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Türk Kadın Sağlığı ve Neonatoloji Dergisi (Turkish Journal of Women's Health and Neonatology) 2024 yılı üçüncü sayısıyla huzurlarınızdayız.

Bu sayımızda üç özgün araştırma, iki olgu sunumunu zevkle okuyacağınızı ümit ediyoruz.

Polikistik over sendromu (PKOS), kadın sağlığını etkileyen karmaşık hormonal bozukluklarla karakterize bir sağlık sorunudur. Anksiyeteye, depresyona, insülin direncine, hipertansiyona ve dislipidemiye yol açar. Bir çalışmada PKOS'lu kadınlar fenotiplere göre gruplandırılmış ve antimüllerian hormon (AMH) sonuçlarının fenotiplerle korelasyonu çalışılmıştır.

Postpartum kanama (PPK), doğum sonrası görülen en önemli obstetrik acillerdendir. Traneksamik asit antifibrinolitik bir ilaç olup ilk olarak 1962 yılında Japon araştırmacılar Shosuke ve Utako Okamoto tarafından üretilmiştir. Bir çalışmada standart doğum sonrası kanama yönetim protokolüne traneksamik asit eklenmesinin doğum sonrası dönemde vital bulgular ve laboratuvar değerleri üzerindeki etkisi araştırılmıştır.

Bir sonraki sayımızda yeni ve ilginç makalelerle buluşmak üzere…

Saygılarımla,
Prof. Dr. Yaprak Üstün
Baş Editör

Türk Kadın Sağlığı ve Neonatoloji Dergisi

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Original Article

Anti-Mullerian Hormone According to Polycystic Ovary Syndrome Phenotypes

Polikistik Over Sendromu Fenotiplerine Göre Anti-Müllerian Hormon Değerleri

Serkan Polat*[1], Osman Nuri Erginay[1]

[1] Department of Obstetrics and Gynecology, Ankara Etlik Zübeyde Hanım Women's Health Training and Research Hospital, Ankara, Türkiye

Abstract

Objective: The aim of this study was to investigate the level of antimullerian hormone in patients with polycystic ovary syndrome (PCOS) according to phenotypic characteristics.

Materials and Methods: This study was designed as a cross-sectional cohort study and included patients attending the PCOS clinic of Etlik Zübeyde Hanım Gynecology Training and Research Hospital. Anti-mullerain hormone (AMH) levels were recorded according to phenotype assessment.

Results: A total of 118 patients with PCOS participated in the study. Accordingly, 47 patients (39.8%) belonged to phenotype A, 15 patients (12.7%) to phenotype B, 37 patients (31.3%) to phenotype C and 19 patients (16.1%) to phenotype D. The mean age of the patients was 22.97±4.98 years. The mean body mass index was 26.1± 4.26 kg/m2. The most common reason for presentation to the PCOS outpatient clinic was irregular menstruation. The most common reason for presentation to the PCOS outpatient clinic was irregular menstruation in phenotype A (80.9%) and phenotype D (84.2%). There was a difference between the groups in the distribution of the presence of polycystic ovarian morphology (PCOM) and the frequency of ovarian dysfunction by phenotype ($p<0.001$, $p<0.001$). A statistically significant difference was found between median AMH levels (ng/ml) according to phenotype ($p<0.001$). The median value was 6.3 ng/ml in phenotype A, 2.4 ng/ml in phenotype B, 6.1 ng/ml in group C and 6.6 ng/ml in phenotype D.

Conclusion: In our study, phenotype A was the most frequently observed group and AMH levels were significantly higher in the phenotype D group than in the other groups.

Keywords: Phenotype; polycystic ovary syndrome; anti mullerian hormone; Ferriman Gallwey score

Corresponding author *: Department of Obstetrics and Gynecology, Ankara Etlik Zübeyde Hanım Women's Health Training and Research Hospital, Ankara, Türkiye.
Email: serkannpolatt63@outlook.com
ORCID: 0009-0002-7422-9994
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Öz

Amaç: Bu çalışmanın amacı polikistik over sendromlu (PKOS) hastalarda fenotipik özelliklere göre antimüllerian hormon düzeyini araştırmaktır.

Gereç ve Yöntemler: Bu çalışma kesitsel bir kohort çalışması olarak tasarlandı ve Etlik Zübeyde Hanım Kadın Hastalıkları Eğitim ve Araştırma Hastanesi PKOS kliniğine başvuran hastalar dahil edilmiştir. Anti-mullerain hormon (AMH) düzeyleri fenotip değerlendirmesine göre kaydedilmiştir.

Bulgular: Çalışmaya toplam 118 PKOS hastası katılmıştır. Buna göre 47 hasta (%39.8) fenotip A, 15 hasta (%12.7) fenotip B, 37 hasta (%31.3) fenotip C ve 19 hasta (%16.1) fenotip D'dir. Hastaların yaş ortalaması 22.97±4.98 yıldır. Ortalama vücut kitle indeksi 26.1± 4.26 kg/m2'dir. PKOS polikliniğine en sık başvuru nedeni adet düzensizliğidir. Fenotip A (%80.9) ve fenotip D'de (%84.2) PKOS polikliniğine en sık başvuru nedeni adet düzensizliğidir. Polikistik over morfolojisi (PKOM) varlığı ve over disfonksiyonu sıklığının fenotipe göre dağılımında gruplar arasında fark vardır ($p<0.001$, $p<0.001$). Fenotipe göre ortanca AMH düzeyleri (ng/ml) arasında istatistiksel olarak anlamlı bir fark bulunmuştur ($p<0.001$). Ortanca değer fenotip A'da 6,3 ng/ml, fenotip B'de 2,4 ng/ml, grup C'de 6,1 ng/ml ve fenotip D'de 6,6 ng/ml'dir.

