteoporoz serum inflamatuar belirteçleri ile ilişkili değildi ve inflamatuar belirteçler osteoporozu tahmin etmede değerli değildi. Ancak, postmenopozal osteoporoz parite, eğitim düzeyi, kilo ve BKİ ile yakından ilişkili olarak saptandı.

Anahtar Kelimeler: Akut faz proteinleri, osteoporoz, postmenopozal, vücut kitle indeksi, parite

Cite as: Halilzade Mİ, Taş EE. Relationship between bone mineral density and inflammatory markers in postmenopausal patients. Jinekoloji-Obstetrik ve Neonatoloji Tıp Dergisi 2024;21(4):335–339.

Geliş/Received: 19.11.2024 • **Kabul/Accepted:** 12.12.2024

Sorumlu Yazar/Corresponding Author: Mohammad İbrahim HALILZADE, University of Health Sciences Ankara City Hospital, Gynecology and Obstetrics Department, Ankara, Türkiye
E-mail: ibrahim_halilzade@hotmail.com

Çevrimiçi Erişim/Available online at: https://dergipark.org.tr/tr/pub/jgon

INTRODUCTION

Osteoporosis is a disease with high morbidity, resulting in increased bone fragility due to low bone mass and deterioration of bone tissue (1). Vertebral fractures are the most common type of fractures associated with osteoporosis. Osteoporosis is particularly common in postmenopausal women and is associated with serious life-threatening vertebral fractures (2). Estrogen deficiency is the main cause of osteoporosis in postmenopausal women. Estrogen acts as a hormone that regulates bone mineral density. However, as it decreases during menopause, osteoporosis accelerates (3).

Pregnancy and lactation have been shown to be associated with osteoporosis in women. Pregnancy and lactation are conditions in which there is a high need for calcium, leading to significant physiological changes in bone mass. However, these changes have been shown to reverse after lactation (4). Despite this, studies have reported that the number of pregnancies is associated with osteoporosis and that osteoporosis increases with parity increases (5). Owing to these risk factors, early diagnosis and treatment of osteoporosis before vertebral fractures occur in women is very important.

Bone mineral density (BMD) measurement is the most important test used for the diagnosis of osteoporosis (6). According to the World Health Organization definition, osteoporosis is diagnosed as a T-score < –2.5 SD at any site (7). However, early and inexpensive methods for diagnosing osteoporosis remain a subject of research. It is known that systemic inflammation negatively affects BMD in patients with autoimmune chronic diseases such as rheumatoid arthritis, regardless of corticosteroid use (8). Therefore, it is suggested that acute-phase reactants, which are markers of inflammation, may be associated with osteoporosis. A large population study showed that C-reactive protein (CRP) values were inversely correlated with BMD scores in both men and women (9). Similarly, some studies have reported an inverse relationship between neutrophil to lymphocyte ratio (NLR) and BMD in postmenopausal women (2). However, some studies have reported that CRP is not an indicator of low BMD, bone loss, or fractures in postmenopausal women (10).

The fact that acute-phase reactants are affected by many diseases as inflammation markers and the conflicting results regarding their relationship with osteoporosis indicate that further studies are needed on this subject. This study aimed to determine the effects of acute-phase reactants and other factors on osteoporosis in postmenopausal women and to investigate inflammation markers that can be used for early diagnosis.

METHODS

This study included 200 postmenopausal patients in the Gynecology and Obstetrics Clinic of our hospital, which is a tertiary center, between 2019 and 2024. Approval from the local ethics committee was obtained from the same hospital (Ankara Bilkent City Hospital Ethics Committee no. 2, Approval No: 24-637). This study was a retrospective, cohort study.

Female patients aged 40-65 who entered menopause naturally were included in the study. Menopause was defined as patients who had not menstruated for two years or more. Patients with surgical menopause or early menopause (under 40 years of age) were excluded from the study. In addition, patients with parathyroid diseases that cause osteoporosis, thyroid disease, malignancy, rheumatological diseases, and infections were excluded. Patients who were started on medication for osteoporosis, who were using regular medication, and who were using hormone replacement therapy were not included in the study.

Patients were divided into two groups: those with a bone mineral densitometry T-score below -2.5 and above -2.5. Those with a BMD T score of 2.5, standard deviations (SD), or more below the mean BMD of the young adult reference population at any site were defined as having osteoporosis. Patients' age, body mass index (BMI (kg/m^2)), parity, delivery type (cesarean or vaginal delivery), and demographic characteristics were retrospectively investigated and recorded. Complete blood count results (hematocrit (Htc), white blood cell (WBC), lymphocyte count, NLR), low-density protein (LDL), vitamin D levels, and CRP levels were compared between the two groups. These markers (Htc, WBC, NLR) were tested automatically as part of a standard complete blood count. Bone mineral densitometry readings of the patients were obtained from the measurements recorded by the DXA method using a Hologic brand QDR 4500W device (Hologic Inc., Bedford, MA, USA) in the bone densitometer unit of the radiology department. The total BMD changes of the lumbar vertebrae were considered using T-scores (since osteoporosis is most commonly seen in the vertebrae (2)).

Data were expressed as mean±standard deviation. The independent samples t-test was used to compare parametric data between the groups. Categorical variables are expressed as numbers and percentages, and the groups were compared using the chi-square test. Variables with $P<0.05$, including parity, weight, BMI, education level, and serum LDL levels were included in the binary logistic regression analysis to identify independent factors associated with osteoporosis. Statistical analyses were performed using the Statistical Package for the Social Sciences for Windows, version 21.0 (IBM, SPSS Corp.; Armonk, NY, USA). Odds ratios (ORs) and 95.0% confidence intervals (CIs) were calculated, and statistical significance was set at $P<0.05$.

RESULTS

This study included 100 postmenopausal patients with osteoporosis (osteoporosis-positive) and 100 postmenopausal patients without osteoporosis (osteoporosis-negative). The mean lumbar T-score in the osteoporosis-positive group was lower than that in the osteoporosis-negative group (-2.9±0.4 vs. -0.8±1.0), and the difference was significant (p<0.01).

The groups (osteoporosis-positive and osteoporosis-negative) did not differ in age, height, duration of menopause, or occupation status (p=0.58, 0.17, 0.10, and 0.17, respectively). However, the mean parity, weight, and BMI were significantly higher in the osteoporosis-negative group than in the osteoporosis-positive group (P <0.01).

The demographic characteristics of the osteoporosis-positive and osteoporosis-negative groups are presented in Table 1.

The groups (osteoporosis-positive vs. osteoporosis-negative) did not differ based on blood Htc, WBC count, NLR, and serum CRP and vitamin D levels (p=0.06, 0.20, 0.86, 0.60, and 0.63, respectively). However, serum LDL levels were significantly lower in the osteoporosis-positive group than in the osteoporosis-negative group (P =0.03). The laboratory characteristics of the osteoporosis-positive and osteoporosis-negative groups are presented in Table 2.

Binary logistic regression analysis revealed that low parity (OR: 0.65; P=0.02) and high educational level (≥university) (OR: 0.42, P=0.01) were independently associated with a low risk of osteoporosis (Table 3).

Table 1. The demographic characteristics of the osteoporosis-positive and osteoporosis-negative groups

Characteristics	Osteoporosis-positive (n=100)	Osteoporosis-negative (n=100)	P
Age (years)	57.8±6.4	57.3±7.2	0.58
Parity	1.9±0.8	2.4±1.1	<0.01
Height (cm)	159.8±5.8	160.0±5.4	0.17
Weight (kg)	66.1±10.5	73.4±14.1	<0.01
Body mass index (kg/m²)	25.9±4.2	28.9±5.8	<0.01
Duration of menopause (years)	8.9±5.3	7.7±5.8	0.10
Education degree			
<University	61 (30.5)	44 (22)	0.01
≥University	39 (19.5)	56 (28)	
Occupation status			
Working	34 (17)	27 (13.5)	0.17
Housewife/Pensioner	66 (33)	73 (365)	

Data are presented as the mean±standard deviation or n (%).

Table 2. The laboratory characteristics of the osteoporosis-positive and osteoporosis-negative groups

Characteristics	Osteoporosis-positive (n=100)	Osteoporosis-negative (n=100)	P
Hematocrit (%)	41.4±3.1	42.2±2.8	0.06
WBC count (x 103/µL)	6.6±1.8	7.0±1.8	0.20
NLR	1.9±0.9	1.9±0.8	0.86
CRP (mg/L)	2.4±1.8	7.0±1.8	0.60
D vitamin	49.8±23.4	48.1±26.4	0.63
LDL	127.8±32.7	140.2±48.2	0.03

Data are presented as the mean±standard deviation or n (%).
Abbreviations: CRP, C-reactive protein; LDL, low-density protein; NLR, neutrophil-to-lymphocyte ratio.

Table 3. Binary logistic regression analysis of risk factors associated with osteoporosis

	P-value	95% CI	OR
Parity	0.02	0.45–0.93	0.65
Weight (kg)	0.30	0.90–1.03	-
Body mass index (kg/m²)	0.78	0.83–1.15	-
Education level (≥university)	0.01	0.22–0.79	0.42
LDL	0.10	0.98–1.00	-

Abbreviations: CI, confidence interval; OR, odds ratio; LDL, low-density protein

DISCUSSION

In our study, we compared the demographic characteristics and laboratory parameters of patients with and without postmenopausal osteoporosis to understand the causes of postmenopausal osteoporosis and to find a simple and cost-effective method that can help in its early diagnosis. There were no differences between the groups in terms of Htc, WBC count, NLR, serum CRP, and vitamin D levels. However, the serum LDL levels were significantly lower in the osteoporosis-positive group than in the osteoporosis-negative group. We demonstrated that high parity and low education levels are independent variables for postmenopausal osteoporosis and increase the risk of osteoporosis.

Osteoporosis is more common in postmenopausal women than in premenopausal women and men. This is primarily due to the decrease in estrogen levels after menopause, which results in decreased bone accumulation and increased bone resorption, especially in weight-bearing bones (11). However, it has been shown that the risk of osteoporosis increases more in the presence of other accompanying factors. Studies have reported that a low educational level is associated with an increased risk of osteoporosis (12). In our study, we also found an increased risk of osteoporosis with a similarly low level of education. It is known that physical activity and increased muscle mass protect against osteoporosis and possible osteoporotic fractures (13). Therefore, low education level has been associated with not engaging in sports activities. However, there are also studies stating that a high educational level is associated with a higher risk of osteoporosis. These studies have suggested that people with a higher level of education do not have sufficient time to exercise (14). In our society, since it has been observed that exercise status increases with increasing education level (15), we think that patients with lower education levels exercise less and, therefore, have a higher risk of osteoporosis.

The relationship between postmenopausal osteoporosis and BMI has been demonstrated in several studies. Low weight and BMI have been reported to increase the risk of osteoporosis (16,17). Bone strength is thought to be preserved in obese patients with a high BMI due to the protective effect of weight bearing on bone and estrogen secretion from fat tissue (18). In parallel, it has been concluded that the risk of osteoporosis is reduced in obese women with high serum LDL levels who are fed a high-fat diet (19). Similarly, in our study, we found that the risk of osteoporosis was higher in postmenopausal women with low weight, BMI, and LDL levels. However, some studies in mouse models have reported that low-grade systemic inflammation due to obesity induces bone loss (20,21). In addition, studies have reported that increased LDL levels support osteoclast formation and increase the risk of osteoporosis by causing increased bone destruction (22). Therefore, the relationship between BMI, LDL, and osteoporosis is still unclear and requires further research.