Sonuç: Çalışmamızda fenotip A en sık gözlenen gruptur ve AMH düzeyleri fenotip D grubunda diğer gruplara göre anlamlı olarak daha yüksektir.

Anahtar Kelimeler: Fenotip; polikistik over sendromu; anti müllerian hormon; Ferriman Gallwey skoru

1. Introduction

Polycystic ovary syndrome (PCOS) is a health problem characterized by complex hormonal disorders affecting public health (1). Stein and Levinthal described PCOS in 1935 with the publication of seven cases and this was the beginning of this syndrome that affects public health today (2). PCOS has a lifelong negative impact on women's health and leads to anxiety, depression, insulin resistance, abdominal obesity, hypertension and dyslipidemia (3). Another negative effect seen in women with PCOS is the increased rate of infertility. Its prevalence is between 8 and 13% depending on the population studied (1,2). In order to standardize the diagnosis of PCOS, 3 classification systems based on phenotypic characteristics have been defined and diagnostic criteria vary according to these classifications which are still valid. The so-called Rotterdam criteria are as follows; Oligo and/or anovulation, Clinical and/or biochemical symptoms of hyperandrogenism, Polycystic ovary morphology on ultrasound, Other conditions that cause androgen increase or are associated with androgen increase should be ruled out before the diagnosis of PCOS is made.

The main phenotypic characteristics of PCOS cases are based on clinical symptoms and/or signs, laboratory findings or imaging findings. Considering the diagnostic classifications and criteria, there are generally 3 main phenotypic features that make up the clinical picture in PCOS cases of reproductive age;

1. Ovulatory and menstrual dysfunction (OD)
2. Clinical features of hyperandrogenemia and/or hyperandrogenism (HA)
3. Morphology of polycystic ovaries (PCOM).

In PCOM, clinical manifestations such as hirsutism, oligo-anovulation, hyperandrogenemia on biochemical tests and ultrasonographic appearance of the ovaries can occur in very different combinations. Hyperandrogenemia is the common phenotypic feature found in all 3 diagnostic classifications. Some clinical and laboratory phenotypic features that are not included in the definition criteria for PCOS but complement the clinical picture and influence disease severity and morbidity have also been described. These include obesity, metabolic abnormalities (insulin resistance/hyperinsulinemia, glucose intolerance/ type 2 DM, metabolic syndrome, dyslipidemia), sleep apnea, psychosocial problems and abnormal gonadotropin dynamics. The most important factors influencing the phenotype in PCOS are ethnic, racial and other cultural factors. These phenotypic traits have similar inheritance patterns and cause similar diseases. The severity of phenotypic traits is also highly variable. Another importance of phenotypic traits is that treatment

needs, types and options differ according to these traits. The OD+HA+PKOM phenotype is considered the complete (classic) phenotype according to the Rotterdam classification and the highest rate is seen in this phenotype. Clinical manifestations (phenotype A: HA + OD + PCOM; phenotype B: HA + OD; phenotype C: HA + PCOM and phenotype D: OD + PCOM). According to the Rotterdam criteria, endocrine and metabolic abnormalities are lowest in the OD+PCOM group among these 4 different phenotypes. The prevalence and distribution characteristics of metabolic abnormalities (insulin resistance, metabolic disease pattern and glucose intolerance) did not differ significantly between the 4 groups. Therefore, metabolic abnormalities and distribution characteristics are not used to distinguish between different clinical PCOS phenotypes.

Serum anti-Müllerian hormone (AMH) can be used to identify PCOS in adults (4). Serum AMH is used in accordance with the PCOS diagnostic algorithm. AMH level is not required for the diagnosis of PCOS in patients with irregular menstrual cycle and hyperandrogenism findings. AMH level is not required in adolescents. In the general population, serum AMH levels usually peak at 20-25 years of age. In the general population, serum AMH levels are lower in individuals with a higher body mass index (BMI). Studies in patients with PCOS have shown that phenotyping is necessary to better monitor clinical outcomes (5). In our study, data were grouped according to phenotype and the correlation of AMH results with phenotypes was tried to be determined.

2. Material and Methods

This study was designed as a cross-sectional cohort study involving patients treated at the Etlik Zübeyde Hanım Gynecology Training and Research Hospital PCOS Clinic. Approval for non-interventional studies was obtained from the Ethics Committee of Etlik Zübeyde Hanım Gynecology Training and Research Hospital prior to the start of the study (approval date: 20/03/2024, No.: 03/13). The study involved 118 subjects who agreed to participate in the study and gave their verbal and written informed consent.

The Rotterdam criteria were used for the diagnosis of PCOS (6). Hyperandrogenism was determined clinically by Ferriman-Gallwey score (>8) and biochemically by serum total testosterone (>1.5 nmol/L) and free androgen index (FAI) (>4). Ovulatory dysfunction was defined as patients with menstrual cycles lasting longer than 38 days (oligomenorrhea).

Inclusion criteria

Between 14 and 40 years after menarche,
No underlying metabolic disease (type 2 diabetes, hypertension, diagnosed anemia),
We have one patient with AMH levels in our hospital,
Female patients attending the PCOS clinic will be included.

Exclusion criteria

Age > 40 years;
Menopause, pregnancy or breastfeeding within the last 6 months;
Hyperandrogenism and/or biochemical hyperandrogenemia due to secondary etiologies, including congenital adrenal hyperplasia, androgen-secreting tumors, Cushing's syndrome, hyperprolactinemia, thyroid dysfunction and adrenal disease),
Pre-existing systemic diseases.

Demographic characteristics, laboratory results and hospital records were obtained. Age, PCOS phenotype, age at first menstruation, menstrual cycle pattern and birth weight were routinely recorded. Body weight (kg) and height (m), body mass index (kg/m2), systolic and diastolic blood pressure (mmHg) and Ferriman & Gallwey (FG) score for hirsutism (mean hirsutism of 7 or more points) were recorded. The cycle length was recorded. The phenotypic characteristics of the PCOS patients were recorded according to the "Hyperandrogenemia and PCOS Association". They were categorized according to the PCOS criteria: Phenotype A: oligomenorrhea + hyperandrogenism + polycystic ovaries (PCO), Phenotype B: oligomenorrhea + hyperandrogenism, Phenotype C: hyperandrogenism + PCO, Phenotype D: Oligomenorrhea + PCO.

In routine practice at the PCOS clinic, around 7 ml of blood is taken in a vacuum gel tube for hormonal and biochemical analysis by medical staff. The blood samples are centrifuged by the examiners at 1000 x g for 20 minutes. In the next step, the supernatant part is separated and transferred to 3 mL Ependorfs. These samples are used to determine the levels of anti-Müllerian hormone (AMH), oestradiol, luteinizing hormone (LH) and follicle stimulating hormone (FSH), which are routinely tested at the PCOS clinic. In addition, patients attending the PCOS outpatient clinic are routinely examined by transvaginal ultrasound (TV-USG) for the number of antral follicles and ovarian volume. Patients are examined transvaginally by the same experienced gynecologist using a Samsung HS70A and the number of antral follicles in both ovaries and the volume

of the right and left ovary are recorded. The Orsini formula (length x depth x width x 0.5235)-[transverse, anteroposterior, longitudinal axes] is used to measure the volume of the ovaries.

Statistical analysis

The data were analyzed using the IBM SPSS V23 program. The Shapiro-Wilk test was used to analyze the data. The Fisher-Freeman-Halton test was used to analyze categorical data and multiple comparisons were performed using the Bonferroni-corrected Z-test. One-way analysis of variance was used to compare the variables that fit the normal distribution with the groups. The Kruskal Wallis test was used to compare the variables that did not conform to the normal distribution with the groups. The results of the analyzes were presented as frequency (percentage) for categorical variables, mean ± standard deviation and median (minimum - maximum) for quantitative variables. The significance level was set at $p<0.050$.

The power analysis was performed with the program G*POWER 3.1 to determine the sample size. The power analysis for sample size calculation was based on the previous study by Barrea et al. (3). Participants who met the inclusion criteria were included in the study. After analyzing the 95% confidence (1-α), 95% test power (1-β) and d= 1.5915486 effect size one-sided independent samples t-test, the number of samples to be taken was set at 80. Since our sample size is above this number, we assume that the test power is higher.

3. Results

The number of patients admitted to our PCOS outpatient clinic between November 2023 and April 2024 was 118. The average age of the patients was 22.97±4.98 years. The mean body mass index was 26.1± 4.26 kg/m2. These data are shown in Table 1, which describes the demographic characteristics. The most common reason for presentation to the PCOS outpatient clinic was irregular menstruation. The most frequently observed phenotypic group was group A. The analysis of clinical characteristics by phenotype is shown in Table 2. According to this, there was no significant difference between the phenotypic groups in terms of age, BMI and FG score median (p=0.773 p=0.501, p=0.985). There was a difference between groups in reasons for use when assessing reasons for use ($p<0.001$). The most common reason for use was irregular menstruation in phenotype A (80.9%) and phenotype D (84.2%). There were also differences between groups in the distribution of the presence of PCOM and the frequency of ovulatory disorders according to phenotype ($p<0.001$, $p<0.001$).

The laboratory parameters according to phenotype are shown in Table 3. No statistically significant difference was found between FSH (mIU/ml), LH (mIU/ml) and FSH/LH median values according to phenotype (p=0.566, p=0.171, p=0.217). A statistically significant difference was found between the median values of 17-hydroxyprogesterone (ng/ml) (p=0.032). The median value was 0.94 ng/ml in phenotype A, 0.45 ng/ml in phenotype B, 1.5 ng/ml in phenotype C and 0.5 ng/ml in group D. There was no statistically significant difference between the median values of dehydroepiandrosterone sulfate (DHEAS) (ng/L) by phenotype (p=0.899). There was a statistically significant difference between the median levels of AMH (ng/ml) according to phenotype ($p<0.001$). The median value was 6.3 ng/ml for phenotype A, 2.4 ng/ml for phenotype B, 6.1 ng/ml for phenotype C and 6.6 ng/ml for phenotype D. There was no statistically significant difference between the median values of insulin and HOMA-IR according to phenotype (p=0.170, p=0.535).