In our study, increased parity as an independent variable was associated with an increased risk of osteoporosis. However, the data on this issue in the literature are contradictory. Studies have reported that when maternal intestinal calcium absorption during pregnancy and lactation is not sufficient to meet the calcium requirement to support fetal skeletal development during pregnancy, the fetal system compensates by taking calcium from the mother's skeleton, which may increase the mother's long-term fracture risk by reducing bone mass (4). In contrast, other studies have reported that increased bone load and higher serum estrogen levels during pregnancy provide protection against maternal bone loss, and that the risk of osteoporosis and fractures decreases as parity increases (23). We believe that the effect of increased calcium requirement during pregnancy on maternal bone density is more effective than the protective effect of increased estrogen; therefore, the risk of osteoporosis increases with parity. In addition, we believe that the decrease in estrogen levels and continuation of calcium requirement during the lactation period after pregnancy also play an important role in increasing the risk of osteoporosis. When increasing parity is also considered to increase breastfeeding periods, the risk of osteoporosis may increase. However, a limitation of our study is that it was retrospective, and the required information of the patients (such as breastfeeding status) cannot be fully obtained.

The relationship between inflammatory markers and BMD has been investigated in previous studies, with conflicting results. As BMD has been shown to be negatively affected in chronic autoimmune diseases with systemic inflammation, the relationship between inflammatory markers and osteoporosis in postmenopausal women without comorbidities has been a matter of curiosity. Koh et al. investigated the relationship between baseline CRP levels and BMD in a study they conducted and demonstrated that high CRP levels were associated with an increased risk of osteoporosis in both premenopausal and postmenopausal women (7). In contrast, Berglundh et al. reported in their study on elderly women (75-80) that a single CRP measurement was not an indicator of low BMD, bone loss, or fracture; however, continuous CRP values ≥ 3 mg/L may be associated with bone loss (10). In addition, many authors have reported that NLR, another inflammatory marker, is closely associated with osteoporosis (24). Yılmaz et al. It has been stated that NLR can predict more than CRP values in postmenopausal women with osteoporosis (25). In addition, several studies have shown that elevated NLR is associated with poor prognosis in patients with osteoporosis (26, 27). Similarly, Lee et al. suggested that NLR is negatively associated with the mean lumbar BMD in postmenopausal patients with chorea. They reported that this is because inflammatory cytokines bind to stromal cells and activate osteoclast-mediated bone resorption by increasing the production of receptor activator of nuclear factor-kappa B (NF-$_{K}$B) ligand (RANKL) and macrophage colony-stimulating factor (28). In addition, a recent study observed that other inflammatory markers,

especially NLR, were negatively associated with BMD and positively associated with osteoporosis risk (29). However, we did not find a significant association between serum NLR and CRP values and BMD in our study. The NLR and CRP levels were not associated with osteoporosis in postmenopausal women. Our patients were women of the same age group, without any additional diseases, and were not very old. The absence of any additional conditions that could affect inflammatory markers is a strength of the present study.

In conclusion, we found that postmenopausal osteoporosis was not associated with serum inflammatory markers in our study. However, postmenopausal osteoporosis is closely associated with parity, education level, weight, and BMI. In particular, high parity and low education level were associated with a high risk of osteoporosis as independent factors.

Ethics Approval

For studies with human subjects include the following: All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2013. Ethics committee approval was obtained from the Clinical Research Ethics Committee No. 2 of our hospital (24-637). Informed consent was obtained from all patients for being included in the study.

Authors' Contributions

MİH: Conceptualization, Writing – original draft, Methodology, Data curation, Resources, EET: Formal analysis, Writing – review & editing. All authors read and approved the final manuscript.

Conflicts of Interest/Competing Interests

On behalf of all authors, the corresponding author states that there is no conflict of interest.

Funding Statement

None

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Jinekoloji - Obstetrik ve Neonatoloji Tıp Dergisi
The Journal of Gynecology-Obstetrics and Neonatology

ÖZGÜN ARAŞTIRMA / ORIGINAL ARTICLE

DOI: 10.38136/jgon.1566274

First trimester bleeding and pregnancy outcomes: A case-control study

İlk trimester kanaması ve gebelik sonuçları: Bir vaka-kontrol çalışması

Isa TEMUR[1], Enes KARAMAN[1]

[1]Niğde Ömer Halisdemir University Faculty of Medicine, Department of Obstetrics and Gynecology, Niğde, Turkey

ABSTRACT

Aim: The objective of this study is to perform a comprehensive assessment of fetal and perinatal results in pregnant women diagnosed with threatened miscarriage during the early trimester, and to evaluate the potential impact of this condition on the progression of pregnancy.

Materials and Methods: In this retrospective study, the study group consisted of 200 patients who were diagnosed with threatened miscarriage and gave birth, while the control group was composed of 200 patients who gave birth without experiencing threatened miscarriage during the same period. The following variables were evaluated: age, gravida, parity, gestational week, and body mass index, as well as fetal and maternal perinatal outcomes.

Results: The analysis of the delivery parameters revealed no statistically significant difference between the groups in terms of mode of delivery (p=1.000). The prevalence of preterm birth and preterm premature rupture of membranes (PPROM) was significantly higher in the case group compared to the control group ($p < 0.001$). No statistically significant difference was observed between the threatened miscarriage group and the control group in terms of the incidence of gestational diabetes, preeclampsia, placenta previa, abruptio placenta, macrosomia and stillbirth (p>0.05).

Conclusions: In pregnant women with threatened miscarriage, the risk of preterm birth and preterm premature rupture of membranes (PPROM) is significantly higher. This finding emphasizes the need for careful monitoring and management of these patients, particularly concerning complications such as preterm birth and PPROM.

Keywords: Threatened miscarriage, perinatal outcomes, preterm labor

ÖZ

Amaç: Bu çalışmanın amacı, erken trimesterde düşük tehdidi tanısı alan gebelerde fetal ve perinatal sonuçların kapsamlı bir değerlendirmesini yapmak ve bu durumun gebeliğin ilerlemesi üzerindeki potansiyel etkisini değerlendirmektir.

Gereç ve Yöntemler: Bu retrospektif çalışmada, çalışma grubu düşük tehdidi tanısı alan ve doğum yapan 200 hastadan oluşurken, kontrol grubu aynı dönemde düşük tehdidi yaşamadan doğum yapan 200 hastadan oluşmuştur. Yaş, gravida, parite, gebelik haftası ve vücut kitle indeksi gibi değişkenlerin yanı sıra fetal ve maternal perinatal sonuçlar da değerlendirilmiştir.

Bulgular: Doğum parametrelerinin analizi, doğum şekli açısından gruplar arasında istatistiksel olarak anlamlı bir fark olmadığını ortaya koymuştur (p=1,000). Erken doğum ve preterm erken membran rüptürü (PPROM) prevalansı vaka grubunda kontrol grubuna kıyasla anlamlı derecede yüksekti (p<0,001). Düşük tehdidi grubu ile kontrol grubu arasında gestasyonel diyabet, preeklampsi, plasenta previa, abruptio plasenta, makrozomi ve ölü doğum insidansı açısından istatistiksel olarak anlamlı bir fark gözlenmemiştir (p>0,05).

Sonuç: Düşük tehdidi olan hamile kadınlarda erken doğum ve preterm erken membran rüptürü (PPROM) riski önemli ölçüde daha yüksektir. Bu bulgu, özellikle erken doğum ve PPROM gibi komplikasyonlar açısından bu hastaların dikkatli bir şekilde izlenmesi ve yönetilmesi gerektiğini vurgulamaktadır.

Anahtar Kelimeler: Düşük tehdidi, perinatal sonuçlar, erken doğum

Cite as: Temur I, Karaman E. First trimester bleeding and pregnancy outcomes: A case-control study. Jinekoloji-Obstetrik ve Neonatoloji Tıp Dergisi 2024;21(4):340–344.

Geliş/Received: 13.10.2024 • **Kabul/Accepted:** 14.12.2024

Sorumlu Yazar/Corresponding Author: Isa TEMUR, Niğde Ömer Halisdemir Üniversitesi, Tıp Fakültesi, Kadın Hastalıkları ve Doğum Anabilim Dalı, Niğde, Türkiye
E-mail: t.isatemur@gmail.com

Çevrimiçi Erişim/Available online at: https://dergipark.org.tr/tr/pub/jgon

INTRODUCTION

In the first trimester of pregnancy, approximately 16-25 out of every 100 pregnant women may experience vaginal bleeding (1, 2). The four principal categories of non-traumatic bleeding in the early stages of pregnancy are ectopic pregnancy, miscarriage, fertilisation of the pregnancy and cervical pathology. These conditions vary in severity and require careful assessment to determine appropriate management. Physical and pelvic assessments should be conducted, and the use of imaging techniques should guide the diagnosis and treatment plan. These assessments are crucial for determining the underlying cause of bleeding and ensuring appropriate management for the patient. The diagnosis of imminent abortion is based on the observation of a closed cervix in conjunction with the presence of vaginal spotting in the early stage of pregnancy. This diagnosis is subsequently confirmed through the detection of fetal heart rate on ultrasound imaging (2,3). Approximately 50% of pregnancies diagnosed as abortus imminens result in pregnancy loss (4). Should the pregnancy persist, the probability of unfavourable maternal and foetal outcomes, including preterm labour, premature rupture of the membranes (PPROM), preeclampsia, placental abruption and intrauterine growth restriction (IUGR), is heightened (5-8). It has been demonstrated that maternal age (9,10), the presence of systemic diseases including diabetes mellitus and hypothyroidism, the necessity for infertility treatment (11), thrombophilia, maternal weight and uterine structural anomalies are factors that elevate the risk of threatened miscarriage. This study sought to investigate whether the threat of miscarriage increases the likelihood of pregnancies being classified as high risk in our clinic, to identify poor neonatal outcomes, and to determine which maternal characteristics influence these outcomes. The answer to these questions may influence our approach to prenatal and postnatal management.

MATERIAL AND METHOD

The study was conducted as a retrospective cross-sectional case-control investigation. The study was approved by the Non-Interventional Ethics Committee of the University of Niğde Ömer Halisdemir University Faculty of Medicine, with decision number 2022/109. The study included a total of 400 pregnant women with gestational ages ranging from 5 weeks to 14 weeks, who had applied to the obstetrics and gynaecology clinic of our hospital between January 2021 and January 2023.

Study Population

The study includes a total of 400 women who have given birth, with 200 of them diagnosed with threatened miscarriage, while the other 200 are women who have given birth without a threatened miscarriage diagnosis. Data on age, gravidity, parity, fetal birth weight, body mass index (BMI), placental pathologies (placenta previa, abruptio placenta), preeclampsia, gestational diabetes mellitus (GDM), macrosomic fetus, preterm birth, PPROM, stillbirth, and the need for neonatal intensive care after birth were collected for both groups.

Exclusion Criteria

During follow-up, patients who experienced either a complete miscarriage (where all pregnancy tissue is expelled from the uterus) or an incomplete miscarriage (where some pregnancy tissue remains in the uterus) were evaluated, along with those who had no fetal heartbeat detected on ultrasound (USG), systemic disease or multiple pregnancies were excluded. Patients who were initially included in the study but whose vaginal bleeding examination revealed cervical erosion and cervical polypoid formation were subsequently excluded. After excluding other causes of vaginal bleeding, pregnant women with vaginal bleeding and pelvic pain, no cervical dilatation, and ultrasonographic evidence of gestational sac or fetal heartbeat were included in the study. The clinical conditions experienced by the patients during and after the delivery, as well as the care needs of the newborns, were obtained from patient records. In our clinic, pregnancies resulting in delivery before 37th gestational week were defined as preterm delivery and babies born over 4 kg were defined as macrosomia. After 20 weeks of gestation, babies born without a heartbeat were considered stillbirth.