Tablo 1. Demographic characteristics of the PCOS patients

	Study Group n:118
Age (years)	22.97±4.98
Body Mass Index (kg/m²)	26.1±4.26
Reason for applying n (%)	
Menstrual irregularity	66 (55%)
Increased hair growth	40 (33%)
Acne	4 (3%)
Child counselling	1 (0.8%)
Failure to lose weight	7 (5.9%)
Polycystic ovarian morphology n (%)	
Yes	103 (87.2%)
No	15 (12.7%)
Oligo/anovulation n (%)	
Yes	80 (67.7%)
No	38 (32.2%)
Phenotypes n (%)	
A	47 (39.8%)
B	15 (12.7%)
C	37 (31.3%)
D	19 (16.1%)
The Ferriman-Gallwey score	15.52±6.47

Table 2. Clinical characteristics of patients according to PCOS phenotypes

	Phenotypes				T-test	p
	A	B	C	D		
Age (years)	23,5 ± 4,9	22,9 ± 6,2	22,6 ± 5	22,4 ± 4,3	1,119	0,773*
Body Mass Index (kg/m^2)	26,8 ± 6,6	28 ± 4,7	25,6 ± 5,3	26,6 ± 5,4	2,363	0,501*
Ferriman Gallwey score	15 (5 - 28)	15 (5 - 29)	15 (5 - 34)	14 (5 - 30)	0,050	0,985**
Reason for applying n (%)						
Menstrual irregularity	38 (80,9)^a	7 (46,7)^{ab}	5 (13,5)^b	16 (84,2)^a	62,108	**<0,001*** **
Increased hair growth	6 (12,8)^a	7 (46,7)^b	27 (73)^b	0 (0)^a		
Acne	2 (4,3)	0 (0)	2 (5,4)	0 (0)		
Child counselling	0 (0)	0 (0)	1 (2,7)	0 (0)		
Failure to lose weight	1 (2,1)	1 (6,7)	2 (5,4)	3 (15,8)		
Polycystic ovarian morphology n (%)						
No	0 (0)^b	15 (100)^a	0 (0)^b	0 (0)^b	78,204	**<0,001*** **
Yes	47 (100)	0 (0)	37 (100)	19 (100)		
Oligo/anovulation n (%)						
No	0 (0)^a	0 (0)^a	37 (100)^b	1 (5,3)^a	128,029	**<0,001*** **
Yes	47 (100)	15 (100)	0 (0)	18 (94,7)		

*Kruskal Wallish H test, **One-Way Analysis of Variance, ***Fisher Freeman Halton Test; a-b: No difference between groups with the same letter; Mean ± standard deviation, Median (minimum-maximum).

4. Discussion

In our study, adolescent and adult PCOS patients were examined with regard to clinical and biochemical parameters. In summary, it was found that the most frequently observed group was phenotype A and AMH levels were significantly higher in the phenotype D group than in the other groups.

With the 2023 ESHRE guideline, elevated AMH levels in the adult group were included in the diagnostic criteria (4). Given the difficulty of ultrasound diagnosis of PCOS, even years after menarche, serum anti-Müllerian hormone (AMH) has been proposed as an alternative marker for PCOM. AMH is a polypeptide. It belongs to the transforming growth factor beta (TGF-B) family and is secreted exclusively by granulosa cells in preantral and small antral follicles. The AMH serum level is significantly higher in women with PCOS than in women with normal ovulation. A strong correlation between the circulating AMH level and the number of antral follicles has been demonstrated (7,8). When we compared AMH levels by phenotype in our study, we found that AMH levels were significantly higher in the phenotype D group compared to the other groups.

In 2009, Piouka et al. found that AMH levels reflect the severity of PCOS (9). Sahmay et al. showed that AMH levels differed between phenotypes and were significantly higher in phenotype A (10). Subsequently, many studies have shown that AMH levels were higher in the phenotype A group than in other groups (11-14). However, in our study, we found that AMH levels were high in the phenotype D group and particularly low in the phenotype B group. We believe that we determined the result in this way because we studied not only the adult group but also the adolescent group.

Bozdag et al. studied 392 women to determine diagnostic AMH levels and found that the AMH levels of women with phenotype A PCOS were significantly higher and the most appropriate AMH threshold for the diagnosis of PCOS was 4.86 ng/mL (15). Dewailly et al. proposed a simplified diagnosis of PCOS based on an AMH threshold of 5 ng/mL (16). Another study determined an AMH value of 6.095 ng/ml for phenotype-A with a sensitivity of 69.2% and a specificity of 86.7% (17). The average of our values is also close to this threshold. Since it may not be easy to perform an ultrasound and examine the ovaries in virginal and obese patients or in regions where an ultrasound is not easily accessible, the AMH level can be used to determine the

Table 3. Results of laboratory outputs obtained according to PCOS phenotypes

	Phenotypes				T test	p*
	A	B	C	D		
FSH (IU/L)	4,66 ± 1,35	4,69 ± 1,01	4,55 ± 2,28	4,89 ± 1,38	2,031	0,566
	4,58 (2 - 8)	5 (3 - 6)	4,56 (1 - 12)	5,13 (2 - 7)		
LH (IU/L)	9,25 ± 4,98	6,75 ± 4,56	9,85 ± 6,68	8,94 ± 6,33	5,012	0,171
	8,06 (2 - 22)	5,46 (3 - 18)	8,76 (1 - 31)	6,81 (2 - 25)		
FSH/LH	0,74 ± 0,52	0,91 ± 0,47	0,79 ± 0,66	1 ± 0,76	4,443	0,217
	0,59 (0 - 3)	0,8 (0 - 2)	0,6 (0 - 3)	0,75 (0 - 3)		
Estrodiol (pg/ml)	47,82 ± 25,78	34,15 ± 19,49	50,45 ± 28,25	53,75 ± 30,45	5,394	0,145
	43 (2 - 162)	35,6 (5 - 85)	43 (5 - 115)	46,4 (5 - 112)		
TSH (IU/L)	2,1 ± 1,26	1,98 ± 0,73	2,69 ± 1,98	2,11 ± 1,48	1,945	0,584
	1,72 (0 - 6)	1,97 (1 - 4)	2,15 (0 - 9)	2 (0 - 6)		
17-hydroxyprogesterone (ng/ml)	1,69 ± 2,44	0,6 ± 0,42	1,91 ± 1,75	1,1 ± 1,26	8,835	**0,032**
	0,94 (0 - 11)[ab]	0,45 (0 - 1)[a]	1,5 (0 - 8)[b]	0,5 (0 - 5)[ab]		
Prolactin (ng/ml)	17,16 ± 7,56	22,03 ± 21,94	17,52 ± 9,08	20,17 ± 11,14	0,63	0,889
	16,7 (6 - 31)	17 (7 - 98)	18 (4 - 39)	18,6 (7 - 45)		
DHEA-SO4 (ng/ml)	250,22 ± 97,46	250,67 ± 138,25	245,76 ± 113,13	251,58 ± 98,14	0,588	0,899
	245 (83 - 461)	245 (102 - 625)	205 (97 - 587)	242 (100 - 451)		
AMH (ng/ml)	7,66 ± 4,25	2,79 ± 1,47	7,52 ± 5,19	8,03 ± 3,67	26,496	**<0,001**
	6,3 (1 - 21)[a]	2,4 (1 - 8)[b]	6,1 (1 - 24)[a]	6,6 (3 - 17)[a]		
Insulin (ng/ml)	4,02 ± 4,13	6,19 ± 3,98	5,37 ± 6,94	5,23 ± 4,38	5,029	0,170
	3,03 (0,01 - 18)	7,7 (0,28 - 13,7)	3,78 (0,09 - 40,3)	4,39 (0,02 - 17,4)		
HOMA-IR	4,74 ± 4,71	4,04 ± 2,71	3,69 ± 2,63	4,64 ± 2,25	2,182	0,535
	3,96 (0,01 - 23,5)	2,86 (0,86 - 9,09)	3,14 (0,01 - 9,09)	4,14 (1,52 - 8,5)		

*Kruskal Wallish H test, a-b: No difference between groups with the same letter; FSH: follicle-stimulating hormone; LH: Luteinizing hormone; TSH: thyroid stimulating hormone; DHEA-SO4: dehydroepiandrosterone sulfate; AMH: Anti-müllerian hormone; HOMA-IR: Homeostatic Model Assessment of Insulin Resistance

PCOS phenotype. As women with PCOS phenotype A should be counseled about the lifelong effects on metabolism and lifestyle changes with healthy eating habits and regular exercise should be strongly recommended, such a quantitative test may be more reliable and accessible than a transvaginal ultrasound. Many morbidities occur in this patient group, from obstetric complications to complications such as cancer and heart disease, that affect menopausal life (18).

Obesity and insulin resistance (IR) are interrelated parameters in the pathophysiology of PCOS (19,20). PCOS phenotype A is usually associated with obesity and IR and is considered the most severe form of PCOS (21). Phenotype B has similar but milder metabolic consequences. Phenotype C is milder as the predominant problem is subfertility. Phenotype D is the mildest form with less obesity, IR or metabolic side effects (22). PCOS phenotypes A and B are more prone to obesity and insulin resistance (20). Since our study only selected patients who presented to the PCOS outpatient clinic and had a diagnosis, their metabolic status was found to be similar and there was no difference between the phenotypes.

The retrospective design and limited number of patients studied is one of the limitations of the study, and the lack of grouping of comparative data by age group is another limitation. In this study, we have no data on the number of antral follicles in the

patients. Secondly, the values for the area under the curve and the ROC analysis for the AMH values according to phenotype could not be provided.

PCOS is one of the most common endocrine disorders worldwide and can affect women of any age. Although many genetic, environmental and hormonal factors are thought to be responsible, the etiopathogenesis is still not fully understood. According to the phenotypic characteristics of the patients presenting in our study, the most common group was phenotype A. The AMH level was significantly higher in the phenotype D group than in the other groups. In group B, the AMH cut-off value, which was considered high, was below 3.32 ng/ml. Our results may shed light on the etiopathogenesis of PCOS. The development of PCOS in adolescence and adulthood could be due to different mechanisms and hormonal changes. Large prospective series of studies are needed to make a definitive statement on this topic.

Author contribution

Study conception and design: SP; data collection: ONE; analysis and interpretation of results: SP and ONE; draft manuscript preparation: SP and ONE. All authors reviewed the results and approved the final version of the manuscript.

Ethical approval

The study was approved by the Ethics Committee for Non-interventional Studies of Etlik Zubeyde Hanım Women Health Education Research Hospital (Protocol no. 03/13 - 20.03.2024).

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Conflict of interest

The authors declare that there is no conflict of interest.