Statistical Analysis

Categorical variables were presented as frequency and percentage, while numerical variables were expressed as mean and standard deviation. Groups were compared using Student's t-test, Mann-Whitney U test, and chi-square test. A p-value of less than 0.05 was considered statistically significant.

RESULTS

The study encompassed a total of 400 cases, with 200 patients constituting the abortus imminens group and 200 patients forming the control group. In the abortus imminens group, mean age was 28.5±4.5 years, median gestational age at birth was 36 (32-41) weeks, and BMI was 28± 3.8 (Table.1).

154 (77%) patients were delivered vajinal and 46 (23%) patients were delivered by caesarean section (Table 2). A comparison of the groups revealed no statistically significant differences in terms of age, gravida, parity or BMI (p=0.213, p=0.168, p=0.512, p=0.112 respectively) (Table 1). The gestational week at termination of

Table 1. Distribution of patients' demographic data by group

	Threatened Abortion (n=200)	Control (n=200)	p-value
Maternal age (years, mean ± SD)	28,5±4,5	29,2±3,8	0,213
Gravida (mean ± SD)	2(1-3)	3(1-4)	0,168
Parity (mean ± SD)	2(0-3)	2(0-3)	0,512
Gestational age at birth (weeks median, min–max)	36(32-41)	39(32-41)	**0,001**
BMI (kg/m², mean ± SD)	28± 3,8	27,3±3,4	0,112
Birth weight (kg, median, min–max)	2867 (2000–4500)	3245 (2000–4500)	**0,001**

BMI: Body mass index
Data are given as mean±standard deviation and median (minimum-maximum).
There is a statistically significant difference of p<0.05.

Table 2. Comparison of Outcomes of Pregnancies in Control and Case Group

	Threatened Abortion (n = 200)	Control (n = 200)	p value
Gestational diabetes (n, %)	12 (%6.0)	10 (%5.0)	0.215
Preeclampsia (n, %)	5 (%2.5)	4 (%2.0)	1.000
Placenta previa (n, %)	9 (%4.5)	9 (%4.5)	1.000
Abruptio placentae (n, %)	7 (%3.5)	4 (%2.0)	0.152
Preterm premature rupture of membrane (n, %)	22 (%11.0)	8 (%4.0)	**0.001**
Caesarean (n, %)	46 (%23.0)	48 (%24.0)	1.000
Vajinal delivery (n, %)	154 (%77.0)	152 (%76.0)	1.000
Preterm birth (n, %)	28 (%14.0)	12 (%6.0)	**0.001**
Macrosomia (n, %)	7 (%3.5)	5 (%2.5)	0.246
Newborn intensive care unit (n, %)	36 (%18.0)	14 (%7.0)	**0.001**
Stillbirth (n, %)	2 (%1.0)	2 (%1.0)	1.000

n: Number; %: Percentage; There is a statistically significant difference of p<0.05.

pregnancy was found to be longer in the control group, with a statistically significant difference (p=0.001) (Table 1). The fetal weight was observed to be lower in the group experiencing a threatened miscarriage, and this difference was found to be statistically significant (p=0.001) (Table 1). The incidence of neonatal intensive care was markedly elevated in the cohort exhibiting threatened miscarriage (p=0.001) (Table 2).

There was no significant difference between the two groups in terms of delivery parameters, specifically mode of delivery (p=1.000 and p=1.000) (Table 2). In the study group, there were 22 (11%) cases of PPROM, while the control group had 8 (4%) cases (Table 2). The incidence of preterm premature rupture of membranes (PPROM) was higher in the group with a high risk of miscarriage, and this difference was statistically significant ($p < 0.001$) (Table 2). Regarding preterm birth frequency, 28 (14%) patients were in the study group, while 12 (6%) patients were in the control group. The rate of preterm birth was significantly higher in the threatened miscarriage group, and this difference was statistically significant ($p < 0.001$) (Table 2). Although the rates of gestational diabetes, preeclampsia, placenta previa, abruptio placenta, and macrosomia were higher in the abortus imminens group, no statistically significant difference was found. Stillbirth rates were similar between the two groups, with no statistically significant difference observed (p=1.000) (Table 2).

DISCUSSION

This study evaluated the effects of threatened miscarriage on pregnancy outcomes, and the findings indicate that such pregnancies are associated with a significantly increased risk of preterm complications. Our study found no association between the incidence of threatened miscarriage and maternal age. However, Basama et al. (12) indicated that vaginal bleeding is more frequently observed in early gestational weeks as maternal age advances, while Yakıştıran B et al. (13) reported that women with threatened abortion tend to have a higher maternal age. In our study, the average gestational age at delivery was 36 weeks in the threatened miscarriage group, compared to 39 weeks in the control group, a difference that was statistically significant ($p < 0.01$). Similarly, Agarwal S et al. (14) found that the average gestational age was significantly lower in cases (35.29 ± 3.48 weeks) than in the control group (38.11 ± 4.77 weeks) ($p = 0.0002$).

Given the correlation between miscarriage risk and preterm delivery found in previous studies, it is reasonable to hypothesize that pregnancies with miscarriage risk will have lower mean gestational age and birth weight compared to those without such risk (2, 6, 14, 15, 16, 17). In our study, the distribution of gravida and parity was found to be similar between the groups, aligning with the existing literature (18-20). First trimester bleeding is suggested as an indicator of underlying placental dysfunction potentially leading to adverse outcomes such as preterm delivery, PPROM, and placental abruption later in pregnancy (6). This association between early pregnancy hemorrhage and preterm labor has been confirmed by other researchers, including Ahmed et al. (21) and Amirkhani et al. (22), who demonstrated a significantly higher risk of preterm delivery in patients with bleeding. Conversely, Strobino et al. (23) found no correlation between threatened miscarriage and preterm labor. Despite this, our study observed an elevated risk of preterm delivery, consistent with the hypothesis that the disruption of the chorionic amniotic plane due to adjacent hemorrhage could increase membrane rupture susceptibility (6). Similarly, Agarwal et al. (14) and Rai et al. (24) reported a significantly increased risk of PPROM and preterm delivery in women experiencing early pregnancy bleeding. Saraswat et al. (2) also highlighted in their meta-analysis that the study group had a higher likelihood of PPROM and preterm labor, aligning with our findings.

Moreover, both preterm delivery and PPROM are associated with low birth weight, as seen in studies by Rai et al. (24) and Patel et al. (25). Our findings corroborate this, with lower fetal weight linked to preterm labor. Consequently, complications like respiratory distress have led to an increased admission of low birth weight neonates to the neonatal intensive care unit (NICU) (26). Consistent with studies on women diagnosed with abortus imminens, we observed that infants born from these pregnancies were more likely to require NICU admission, with this need being statistically significant ($p<0.05$).

Although some studies, such as those by Evrenos et al. indicate higher rates of gestational diabetes mellitus (GDM) in pregnancies with threatened abortion, our study found no significant difference in GDM incidence between the groups (1). Similarly, while Weiss et al. (6) suggested an elevated risk of preeclampsia in pregnancies at risk of miscarriage, our study, in line with Saraswat et al. (2) and Kanmaz AG et al. (27), showed no significant change in preeclampsia incidence.

Regarding mode of delivery, our study did not reveal an increase in cesarean section rates in pregnancies with miscarriage risk, consistent with findings by Saraswat L. et al. (2) and Davari-Tanha et al. (28). In terms of placental complications, such as placenta previa and placental abruption, our findings showed no statistically significant differences between the groups, aligning with some studies while contrasting with others like those of Johns et al. (29).

Furthermore, the incidence of macrosomia and stillbirths in pregnancies at risk of miscarriage was comparable to the control group. Although discrepancies exist in the literature regarding stillbirth frequency in such pregnancies, our findings support those studies identifying an increased need for NICU admission in cases of first trimester bleeding ($p<0.001$). Given the elevated prevalence of complications directly affecting the fetus, such as preterm birth and miscarriage, it is reasonable to anticipate higher NICU admission rates in pregnancies deemed at risk, as our study and others (2, 19) have shown.

Currently, definitive information is lacking about complications pregnant women may encounter later in gestation when experiencing a threatened miscarriage in the first trimester. Nonetheless, our study contributes valuable data to the existing literature, being one of the few single-center studies with a large sample size that compares pregnancy complications between women with and without miscarriage risk. Although the retrospective nature of our study is a limitation, rigorous patient selection criteria were employed to minimize bias.

CONCLUSIONS

Threatened abortion is an important condition in predicting poor obstetric outcomes in terms of both maternal and fetal outcomes. The incidence of preterm labor and PPROM has increased in the prognosis of abortus imminens cases. In clinical practice, pregnant women should be informed and closely monitored in the follow-up of abortus imminens cases.

Ethics Committee Approval
The study has been granted ethical approval by the non-interventional ethics committee of Nigde Omer Halisdemir University Faculty of Medicine, under decision number 2022/109.

Informed Consent
Informed consent forms were obtained from all participants in the study.

Author Contributions
Concept-IT; Design-IT, EK; Supervision-IT; Resources-IT, EK; Materials-IT; Data Collection and/or Processing-IT; Analysis and/or Interpretation-IT, EK; Literature Search-IT, EK; Writing Manuscript-IT, EK; Critical Review-IT, EK.

Declaration of Interests
The authors declare that there is no conflict of interest.

Funding
None

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Jinekoloji - Obstetrik ve Neonatoloji Tıp Dergisi
The Journal of Gynecology-Obstetrics and Neonatology

ÖZGÜN ARAŞTIRMA / ORIGINAL ARTICLE

DOI: 10.38136/jgon.1556762

The predictive role of inflammatory biomarkers based on first trimester complete blood count parameters for the risk of HELLP syndrome: A case-control study

HELLP sendromu riski için ilk trimester tam kan sayımı parametrelerine dayalı inflamatuar biyobelirteçlerin öngörücü rolü: Bir vaka-kontrol çalışması

Sadullah OZKAN[1], Fahri Burcin FİRATLİGİL[1], Dilara KURT[1], Ahmet KURT[1], Serap TOPKARA SUCU[1]
Sadun SUCU[1], Murat Levent DERELİ[1], Sevki CELEN[1]

[1]Division of Perinatology, Department of Obstetrics and Gynecology, Ankara Etlik City Hospital, Ankara, Turkey

ABSTRACT

Aim: To conclude the predictive role of inflammatory biomarkers based on first trimester complete blood count parameters for the risk of HELLP syndrome.

Materials and Methods: This case-control study was included 45 of 73 pregnant women with HELLP syndrome. Clinical data and laboratory results were retrieved by medical and hospital records. We compared the inflammatory biomarkers based on first trimester complete blood count parameters for the risk of HELLP syndrome.

Results: We recruited 45 cases (pregnant women with HELLP syndrome) and 45 controls (healthy pregnant women), matched for body mass index, gravidity, parity and gestational week. The lymphocyte, platelets - lymphocyte ratio, neutrophil - lymphocyte ratio and systemic inflammation index values were statistically significant between the groups in the first trimester blood test results. There was no significant difference in systemic inflammation response index and pan-immune inflammation value between groups in the first trimester blood test results.

Conclusions: The main problem with HELLP syndrome is that it does not occur all at once, but that there is a certain inflammatory process. We can relate this process to the inflammatory parameters in the first trimester. Although this study does not aim to use the inflammatory markers for the diagnosis and treatment of HELLP syndrome, inflammatory parameters can be a trigger for the development of HELLP syndrome. However, none of the investigated indices proved to be an effective predictor in the first trimester. Nevertheless, simple and non-invasive predictive indices can be valuable tools for the prediction and management of HELLP syndrome.

Keywords: HELLP syndrome; lymphocyte; platelet; pregnancy; systemic inflammation response index

ÖZ

Amaç: İlk trimester tam kan sayımı parametrelerine dayanan inflamatuar biyobelirteçlerin HELLP sendromu riski için öngörücü rolünü sonuçlandırmak.

Gereç ve Yöntemler: Bu vaka-kontrol çalışmasına HELLP sendromu olan 73 gebeden 45'i dahil edildi. Klinik veriler ve laboratuvar sonuçları tıbbi ve hastane kayıtlarından elde edildi. HELLP sendromu riski için ilk trimester tam kan sayımı parametrelerine dayanan inflamatuar biyobelirteçleri karşılaştırdık.

Bulgular: Vücut kitle indeksi, gravidite, parite ve gebelik haftası açısından eşleştirilmiş 45 vaka (HELLP sendromlu gebe kadınlar) ve 45 kontrol (sağlıklı gebe kadınlar) alındı. İlk trimester kan testi sonuçlarında lenfosit, trombosit - lenfosit oranı, nötrofil - lenfosit oranı ve sistemik inflamasyon indeksi değerleri gruplar arasında istatistiksel olarak anlamlıydı. İlk trimester kan testi sonuçlarında sistemik inflamasyon yanıt indeksi ve pan-immün inflamasyon değerinde gruplar arasında anlamlı bir fark yoktu.

Sonuçlar: HELLP sendromu ile ilgili temel sorun, bir anda ortaya çıkmaması, ancak belirli bir inflamatuar sürecin olmasıdır. Bu süreci ilk trimesterdeki inflamatuar parametrelerle ilişkilendirebiliriz. Bu çalışma HELLP sendromunun tanı ve tedavisi için inflamatuar belirteçleri kullanmayı amaçlamasa da, inflamatuar parametreler HELLP sendromunun gelişimi için tetikleyici olabilir. Bununla birlikte, incelenen indekslerin hiçbirinin ilk trimesterde etkili bir belirleyici olduğu kanıtlanmamıştır. Bununla birlikte, basit ve invazif olmayan öngörücü endeksler, HELLP sendromunun öngörülmesi ve yönetimi için değerli araçlar olabilir.

Anahtar Kelimeler: HELLP sendromu; lenfosit; trombosit; gebelik; sistemik inflamasyon yanıt indeksi

Cite as: Ozkan S, Firatligil FB, Kurt D, Kurt A, Topkara Sucu S, Sucu S et al. The predictive role of inflammatory biomarkers based on first trimester complete blood count parameters for the risk of HELLP syndrome: A case-control study. Jinekoloji-Obstetrik ve Neonatoloji Tıp Dergisi 2024;21(4):345–352.

Geliş/Received: 26.09.2023 • **Kabul/Accepted:** 07.12.2024

Sorumlu Yazar/Corresponding Author: Sadullah ÖZKAN, Ankara Etlik City Hospital, Division of Perinatology, Department of Obstetrics and Gynecology, Ankara, Turkey
E-mail: sadullahozkan@gmail.com

Çevrimiçi Erişim/Available online at: https://dergipark.org.tr/tr/pub/jgon

INTRODUCTION

HELLP syndrome with hemolysis -H-, elevated liver enzymes -EL- and low platelets -LP-, which is thought to be part of the pre-eclampsia spectrum, can occur in 0.5-0.9% of all pregnancies and in 10-20% of those with severe pre-eclampsia (1).

HELLP syndrome is a rare pregnancy-related condition that can be detected by simple blood and urine tests and is often associated with cerebral edema and multiple organ failure (2,3). The maternal and fetal mortality rate can reach 23.1% - 56.9% (4). As mentioned above, it is characterized by microangiopathic hemolysis, elevated liver enzymes and low platelet counts and is associated with severe clinical complications leading to maternal end-organ failure and even death (5). Patients often complain of abdominal pain, nausea and vomiting, which can worsen within a few hours (6). Patients may also have elevated blood pressure and proteinuria (6). The most feared complications of HELLP syndrome are cerebral hemorrhage and liver rupture (6).

Since the first description of HELLP syndrome in 1982, the diagnosis and treatment of this syndrome has been the subject of controversy. The difficulty with this syndrome is that there are no standardized diagnostic criteria and tests for prediction (5). In addition, HELLP syndrome is often difficult to distinguish from other pregnancy-related conditions and can lead to increased mortality. Although patients have elevated liver enzymes and low platelet, predictive tests with high sensitivity and specificity are currently being sought (5). The exact pathological mechanisms involved in the development of HELLP syndrome have never been fully elucidated. What is known is that there is widespread endothelial cell damage, particularly in the liver, leading to hemolysis, schistocytes and Burr cells and limited vascular involvement (7). In addition, activated platelets attach to damaged vascular endothelial cells, leading to platelet consumption (7). It is still controversial whether HELLP syndrome is a severe form of pre-eclampsia or a disease in its own right (8,9). The laboratory tests and clinical picture of pre-eclampsia and HELLP syndrome are different (6,8,9). In HELLP syndrome, the inflammatory reaction is more pronounced and mainly affects the liver and the coagulation system (8,9). However, the role and contribution of inflammation to neutrophil activation and endothelial dysfunction during the development of HELLP syndrome has been largely overlooked. One study found that the inflammatory marker neutrophil/lymphocyte ratio (NLR) was higher and platelet/lymphocyte ratio (PLR) was lower in women with HELLP syndrome (9). NLR and PLR have traditionally been used in various fields of medicine (10). Nowadays, however, it is becoming increasingly important to use a combination of these inflammatory markers (10-13).

In this study, the parameters of the complete blood count (CBC) in the 1st trimester in pregnant women with HELLP syndrome are evaluated, the Systemic Immune Inflammation Index (SII), the Systemic Inflammation Response Index (SIRI) and the Pan-Immune Inflammation Value (PIV) are calculated and it is investigated whether there is a correlation between these values and HELLP syndrome and whether they can be used to predict HELLP syndrome in early pregnancy.

MATERIAL AND METHODS

This case-control study was conducted retrospectively at the Obstetrics and Perinatology Clinics of an Education and Training Hospital between January 1, 2015 to January 1, 2022. This study was performed in accordance with the principles of the Helsinki Declaration, and it was approved by the local ethics committee (with the number: 05/29; April, 2022).

Inclusion and Exclusion Criteria

Singleton pregnancies with HELLP syndrome as study group and healthy singleton pregnancies with spontaneous labor as control group were included in the study.

Known maternal infections (acute or chronic), use of corticosteroids before the 20th week of pregnancy, hematologic diseases (idiopathic thrombocytopenic purpura, thrombotic thrombocytopenic purpura, hematologic malignancies, etc.), chronic systemic diseases that may alter CBC (lupus, renal or hepatic dysfunction, rheumatoid arthritis, asthma, etc.), pregnancies with known chromosomal abnormalities or congenital malformations were excluded from the study.

Data

The study required a sample of 45 pregnant women with HELLP syndrome for the study group and 45 healthy pregnant women for the control group. The study included a total of 90 pregnant women.

The data required for this study were obtained retrospectively from patient files and hospital records. For this purpose, data such as age, gravidity, parity, number of abortions, previous pregnancy history, body mass index, ultrasound findings, any concomitant diseases, information on previous operations, 1st trimester CBC parameters, routine biochemical findings, complete urinalysis, blood values on admission to the clinic (in third trimester), outcome of the current pregnancy and whether pregnancy complications occurred were used.

Study Design

Singleton pregnant women with HELLP syndrome who were cared for in the perinatology clinic and whose pregnancy ended in the

same clinic were included in the study group (Group I). Healthy singleton pregnant women with spontaneous labor who were cared for in the obstetric clinic and whose pregnancy ended in the same clinic were included in the control group (Group II). We planned to form the control group by randomization from pregnant women population who meet the exclusion criteria. We planned to perform the randomization in chronological order by including in the control group the pregnant women who were admitted to the hospital immediately after the patient from the study group was admitted to the hospital, were in the same week, and met the exclusion criteria.

We examined inflammatory biomarkers at the first trimester's routine CBC test (NEUT, PLT, MONO and LYM) of both groups to calculate SIRI (NEUT x MONO / LYM); SII (NEUT × PLT / LYM) and PIV (NEUT x PLT x MONO / LYM) (11-13). The SIRI, SII and PIV values of both groups were compared.

Laboratory analysis of blood samples and diagnosis of HELLP syndrome

The CBC parameters were analyzed with the Advia® 120 Hematology System (Siemens Healthcare Diagnostics Inc., Deerfield, Illinois) and the biochemical parameters with the Advia® 2400 Clinical Chemistry System (Siemens, Tarrytown, NY, USA). The diagnosis of HELLP syndrome was made on the basis of the criteria of the American College of Obstetricians and Gynecologists (14).

Statistical Analyses

The statistical analysis procedures were performed using Jamovi, an open statistical software, to analyze the data. The normal distribution of the variables was assessed using visual representations (histogram, probability plots) and analytical techniques (Kolmogrov-Simirnov/Shapiro-Wilk test). A Levene test was performed to assess the homogeneity of variance. The descriptive analysis included the presentation of mean values and standard deviations for variables that follow a normal distribution. A comparison of these factors between the groups was performed using a t-test for independent samples. Descriptive analysis for the non-normally distributed numerical data was performed using medians and quartiles (Q1-Q3). Comparisons of these factors between groups were performed using Mann-Whitney U-tests. Descriptive analysis for the categorical variables was performed using frequencies and percentages. Statistical analysis of relationships between categorical variables was performed using either the chi-square test or Fisher's exact test (in cases where the assumptions of the chi-square test are not applicable due to low expected cell counts). The capacity of various parameters that can be used to predict HELLP syndrome, were analyzed using ROC (Receiver Operating Characteristics) curve analysis. When a significant cut-off value was observed, the sensitivity, specificity, AUC (Area Under Curve) value, positive likelihood ratio and negative likelihood ratio were presented. ROC curves and areas under curve of these parameters were compared among themselves. A p-value below 0.05 was considered to indicate a statistically significant result.