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Yazarlar herhangi bir çıkar çatışması olmadığını beyan etmiştir.

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Original Article

Effect of Tranexamic Acid Use on Estimated Blood Loss in Postpartum Hemorrhage

Traneksamik Asit Kullanımı Postpartum Kanamada Tahmini Kan Kaybına Olan Etkisi

Mustafa Canbulut*[1], Meltem Buz Baydilli[2], Özge Yücel Çelik[1]

[1]Department of Obstetrics and Gynecology, Ankara Etlik Zübeyde Hanım Women's Health Training and Research Hospital, Ankara, Türkiye
[2]Department of Anesthesia, Ankara Etlik Zübeyde Hanım Women's Health Training and Research Hospital, Ankara, Türkiye

Abstract

Objective: Postpartum hemorrhage is one of the most critical obstetric emergencies. This study aims to evaluate the effect of tranexamic acid on vital signs in cases of postpartum hemorrhage.

Material and Method: In this retrospective case-control study, the vital and laboratory values of the patients were recorded at the time of initial hospitalization, and at 2 and 6 hours after delivery. Mean arterial pressure (MAP) was calculated as Diastolic Blood Pressure + 1/3 (Systolic Blood Pressure- Diastolic Blood Pressure). The 2nd and 6th hour ΔHb was determined as the difference between the admission Hb and the Hb at 2 and 6 hours, respectively. Patients who received tranexamic acid treatment were compared to those who did not, based on these data.

Results: A total of 156 patients with postpartum hemorrhage who underwent cesarean section were included in our study. Of these patients, 83 received tranexamic acid treatment in addition to postpartum hemorrhage protocols and were included in the study group. The group that received the standard protocol without tranexamic acid treatment was included in the control group, consisting of 73 patients. The mean age of the patients in the study was 30.86±6.09 years, and the mean body mass index was 30.06±5.18 kg/m². Mean arterial pressure was higher in the study group compared to the control group (68.51±34.92 mm Hg vs. 56.20±40.33 mm Hg; p=0.001). The difference in hemogram values at 2 hours and 6 hours was significantly lower in the group that did not receive tranexamic acid compared to the study group (p=0.018, p=0.001).

Conclusion: It was observed that the addition of tranexamic acid to the treatment of postpartum hemorrhage significantly increased the mean arterial pressure of the patients and resulted in notable differences in hemogram changes.

Keywords: Postpartum hemorrhage; tranexamic acid; vital signs; blood loss

Corresponding author *: Department of Obstetrics and Gynecology, Ankara Etlik Zübeyde Hanım Women's Health Training and Research Hospital, Ankara, Türkiye.
Email: canbulutmustafa@gmail.com
ORCID: 0009-0001-6408-566X
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Öz

Amaç: Postpartum kanama en önemli obstetrik acillerden birisidir. Traneksamik asidin postpartum kanamada vital bulgular üzerindeki etkisinin değerlendirilmesi planlanmıştır.

Gereç ve Yöntem: Bu retrospektif vaka kontrol çalışmada, hastaların vital ve laboratuvar değerleri için hastaneye ilk yatışında alınan değerler ile doğum sonrası 2. ve 6. saatlerindeki değerler alınmıştır. Ortalama arteryel basınç (MAP) = Diyastolik kan basıncı + 1/3 (sistolik kan basıncı – diyastolik kan basıncı) formülü ile hesaplanmıştır. 2. ve 6. saat ΔHb'leri hastanın giriş Hb ile 2. ve 6. saatlerindeki Hb'leri arasındaki fark olarak hesaplanmıştır. Traneksamik asit tedavisi alanlar ve almayanlar bu veriler üzerinden kıyaslanmıştır.

Bulgular: Çalışmamıza, postpartum kanaması olan ve sezaryan geçirmiş toplam 156 hasta dahil edilmiştir. Bu hastaların 83'üne postpartum kanama protokollerine ek olarak traneksamik asit tedavisi de verilmiştir ve çalışma grubuna dahil edilmiştir. Standard protokolün uygulanıp, traneksamik asit tedavisi almayan grup ise kontrol grubuna dahil edilmiştir ve bu grupta 73 hasta bulunmaktadır. Çalışmaya dahil edilen hastaların yaş ortalaması, 30.86±6.09 yıl iken, vücut kitle indexi ortalaması 30.06±5.18 kg/m2'dir. Çalışma grubunda ortalama arteriyel basıncın kontrol grubuna göre daha yüksek olduğu tesbit edilmiştir(56.20±40.33mm Hg, 68.51±34.92 mm Hg; p=0.001) . Yapılan çalışmada ek tedavi olarak traneksamik asit almayan grupta 2 saat ve 6 saat hemogram değerlerindeki farklılık çalışma grubuna göre anlamlı olarak daha düşüktür (p=0.018, p=0.001).

Sonuç: Postpartum kanama tedavisine eklenen traneksamik asit ile hastaların özellikle ortalama arteriyel basınçlarda yükselme olduğu ve hemogram değişimlerinde farklılık olduğu gözlemlenmiştir.