RESULTS

In the present study, 45 of 73 pregnant women who were admitted to perinatology clinics with suspected HELLP syndrome between 2015 and 2022 and whose final diagnosis was HELLP syndrome formed the study group (Group I) and 45 pregnant women who were enrolled in the study according to the randomization system formed the control group (Group II) (Figure 1). There was no significant difference between the groups in terms of gravidity,

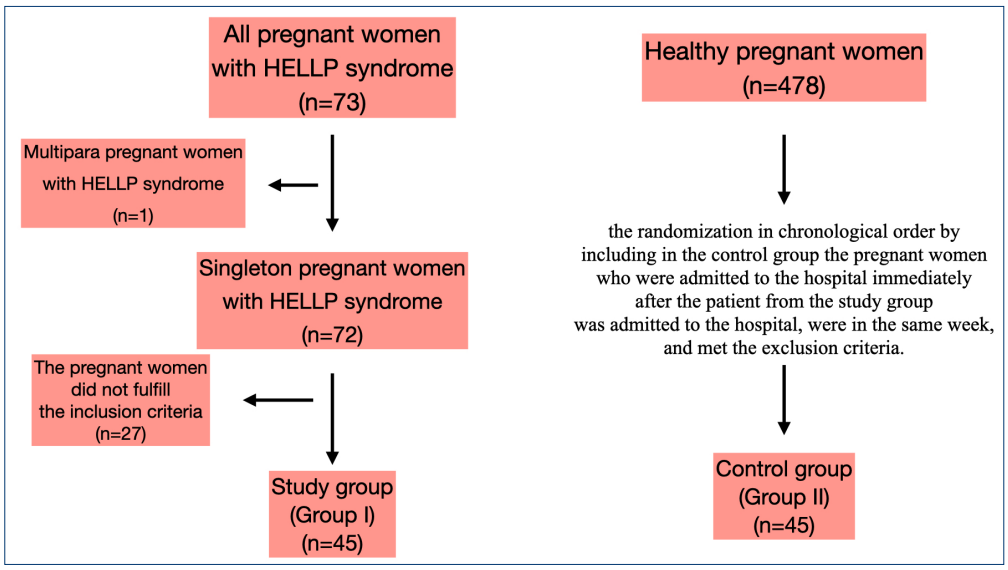

Figure 1. Flow-chart of the participants

parity, miscarriage and gestational week (admission to the clinic) (p> 0.05). Maternal age was higher in group I than in group II (p=0.001) (Table I).

The comparison of the inflammatory ratios and other blood parameters between the groups is shown in Table 2. The lymphocyte (LYM), platelets (PLT) - LYM ratio (PLR), neutrophil (NEUT) - LYM ratio (NLR) and SII values were statistically significant (p<0.05) between the groups in the first trimester blood test results. There was no significant difference in SIRI and PIV values between groups in the first trimester blood test results. These comparisons of all blood parameters between groups are shown in Table II.

NLR, PLR, SII and LYM have discriminatory properties for the prediction of HELLP syndrome in the ROC analysis of first trimester blood parameters and indices with statistical significance between

Table 1. Demographic and clinical characteristics of the study population

Variable	Group I (n=45)	Group II (n=45)	p
Age (years)	30 (27-34.5)	26 (24-29)	**0.001**
BMI (kg/m^2)	30 ± 4.3	29 ± 4.7	0.348
Gravidity (n)	2 (1-3)	2 (1-3)	0.475
Parity (n)	1 (0-1)	1 (0-2)	0.403
Miscarriage (n)	0 (0-0.5)	0 (0-1)	0.646
Gestational week (Admission to clinics)	33 (28-35)	32 (29-35)	0.891

BMI: body-mass index; n: numbers.
Data are expressed as median (Q1-Q3) and mean ± standard deviation.
A p value of <0.05 indicates a significant difference. Statistically significant p-values are in bold.

Table 2. Comparison of blood parameters, complete blood count-derived ratios between groups

Variable	Group I	Group II	p
First trimester blood parameters			
Neut (10^3/µL)	5.56 ± 2.16	5.51 ± 1.32	0.911
Lym (10^3/µL)	2.26 (1.62 - 2.50)	1.67 (1.33 - 2.26)	**0.044**
Mono (10^3/µL)	0.46 ± 0.16	0.44 ± 0.12	0.593
Plt (10^3/µL)	212.0 (165.5 - 295.2)	255.0 (218.5 -288.0)	0.137
WBC (10^9/L)	8.69 (6.68 -10.49)	8.11 (6.77 -9.18)	0.274
Hgb (g/dL)	12.9 (12 - 13.5)	12.5 (11.8 - 13.1)	0.208
NLR	2.46 (1.75 - 3.21)	3.18 (2.42 - 4.14)	**0.044**
PLR	111.9 (78.5 - 132.5)	142. 1 (114.9 - 181.9)	**0.007**
SII (10^3/µL)	543.29 (415.77 - 674.05)	757.62 (607.69 -106.46)	**0.002**
SIRI (10^3/µL)	1.15 (0.61 - 1.62)	1.25 (0.95 - 2.06)	0.308
PIV (10^6/µL2)	253.90 (129.41 - 392.63)	326.35 (230.38 - 446.80)	0.131
Third trimester blood parameters (blood values on admission to the clinic)			
Neut (10^3/µL)	10.02 (7.48 -14.23)	6.19 (5.42 - 6.79)	**<0.001**
Lym (10^3/µL)	1.50 (1.11 - 2.25)	1.63 (1.42 - 1.97)	0.351
Mono (10^3/µL)	0.45 (0.35 - 0.69)	0.51 (0.44 - 0.62)	0.142
Plt (10^3/µL)	92.0 (72.0 - 132.0)	222.0 (187.0 - 259.0)	**<0.001**
NLR	5.65 (3.27 - 11.78)	3.79 (2.84 - 4.39)	**<0.001**
PLR	61.54 (37.48 - 105.18)	128.75 (109.05 - 167.45)	**<0.001**
AST (U/L)	91 (53.50 - 191)	12 (8 - 15)	**<0.001**
ALT (U/L)	94 (30 - 150)	14 (11 - 17)	**<0.001**
SII (10^3/µL)	536.92 (285.23 - 123.95)	770.24 (610.42 - 102.92)	0.086
SIRI (10^3/µL)	2.82 (1.73 - 5.05)	1.84 (1.38 - 2.58)	**0.002**
PIV (10^6/µL2)	281.33 (140.83 - 639.19)	462.09 (271.81 - 560.56)	0.060

ALT: alanine transaminase; AST: aspartate aminotransferase; Hgb: hemoglobin; Hct: hematocrit; Lym: lymphocyte; MCV: mean corpuscular volume; Mono: monocyte; Neut: neutrophil; NLR, neutrophil-to-lymphocyte ratio; PIV: pan-immune inflammation score; Plt: platelet; PLR, platelet-to-lymphocyte ratio; SII: systemic immune inflammation index; SIRI: systemic inflammatory response index; WBC: white blood cell
Data are expressed as median (Q1-Q3) and mean mean ± standard deviation. A p value of <0.05 indicates a significant difference. Statistically significant p-values are in bold.

groups for the differential diagnosis in patients with suspected HELLP syndrome. The SII has the highest area under curve (AUC) value (AUC:0.720, cut-off: ≤ 676, p <0.001, sensitivity:78%, specificity:64%). The AUC values, the cut-off values, the CI 95%, sensitivity and the specificity of the statistically significant parameters are shown in Table III and Figure 2. The p-values showing the superiority of these parameters for use in the first trimester prediction of HELLP syndrome are shown in Table IV. None of the parameters listed in Table IV proved to be better than the other.

For the pregnant women in the study group whose blood values were analyzed in the first trimester, the changes in demographic or blood values, the changes in the parameters used to determine the risk of HELLP syndrome, and the data on the pregnant women's risk of developing HELLP syndrome are shown in Table V. Increases in LYM and PLR are considered protective factors, while increases in maternal age and NLR are considered risk factors. Each 1 year increase in maternal age increases the risk of HELLP syndrome by 1.1 times.

Table 3. ROC curve analysis for various parameters that can be used to predict HELLP syndrome

Variable	AUC	CI 95%	p	Cut-off value	Sensitivity (%)	Specificity (%)	+ LHR	- LHR
SII (103/µL)	0.642	0.598-0.822	**<0.01**	≤676	78	64	2.16	0.34
				≤512	40	90	1.85	0.46
NLR	0.642	0.517-0.755	**0.044**	≤2.87	71	61	3.37	0.78
				≤1.75	28	90	2.64	0.82
PLR	0.689	0.565 – 0.796	**0.005**	≤132.75	78	61	2.01	0.59
				≤91.2	38	90	4.50	0.36
LYM (103/µL)	0.632	0.517-0.755	**0.037**	>2.22	53	75	2.12	0.63
				>2.73	19	90	3.37	0.86

AUC: area under curve; CI: confidence interval; LHR: likelihood ratio; LYM: lymphocyte; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; SII, systemic immune-inflammatory index.
A p value of <0.05 indicates a significant difference. Statistically significant p-values are in bold.

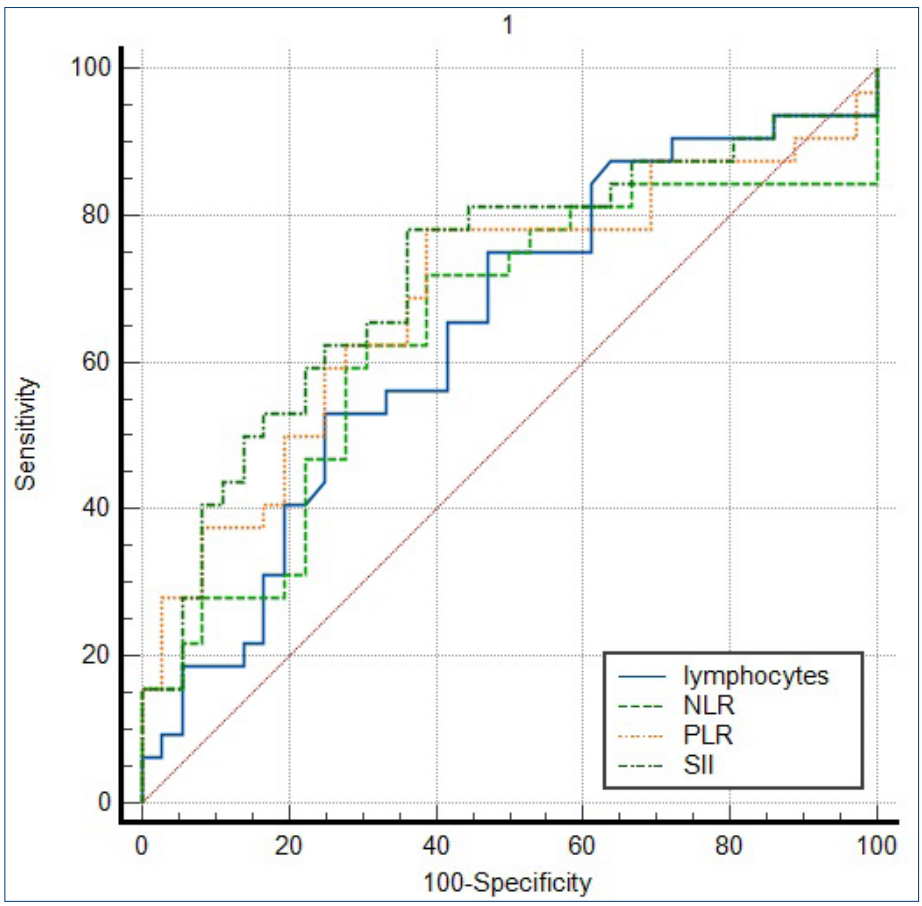

Figure 2. ROC curve for the variables

Table 4. ROC curve analysis for various parameters that can be used to predict HELLP syndrome

Variable	WBC	Neut	NLR	PLR	PLT	SIRI
WBC		0.952	**0.056**	0.827	**0.513**	**<0.001**
Neut	0.952		0.011	0.853	0.501	**<0.001**
NLR	**0.056**	**0.011**		0.285	**0.031**	0.201
PLR	0.827	0.853	**0.285**		0.141	0.083
PLT	0.513	0.501	**0.031**	**0.141**		**0.002**
SIRI	**<0.001**	**<0.001**	0.201	**0.083**	**0.002**	

NEUT: neutrophil; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; PLT: platelet; ROC: receiver operating characteristic; SIRI: systemic inflammatory response index; WBC: white blood cell.

Table 5. Regression models for HELLP syndrome

Variables	OR (95%CI)	p value
Age	1.10 (1.0 – 1.21)	**0.033**
LYM	1.00 (1.00 – 1.00)	0.095
NLR	0.80 (0.56 – 1.15)	0.230
PLR	0.99 (0.98 – 1.00)	**0.031**
PLR / 10	0.89 (0.79 – 0.99)	**0.031**
SII	1.00 (1.00 – 1.00)	0.140

CI: confidence interval; LYM: lymphocyte; NLR: neutrophil-to-lymphocyte ratio; OR: odds ratio; PLR: platelet-to-lymphocyte ratio; SII, systemic immune-inflammatory index. A p value of <0.05 indicates a significant difference. Statistically significant p-values are in bold.

DISCUSSION

The study investigated the inflammatory biomarkers and inflammatory ratios based on the first trimester CBC in the prediction of HELLP syndrome. According to the results, a higher maternal age and a higher NLR value from the first trimester to the week of delivery are considered risk factors for HELLP syndrome. Additionally, logistic regression analysis clearly showed that a decreased LYM level and a higher maternal age are independent risk factors for the development of HELLP syndrome.

The underlying pathophysiological mechanism of HELLP syndrome is not yet fully understood (15). However, it may be associated with conditions such as placental origin, autoimmunity, mutations in the coagulation factor V gene and fatty acid oxidation disorders (15). Following an unexplained spasm of the small blood vessels of the maternal system, the red blood cells are compressed and ruptured as they travel through these vessels, resulting in hemolysis (16); hypoxia and tissue ischemia due to vasospasm and hemolysis result in damage to major organs, liver enzymes are released after liver injury, leading to an increase in liver enzymes (15,17); exposure to collagen tissue after endothelial cell injury leads to platelet activation, aggregation and excessive consumption, which in turn leads to a decrease in PLT count (18). Also, it is already known that the pathophysiological changes of HELLP syndrome in the maternal body are particularly similar to those of severe pre-eclampsia (15,16,19). Some studies have shown that inflammation is one of the causes of the pathophysiological changes underlying HELLP syndrome. In a study that demonstrated the relationship between inflammation and HELLP syndrome, it was assumed that the development of HELLP syndrome is associated with an even stronger endovascular inflammatory reaction than in pre-eclampsia (20). In another study, in the context of HELLP syndrome and the inflammatory process, it was found that the expression of ''for cluster of differentiation" (CD) markers on polymorphonuclear leukocytes (PML) leads to a change that resembles the inflammatory response and that the up-regulation of CD11b to bind to PLT Factor 4 leads to the formation of PLT-PML complexes (21). These aggregates lead to an increase in thrombotic microangiopathies with further tissue damage and thrombocytopenia (21). This reciprocal effect of platelets and leukocytes has been shown to play an important role in HELLP syndrome (21). However, the technical challenges associated with the use of these antigens and their high cost limit their widespread use in practice. Therefore, a clinically useful and cost-effective predictive test is needed to identify individuals at risk for HELLP syndrome. First trimester prediction of HELLP syndrome has already been established based on maternal characteristics, ultrasound findings and biochemical markers [pregnancy-associated protein-A (PAPP-A), free β-human chorionic gonadotropin, and placental growth factor (PLGF)] (1). In English-language medical research, SII, SIRI and PIV together have

not yet been studied as inflammatory biochemical markers for the prediction of HELLP syndrome.

There are some studies that use inflammatory markers on outcomes of pregnancies with maternal systemic diseases (22,23) and also some studies that use inflammatory markers or aspartate aminotransferase to PLT ratio index (APRI) score to predict HELLP syndrome (24,25). Sahin et al (22) investigated inflammatory markers in the prediction of composite adverse outcomes in pregnant women with systemic lupus erythematosus (SLE). They showed that SII, SIRI, and NLR may be used to predict adverse pregnancy outcomes in pregnant women with SLE (22). Another study by Sahin et al (23) SII, SIRI, and NLR may be used to predict adverse pregnancy outcomes in pregnant women with Familial Mediterranean fever. Ipek et al (24) investigated the predictive role of some inflammatory markers for the risk of HELLP syndrome. The study showed that none of the investigated indices was found effective in the first trimester in the prediction (24). Tolunay et al (25) investigated the efficiency of the APRI score in predicting HELLP syndrome in the first trimester. The study concluded that there is a correlation between APRI levels in the first trimester and the prediction of HELLP syndrome, which can develop in the later weeks of pregnancy (25).

In the present study, we evaluate the predictive role of inflammatory biomarkers based on first trimester CBC parameters for the risk of HELLP syndrome. The results of the present study show that an increase in LYM and PLR is considered a protective factor, whereas an increase in maternal age and NLR is considered a risk factor. For every 1-year increase in maternal age, the risk of HELLP syndrome increases 1.1-fold. However, when we analyzed the results in detail, we found that the most important determining factor for the HELLP syndrome was the number of LYM (which is the main component in all inflammatory ratios). This was because the number of LYMs decreased dramatically in pregnant women who developed HELLP syndrome.

In conclusion, the main problem with HELLP syndrome is that it does not occur all at once, but that there is a certain inflammatory process. We can relate this process to the inflammatory parameters in the first trimester. Although this study does not aim to use the inflammatory markers for the diagnosis and treatment of HELLP syndrome, inflammatory parameters can be a trigger for the development of HELLP syndrome. However, none of the investigated indices (SIRI, PIV and SII) proved to be an effective predictor in the first trimester. Nevertheless, simple and non-invasive predictive indices can be valuable tools for the prediction and management of HELLP syndrome. We believe that randomized, controlled and multicenter studies are needed for this purpose.

The strengths and limitations

The study was conducted in a large tertiary referral center where the same algorithms and treatment modalities were used for HELLP syndrome is the strength of the study. But the study had a retrospective design, so it has some limitations due to its nature. This is because we were missing some of the participants' data/information. The lack of a power analysis is also an inherent limitation of the study.

Ethics Committee Approval

This study was performed in accordance with the principles of the Helsinki Declaration, and it was approved by the local ethics committee (with the number: 05/29; April, 2022).

Competing interests

The authors declare that they have no competing interests.

Funding Statement

There is no financial disclosure to be made for this study.

Acknowledgments

We are grateful to all participants and their families who spent their precious time and participated in this research program. We are also thankful for the tireless efforts of the research team members

Authors' contributions

Conceptualization, S.O., F.B.F and S.S.; methodology, S.O., F.B.F, Y.A.R, and S.T.S.; software, D.K. and A.K.; validation, S.O., S.S. and Y.A.R; formal analysis, S.S. and S.T.S.; investigation, S.O., F.B.F. and M.L.D.; resources, A.K.; data curation, D.K. and A.K.; writing—original draft preparation, F.B.F. and S.O.; writing—review and editing, S.S. and S.C.; visualization, S.O., S.C., M.L.D. and Y.U-E.; supervision, Y.E-U.; project administration, S.O. and Y.E-U. All authors have read and agreed to the published version of the manuscript.

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Jinekoloji - Obstetrik ve Neonatoloji Tıp Dergisi
The Journal of Gynecology-Obstetrics and Neonatology

ÖZGÜN ARAŞTIRMA / ORIGINAL ARTICLE

DOI: 10.38136/jgon.1597630

Rare fetal tumors

Nadir fetal tümörler

Ümit TAŞDEMİR[1], Ömer Gökhan EYİSOY[1], Murad GEZER[1], Ayşenur CELAYİR[2], Mucize ERİÇ ÖZDEMİR[1], Oya DEMİRCİ[1]

[1]Department of Obstetrics, Division of Perinatology, Zeynep Kamil Kadın ve Çocuk Hastalıkları Eğitim ve Araştırma Hastanesi, Istanbul, Turkey
[2]Department of Pediatric Surgery, Zeynep Kamil Kadın ve Çocuk Hastalıkları Eğitim ve Araştırma Hastanesi, Istanbul, Turkey

ABSTRACT

Aim: Congenital tumors in fetuses are exceedingly uncommon. The majority of these tumors will be primarily addressed through intrauterine surveillance. They may occur without any clinical symptoms or could lead to serious complications, such as hydrops. Recent progress in prenatal genetic diagnostics and imaging techniques has significantly enhanced the ability to detect fetal tumors and congenital anomalies.

Materials and Methods: A retrospective case series was conducted at a tertiary referral center over a ten-year period, from January 1, 2014, to January 1, 2024, on confirmed cases of fetal tumors identified within our perinatology center. Patients suspected of having fetal tumors underwent biweekly ultrasonographic assessments to monitor critical parameters. Relatively more common cases of fetal tumors (lymphangioma and sacrococcygeal teratoma) were not included in the study.

Results: A total of 16 cases of various type of fetal tumors from different origins were identified. Associated anomalies were identified in three cases, including two cases of epignathus and the case of glioblastoma multiforme. Fetal growth restriction, fetal anemia and amniotic fluid abnormalities were not detected in any of the cases during prenatal monitoring. Hydrops occurred only in one case involving an intrapericardial teratoma. Eleven cases managed to reached delivery and four of them required surgery. Malignancy was detected in 2 cases after surgical intervention

Conclusion: Ultrasonography is the first step imaging method for evaluation of the fetal tumors. However, it is not always easy to determine the location and histology diagnosis of the mass by ultrasonography.

Keywords: Fetal tumor,rare tumor, prenatal diagnosis, ultrasonography

ÖZ

Amaç: Fetüslerde konjenital tümörler son derece nadirdir. Bu tümörlerin büyük çoğunluğuna prenatal dönemde tanı koyulabilmektedir. Bazen herhangi bir klinik bulgu oluşturmazken, bazen de hidrops gibi ciddi komplikasyonlara yol açabilirler. Prenatal genetik tanı ve görüntüleme tekniklerindeki son gelişmeler, fetal tümörleri ve konjenital anomalileri tespit etme becerisini önemli ölçüde artırmıştır.

Gereç ve Yöntemler: Bu retrospektif çalışmada 1 Ocak 2014 ve 1 Ocak 2024 tarihleri arasında üçüncü basamak bir hastanede tanısı doğrulanmış fetal tümör vakaları değerlendirilmiştir. Fetal tümör olduğundan şüphelenilen hastalar kritik parametreleri değerlendirmek için iki haftada bir ultrasonografik değerlendirmeye tabi tutulmuştur. Nispeten daha sık görülen fetal tümör vakaları (lenfanjiom ve sakrokoksigeal teratom) çalışmaya dahil edilmemiştir.

Bulgular: Farklı kökenlerden gelen çeşitli tiplerde toplam 16 fetal tümör vakası tespit edilmiştir. İki epignathus ve bir glioblastoma multiforme vakası olmak üzere üç vakada ek anomaliler gözlenmiştir. Prenatal takip sırasında hiçbir vakada fetal büyüme kısıtlılığı, fetal anemi ve amniyotik sıvı anormallikleri tespit edilmemiştir. Sadece intraperikardiyal teratom içeren bir olguda hidrops meydana gelmiştir. On bir olgu doğuma ulaşmayı başarırken, dördüne cerrahi müdahale uygulandı. Cerrahi müdahale sonrasında 2 olguda malignite tespit edildi

Sonuç: Ultrasonografi fetal tümörlerin değerlendirilmesinde ilk basamak görüntüleme yöntemidir. Ancak ultrasonografi ile kitlenin yerini ve histolojik tanısını belirlemek her zaman mümkün değildir.