Anahtar Kelimeler: Postpartum kanama; traneksamik asit; vital bulgular; kan kaybı

1. Introduction

Postpartum hemorrhage is one of the most critical obstetric emergencies and a major cause of maternal mortality in both developed and developing countries worldwide. Postpartum hemorrhage affects 5-6% of all pregnancies worldwide and is responsible for 25% of maternal deaths (1). Postpartum hemorrhage can be caused by various factors. The etiology generally includes uterine atony, trauma-related lacerations, placental retention and bleeding diatheses. In addition, conditions such as pre-eclampsia, placenta accreta spectrum, placenta previa and multiple pregnancies increase the risk of hemorrhage.

Most deaths from obstetric hemorrhage occur within the first few hours, and 90% of these deaths are preventable. Early diagnosis and treatment saves lives. Visual assessment of bleeding can be deceptive and may not reflect the actual amount of blood loss. Therefore, symptoms of hypovolemia should be monitored after each birth. According to the World Health Organization (WHO), bleeding of more than 500 ml within 24 hours of delivery is defined as postpartum hemorrhage. Severe postpartum hemorrhage is characterized by bleeding of more than 1000 ml within 24 hours (2). Many health organizations recommend active management of the third stage of labor to prevent postpartum hemorrhage. Several studies have shown that active management reduces the amount of postpartum hemorrhage. Active management consists of three components.

1. Administration of uterotonics (oxytocin)
2. Massage of the uterus
3. Controlled pulling of the umbilical cord

Several studies have shown that the prophylactic use of uterotonics reduces the need for therapeutic doses of these drugs (3). Although it makes no difference whether 10 units of oxytocin are administered intramuscularly (IM) or intravenously (IV), this remains the most effective prophylactic method with the fewest side effects and is still used as the first choice today. According to the FIGO (International Federation of Obstetrics and Gynecology) guideline for the prevention of postpartum hemorrhage (4):

1. The use of uterotonics to prevent postpartum hemorrhage in the third stage of labor is recommended for all deliveries. Oxytocin 10 units can be administered either intramuscularly (IM) or intravenously (IV), regardless of the mode of delivery.

2. If oxytocin is not available, 200 µg ergometrine/methylergometrine intramuscularly (IM) or intravenously (IV), 400-600 µg oral misoprostol or 100 µg carbetocin IM or IV can be administered as an alternative.

3. For bleeding greater than 500 mL, the combination of oxytocin with methylergometrine or misoprostol may be more effective; however, the possible side effects must be carefully considered.

4. Oral misoprostol may be administered in the absence of a physician experienced in labor; however, controlled cord traction is not recommended.

5. Continuous uterine massage is not recommended for patients receiving prophylactic oxytocin.

6. Uterine examination is recommended for all women to detect atony.

Oxytocin: Oxytocin, released from the posterior pituitary gland, triggers uterine contractions by initiating intracellular calcium release and increasing local prostaglandin production. There are no oxytocin receptors in the uterus until the 13th week of pregnancy, but the number of receptors gradually increases thereafter. Consequently, pregnancies respond to lower doses of oxytocin. Repeated doses lead to a desensitization of the receptors and thus to a lower response (5).

Misoprostol: Misoprostol is a prostaglandin E1 analog that triggers uterine contractions. It can be administered orally, sublingually, buccally and rectally. Its ease of use and storage conditions are significant advantages over oxytocin. FIGO and WHO recommend a dosage of 400-600 µg orally if oxytocin is not available (6). The most common side effect is fever, which typically begins with chills. Fever can be treated with paracetamol.

Ergot alkaloids: ergometrine and methylergometrine are agonists of serotonergic receptors in smooth muscle, weak agonists of dopaminergic receptors and partial agonists of alpha-adrenergic receptors. They trigger rapid and rhythmic uterine contractions. Due to their vasoconstrictive effect, they are contraindicated in patients with hypertension, Raynaud's phenomenon and coronary heart disease. A dose of 0.2 mg is administered intramuscularly (IM) and can be repeated every 2-4 hours.

Carbetocin: Carbetocin is a long-acting synthetic analog of oxytocin that has the same pharmacological properties but a 4 to 10 times longer duration of action. It is administered as a single dose of 100 mcg intravenously (IV) after a normal vaginal delivery or cesarean section (7). It is used prophylactically.

Tranexamic acid (TXA): Tranexamic acid has been shown to be beneficial when used in combination with uterotonics, with effects extending beyond its antifibrinolytic properties (8). A dose of 1 gram is administered intravenously (IV) over 10 minutes. Although there is a theoretical concern of an increased risk of thrombosis, studies have shown that it does not statistically increase the risk of thrombosis compared to the control group (9).

In light of this information, this study investigated the effect of adding tranexamic acid to the standard postpartum hemorrhage management protocol on vital signs and laboratory values in the postpartum period.

2. Material and Methods

Patients who delivered between January 1, 2023 and February 1, 2024 at Etlik Zübeyde Hanım Gynecology and Obstetrics Training and Research Hospital, a reference hospital, were evaluated by retrospective chart review. Approval for non-interventional studies was obtained from the Ethics Committee of Etlik Zübeyde Hanım Research and Training Hospital prior to the start of the study (approval date: April 24, 2024; issue no.: 04/08).

The study enrolled 156 patients who had no known medical conditions, had an uneventful pregnancy, were of reproductive age, had a BMI <29.9, had a singleton pregnancy, had delivered by cesarean section, and had postpartum hemorrhage according to the study criteria. Exclusion criteria were multiple pregnancy, fetal anomaly, maternal age under 18 years or over 45 years, duration of pregnancy under 25 weeks, severe anemia (Hb <7 g/dL), stillbirth, maternal bleeding disorders, maternal heart diseases and maternal infections (chorioamnionitis, sepsis).