Anahtar Kelimeler: Fetal tümör, nadir tümör, prenatal tanı, ultrasonografi

Cite as: Taşdemir Ü, Eyisoy ÖG, Gezer M, Celayir A, Eriç Özdemir M, Demirci O. Rare fetal tumors. Jinekoloji-Obstetrik ve Neonatoloji Tıp Dergisi 2024;21(4):353–358.

Geliş/Received: 06.12.2024 • **Kabul/Accepted:** 19.12.2024

Sorumlu Yazar/Corresponding Author: Ümit TAŞDEMIR, Üsküdar Opr. Dr. Burhanettin Üstünel Cad. No:10, İstanbul, Türkiye
E-mail: drumittasdemir@gmail.com

Çevrimiçi Erişim/Available online at: https://dergipark.org.tr/tr/pub/jgon

INTRODUCTION

Congenital tumors in fetuses are exceedingly uncommon. These tumors typically consist of embryonal or fetal tissues that arise due to inadequate cytodifferentiation or maturation during the stages of embryonic or fetal development. Malignant tumors are rarely observed in neonates and are infrequently associated with neonatal mortality or morbidity (1).

Most of these tumors will be managed primarily through intrauterine monitoring; however, if fetal hydrops occurs as a result of particular tumors or their specific locations, in-utero therapy or specialized delivery methods may be necessary to improve neonatal care (2).

Recent advancements in prenatal genetic diagnosis, along with improvements in prenatal imaging and the assessment of fetal anomalies, have significantly enhanced the ability to prepare families for counseling. These developments have also revealed new horizons for considering prenatal interventions for congenital defects that could lead to fatal outcomes, including fetal tumors (3). Developments in fetal therapy and surgical techniques, particularly those involving minimally invasive methods, have not only facilitated the survival of uncommon tumor cases but have also enhanced long-term prognoses.

Due to the rarity of fetal tumors, most literature reports are based on experiences involving only a limited number of cases.The aim of current study to evaluate clinical characteristics and outcomes of the rare fetal tumors.

MATERIALS AND METHODS

A retrospective case series was conducted at a tertiary referral center over a ten-year period, from January 1, 2014, to January 1, 2024, focusing on confirmed cases of fetal tumors identified within our perinatology center. We systematically examined the ultrasound database alongside prenatal genetic counseling records for cases that were diagnosed with fetal tumors. Relatively more common cases of fetal tumors (lymphangioma and sacrococcygeal teratoma) were not included in the study.

Patients suspected of having fetal tumors underwent biweekly ultrasonographic assessments to monitor critical parameters including amniotic fluid index, fetal growth restriction, fetal anemia, ascites, and any associated anomalies. The volume of amniotic fluid was assessed using the amniotic fluid index, with values <50 mm indicating oligohydramnios and values > 250 mm indicating polyhydramnios. Fetal growth restriction (FGR) was identified when the abdominal circumference is below the 3rd percentile in biometric assessments. The diagnosis of fetal anemia was established when the peak systolic velocity in the middle cerebral artery is ≥1.5 multiples of the median (MoM).

All cases were followed-up in an outpatient setting. There was no established maximum gestational age regarding the timing of delivery. In cases which the fetal prognosis is unfavorable, it is advised to consider termination following a thorough discussion with the family. The method of delivery was decided by the clinicians according to the labor's progression.

All cases received genetic counseling, and fetal karyotyping was suggested. For those patients who did not will to have genetic diagnostic tests, chromosome analysis was performed in the postnatal period, in conjunction with the routine heel prick blood test. In all cases, the definitive diagnosis of fetal tumors was validated through the pediatric surgery team (in cases that require surgery), autopsy (in terminated cases), or further imaging methods (Ultrasonography, CT, and MRI). The most recent data concerning the cases was gathered through evaluations conducted by pediatricians and pediatric surgeons, along with direct conversations with the parents involved.

All examinations were performed by expert specialists in maternal-fetal medicine utilizing a 5 MHz convex transducer and a 9 MHz transvaginal transducer (VOLUSON E6, GE). Descriptive data are presented as median/range, mean±SD or numbers and %. Statistical analyses were carried out using the Statistical Package for the Social Sciences Version 26.0 (SPSS, IBM, Chicago, IL, USA). The study protocol received approval from the local ethics committee (Date 09/10/2024 No:69).

RESULTS

From 2014 to 2024, a total of 16 cases of various type of fetal tumors from different origins were followed-up in our maternal-fetal medicine center, all of which were confirmed through postnatal period by surgery or further imaging methods in living cases and by autopsy in terminated cases. The median age of the cohort was 28 (range 20-41) years old and the median gestational age for the first admission was 24.5 (range 13-39) weeks. Demographic, clinical characteristics and perinatal outcomes of the study group were summarized in Table 1. The most common reason for referral to our center was abdominal mass with six cases (37.5 %).

Associated anomalies were identified in three cases, including two cases of epignathus and the case of glioblastoma multiforme (GBM). One case of epignathus was associated with bilateral cleft lip-palate and micrognatia, while the other was associated with hydrocephalus, hypertelorism and diaphragmatic hernia. A double aortic arch was identified in the case of GBM. Fetal

growth restriction, fetal anemia and amniotic fluid abnormalities (polyhydramnios or oligohydramnios) were not detected in any of the cases during prenatal monitoring. Hydrops occurred only in one case involving an intrapericardial teratoma.

Table 1. Demographic, clinical characteristics and perinatal outcomes of the study group

Age, years (median/range)	28 (20-41)
Parity (median/range)	1.5 (1-5)
Consanguineous marriage (n,%)	1 (6.3)
GA at prenatal diagnosis, weeks (median/range)	27 (17-39)
Reason for referral	
Abdominal mass	6 (37.5)
Hydrocephaly	3 (18.8)
Cranial mass	2 (12.5)
Cardiac anomaly	2 (12.5)
Neck mass	1 (6.3)
Vertebral mass	1 (6.3)
Multiple anomaly	1 (6.3)
Associated anomalies (n,%)	3 (18.8)
Karyotype result	
Normal (n,%)	13 (81.3)
Unknown (n,%)	3 (18.8)
Perinatal outcomes	
Termination	5 (31.3)
Delivery	11 (68.7)
Mode of delivery	
Vaginal (n,%)	6 (37.5)
Cesarean (n,%)	5 (31.3)
GA at delivery, weeks (median/range)	38 (33-40)
Birthweight, gram (mean±SD)	3012 ±644
Postnatal surgery (n,%)	4 (25)

GA: gestational age

All cases underwent genetic counseling and were presented with the opportunity for genetic diagnostic testing; nonetheless, prenatal genetic analysis was performed in only two cases via amniocentesis. In three cases that resulted in termination, genetic analysis was not carried out, while postnatal karyotype analysis in the remaining cases indicated normal findings (Table 1).

Types of tumors and locations, prenatal diagnosis and prenatal-postnatal outcomes were summarized in Table 2. Postnatal diagnoses and number of cases are as follows: 2 choroid plexus papilloma, 1 GBM, 1 immature teratoma, 2 epignathus, 1 neck hemangioma, 1 abdominal hemangioma, 3 unidentified adrenal mass, 2 liver hemangioma, 2 intrapericardial teratoma and 1 soft tissue infantile fibrosarcoma. Eleven cases managed to reached delivery and four of them required surgery. Malignancy was detected in 2 cases after surgical intervention, leading these patients to receive advanced treatment options. In 3 out of 5 cases where neuroblastoma was suspected prenatally, adrenal masses were detected during the postnatal assessment. Nevertheless, a definitive diagnosis was still difficult to achieve, despite the use of advanced imaging methods (Ulrasonography, CT, MRI) and the analysis of particular tumor markers. A retroperitoneal hemangioma and liver hemangioma were other definitive diagnoses in remaining two cases. GBM and choroid plexus papilloma were found postnatally in 2 cases who were followed up with a prenatal prediagnosis of cranial hemorrhage. In remaining cases although a definitive diagnosis could not be made in the prenatal period, the fetal tumor and its characteristics were correctly identified.

Table 2. Types of tumors and locations, prenatal diagnosis and prenatal-postnatal outcomes

Location and tumor types	No (%)	Prenatal diagnosis (n)	Termination (weeks)	Operation	Current status
Kranium					
CPP	2 (12.5)	Hemorrhage (1) CPP (1)	+ (34) -	- +	- Intraoperative exitus at 3 months
GBM	1 (6.3)	Hemorrhage	-	+	Living after CT and RT
Immature teratoma	1 (6.3)	Solid tm	+ (26)	-	
Epignatus	2 (12.5)	Epignatus Epignatus	+ (18) -	- -	- Exitus at 11 days
Neck					
Hemangioma	1 (6.3)	Hemangioma	+ (25)	-	-
Abdomen					
Hemangioma	1 (6.3)	Neuroblastoma	-	+	Living
Adrenal mass (unidentified)	3 (18.8)	Neuroblastoma (3)	-	-	Living
Liver hemangioma	2 (12.5)	Neuroblastoma (1) Liver hemangioma (1)	- -	- -	Living Living
Heart					
Teratoma	2 (12.5)	Mesenchymal tm (1) Teratoma (1)	+ (27) -	- -	- Living
Soft tissue					
Infantile fibrosarcoma	1 (6.3)	Soft tissue tm	-	+	Living after KT

CPP: choroid plexus papilloma; CT: chemotherapy; GBM: glioblastome multiforme; RT: radiotherapy; tm: tumor

DISCUSSION

Fetal tumors are uncommon (4). However, the extensive application of contemporary ultrasound methods has led to a greater identification of these tumors during prenatal examinations. Although certain neoplasms can emerge in the early stages of pregnancy, most typically manifest later in the gestational period.

Fetal tumors frequently occur in the abdominal region, making it one of the most prevalent locations (5). In our study it was the most common site with 6 cases (37.5 %). Of these cases, it becomes evident that they are predominantly located in and around the adrenal gland, leading us to suspect the presence of an adrenal mass. One of the masses initially presumed to be located in the adrenal gland was actually identified in the retroperitoneal space, while another was discovered in the liver (Figure 1). Our primary challenge in abdominal tumors was in pinpointing the mass's location rather than diagnosing it. The findings indicate that rare tumors originating from uncommon sources were often misdiagnosed (5). Therefore it suggests that, alongside ultrasound, more sophisticated diagnostic techniques may be required for accurate diagnose of intraabdominal tumors. Despite the diagnostic difficulties, it should be noted that cases with adrenal masses and hemangiomas of the liver are followed up in the postnatal period without any intervention. It is important to acknowledge that, based on the diagnosis and results concerning, the abdominal tumors observed in the study group had benign nature, and had favorable prognosis for all cases.

Choroid plexus tumors are papillary neoplasms originate from neuroectodermal tissue, specifically developing from the choroid plexus epithelium located within the cerebral ventricles (6). The rarity of these tumors, along with their similarity to more common intracranial diseases such as hemorrhage, infection,

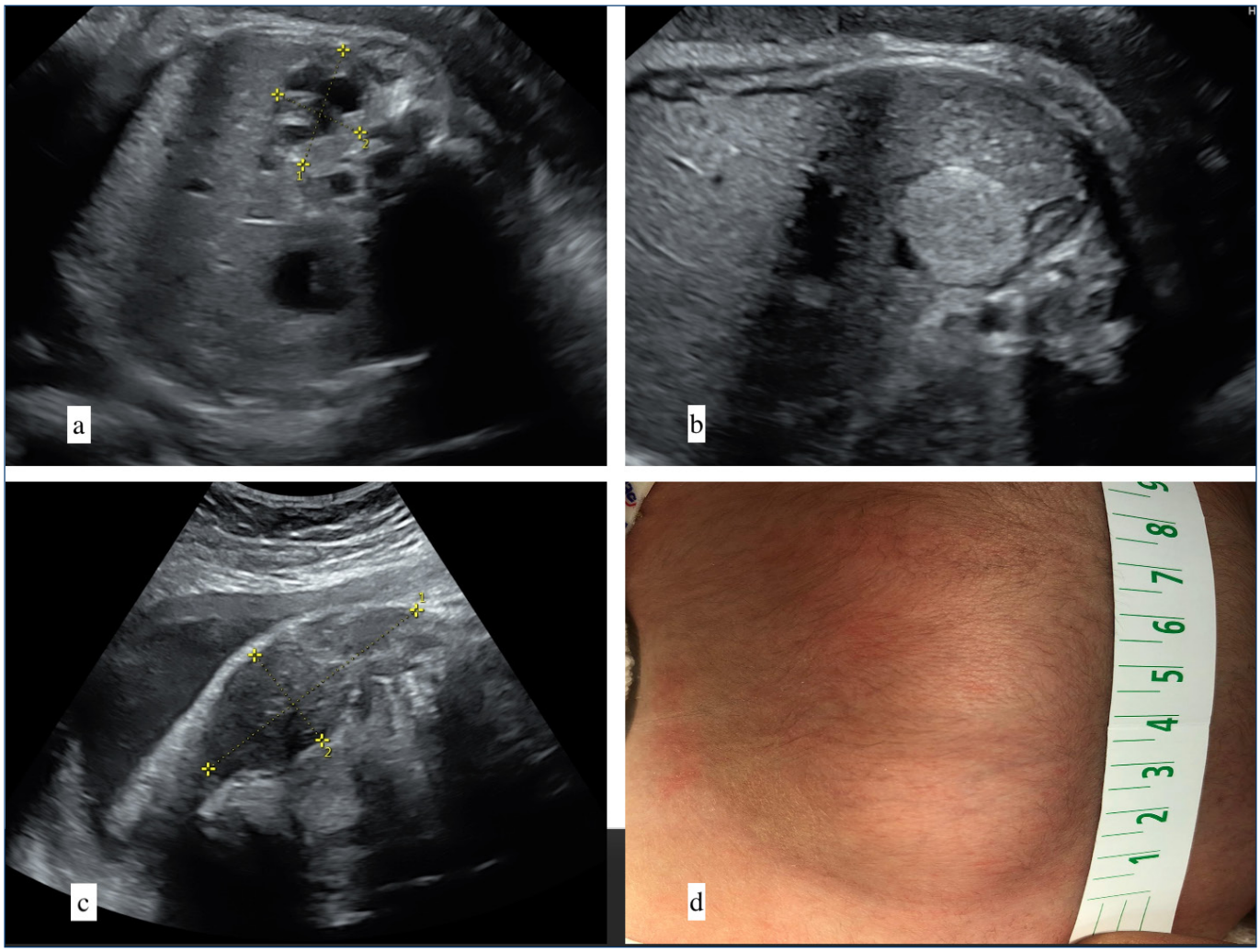

Figure 1. a) Heterogenous mass with solid and cystic areas in right upper quadrant at 38 weeks of gestation. The mass was confirmed to be located in the adrenal gland postnatally, but the diagnosis is unclear, **b)** Solid homogenous mass in right upper quadrant at 35 weeks. Prenatal diagnosis was neuroblastoma. A liver hemangioma was diagnosed postnatally, **c)** Soft tissue mass in right lower back at 33 weeks, **d)** Postnatal appearance of the mass. Surgery confirmed malign infantil fibrosarcoma.

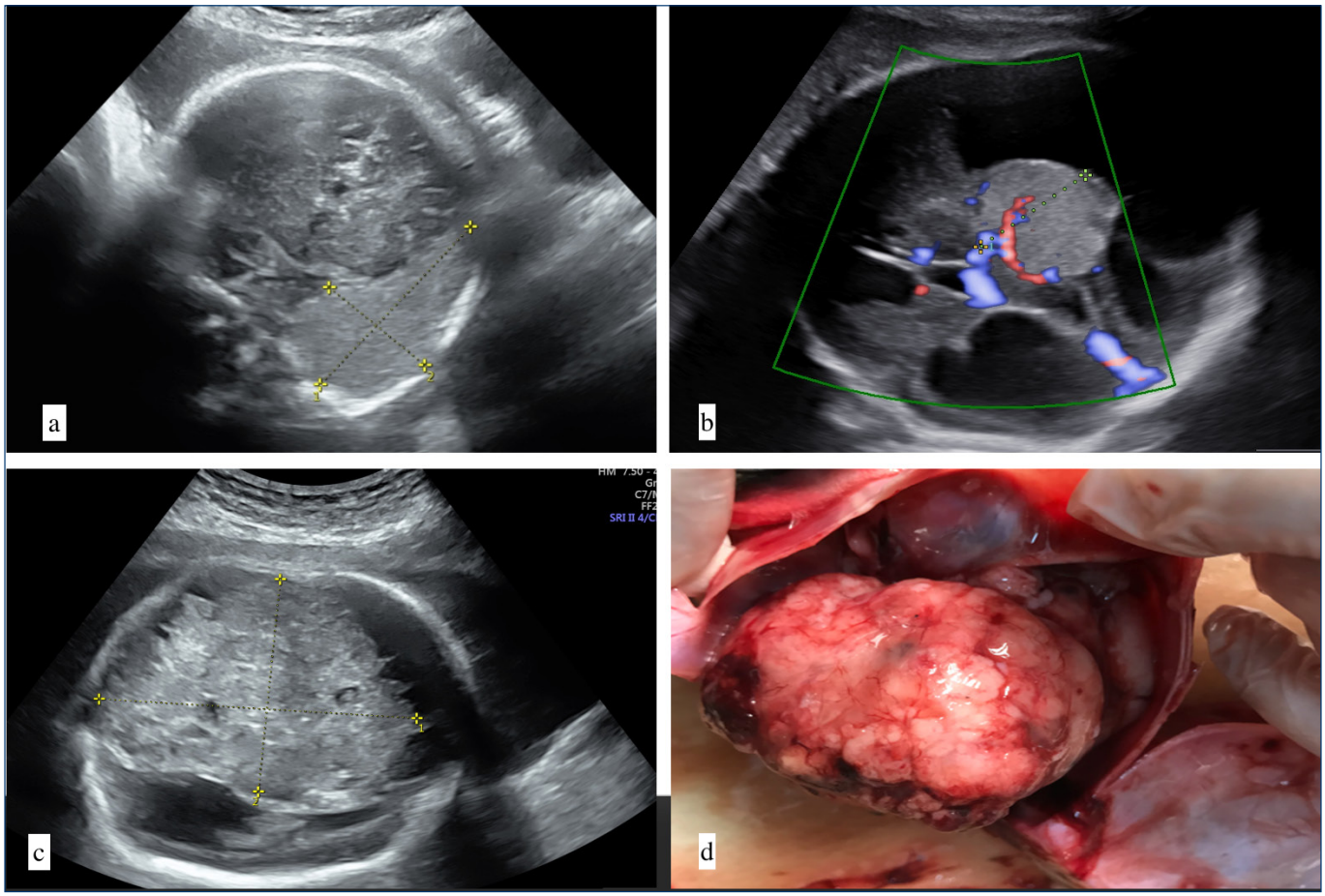

Figure 2. a) Coronal section of cranium at 36 weeks of gestation. Homogeneous mass mimicking haemorrhage. Postnatal surgery confirmed the diagnosis of glioblastoma multiforme, **b)** Choroid plexus papilloma at 32 weeks. Homogeneous hyperechogenic mass with significant blood supply, **c)** Transverse section of cranium at 25 weeks. Heterogenous solid mass occupying almost whole cranium with echogenic areas within, **d)** Macroscopic appearance of immature teratoma in the same case during fetal autopsy.

and hydrocephalus due to congenital anomalies, may result being misdiagnosed (7). In the study group, two cases of choroid plexus papilloma were identified (Figure 2); however, a prenatal diagnosis was successfully established in one case. The other case was initially diagnosed as intracranial hemorrhage.

As choroid plexus tumors, various other solid intracranial masses, can be misinterpreted as intracranial hemorrhage (8). Necrotic and hemorrhagic areas within the tumor may create a heterogeneous appearance similar to hemorrhage. One case in our study with postnatal diagnosis of GBM, was misinterpreted as intracranial hemorrhage due to morphological changes seen in the growing tumor during pregnancy (Figure 2). Intracranial teratomas are more clearly delineated via ultrasound imaging due to their solid tumor characteristics and echogenic structure (9). The case of intracranial teratoma in our study had an echogenic solid mass that almost completely filled the cranium and the pregnancy was terminated due to poor prognosis (Figure 2). Epignathus in two cases was identified as a part of multiple anomalies. Prenatal ultrasonography revealed protruding echogenic oral mass that is very spesific to an epignathus case like previously reported (10).

Fetal intrapericardial teratomas are very rare and in benign nature. However, due to their specific location, they can be fatal for the fetus, causing severe pleural effusion, cardiac tamponade and eventually fetal hydrops (11) . A case within the study group was terminated at 27 weeks of gestation as a result of significant compression of the left ventricular outflow tract, which led to the development of fetal hydrops. In the other case, a cystic mass that exerted slight pressure on the right ventricular outlet, which progressively diminished during the postnatal follow-up. Nevertheless, given that there have been no reported cases of regressing intrapericardial teratoma in the existing literature, and considering that our postnatal diagnosis relies on imaging techniques, the identification of teratoma in this particular case is suspicious (12-14)

The most unusual case in current study was identified at 30 weeks of gestation with a mass located at the back of the fetus, distorting the vertebral column extending from left thoracal

region to lower lomber region. The mass, which did not lead to any complications (15) during the prenatal period, was surgically removed after delivery and diagnosed as infantile fibrosarcoma (Figure 1). As another case, a huge hemangioma at the neck that have a large feeding artery arising from carotis had steal effect. In doppler examinations, reverse flow in aortic arch was detected and significant portion of carotis flow was diverted to the mass. The pregnancy was terminated due to a poor fetal prognosis, and similar cases have been reported in the current literature (16).

The overall survival rate was in our study group was 56.3 % and lower than previously reported (3, 17). This may be explained by the poorer prognosis of intracranial tumors and the presence of cases with multiple anomalies.

Ultrasonography is the first step imaging method for evaluation of the fetal tumors. However, it is not always easy to determine the location and histology diagnosis of the mass by ultrasonography. Advanced imaging methods like MRI may be utilized to confirm the diagnosis (9, 18). Although a definitive diagnosis may be established during the prenatal period, there exists a paucity of evidence-based information for management strategies of fetal tumors.

CONCLUSION

In conclusion, as fetal tumors are rare, they may have serious effect on the mother and fetus. Prenatal ultrasound is first step method to diagnose the location and type of the tumor and for prenatal surveillances. Prenatal diagnosis facilitates a multidisciplinary approach, enabling the prediction of potential complications and the consideration of proper management strategies, thereby enhancing perinatal outcomes.

Author Contributions

TU, EOM, DO; CA: conceptualization, methodology, supervision; TU, EOG, GM: data curation; TU, EOG, DO, CA: formal analysis; TU: writing- original draft

Acknowledgements

The authors would like to thank to department of pediatrics, pediatric surgery and pediatric gastroenterology for their support on data collection.

Conflict of Interests

Authors declare no conflict of interest for this article.

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