The total sample size was determined retrospectively from the hospital records. The files of all patients who had received intrapartum tranexamic acid were analyzed individually. The patients' medical records were accessed via their files and the hospital's patient files. Demographic data (age, parity, body mass index [BMI = weight/height² = kg/m²] before and during pregnancy, concomitant diseases, smoking status), information on delivery (type of delivery, birth weight, type of delivery, Single or multiple pregnancy and whether assisted reproductive techniques were used), vital signs (pulse rate 2 and 6 hours after delivery) and laboratory values (hemoglobin [Hb], white blood cell count, hematocrit and platelet count). For the vital and laboratory values of the patients, the values recorded on admission to hospital and 2 and 6 hours after delivery were used. Mean arterial pressure (MAP) was calculated using the following formula: MAP = Diastolic blood pressure + 1/3 (Systolic blood pressure - Diastolic blood pressure). The ΔHb of the 2nd and 6th hour was calculated as the difference between the Hb at admission and the Hb after 2 and 6 hours, respectively.

Adverse effects considered in the study included blood transfusion, repeat parotomy, repair of vaginal lacerations in the operating room, curettage, hysterectomy, balloon tamponade, arterial ligation, need for intensive care, and multiple organ failure (including impaired renal function tests, impaired liver function tests, consumption-related coagulopathy, and pulmonary edema). The study enrolled 156 patients with no known medical problems who had had an uneventful pregnancy, were of childbearing age, had a BMI <29.9 and had singleton pregnancies.

Exclusion criteria for subjects: multiple pregnancies, fetal anomalies, pregnancies in those under 18 or over 45 years of age, pregnancies of less than 25 weeks, severe anemia (Hb <7 g/dL), stillbirth, maternal bleeding disorders, maternal heart diseases, maternal infections (chorioamnionitis, sepsis).

Statistical analysis

All statistical analyses were performed using the SPSS 25.0 package program (SPSS Inc., Chicago, IL). The conformity of continuous numerical variables to normal distribution was checked by the Shapiro-Wilk test. Quantitative variables were expressed as mean ± standard deviation or median (minimum-maximum), and qualitative variables were expressed as relative frequency (%). The Kruskal-Wallis test was used to compare non-normally distributed parametric variables across three groups. For normally distributed variables, a one-way ANOVA was performed for group comparisons. The Mann-Whitney U test and Student's t-test were used to compare parametric variables between two groups with and without normal distribution, respectively. The Pearson chi-square test was used to compare categorical variables between groups. A p-value <0.05 was considered statistically significant.

3. Results

A total of 156 patients were included in our study. Tranexamic acid was administered to 83 of these patients, while 73 patients were included in the control group. The mean age of the patients was 30.86±6.09 years, and the mean body mass index was 30.06±5.18 kg/m². The demographic data of the two groups are presented in Table 1. According to Table 1, there was no significant difference between the two groups in terms of age, body mass index, smoking status, reasons for cesarean delivery, and baby birth weight.

Table 1. Demographic data of the participants			
	Control group (n=73)	Study group (n=83)	P
Age (years)	31.01±5.980	30.72±6.218	.643
Parity	2.00±1.17	1.59±1.51	.051
Body mass index (kg/m2)	30.45± 4.37	29.72±5.77	.085
Smoking			
No	56 (89.1%)	71 (95.0%)	.108
Yes	17 (10.9%)	12 (5.0%)	
Indication for caesarean section			.147*
Cephalopelvic discordance	6	17	
Oligohydramnios	-	3	
Previous caesarean section	49	38	
Placental abnormality	1	2	
Malpresentation	5	8	
Multiple pregnancy	2	2	
Fetal distress	8	10	
Macrosomy	2	3	
Birth weight (gram)	3066.18±569.07	3050.82±625.50	.334

Table 2. Comparison of vital parameters in study groups			
	Control group (n=73)	Study group (n=83)	P
Pulse			
0.hour[c]	86.8±13.2	90.8±14.1	.239
2. hour[c]	83.4±12.8	83.7±14.3	.966
6. hour[c]	87.7±12.8	87.5±11.3	.740
Systolic blood pressure (mm Hg)			
0. hour[c]	119.31±14.31	118.08±11.30	.208
2. hour[c]	115.55±13.07	113.83±12.97	.701
6. hour[c]	113.63±10.05	111.47±12,36	.489
Diastolic blood pressure (mm Hg)			
0. hour[c]	65.94±9.70	68.65±9.47	.943
2. hour[c]	69.98±9.31	68.89±7.99	.428
6. hour[c]	69.33±7.37	68.56±8.48	.287
Mean arterial blood pressure			
0. hour[c]	**56.20±40.33**	**68.51±34.92**	**.001**
2. hour[c]	**57.16±41.03**	**67.50±34.34**	**<.001**
6. hour[c]	**56.44±40.19**	**66.69±33.98**	**<.001**

Table 3. Prevalence of maternal adverse effects due to postpartum bleeding	
Maternal Adverse effects	Prevelance n (%)
Transfusion	18 (11.5%)
Relaparotomy	1 (%0.6)
Artery Ligation	3 (%1.9)
Hysterectomy	1 (%0.6)
Need for referral / intensive care	1 (%0.6)

In Table 2, the vital signs of the patients who received tranexamic acid were compared with those of the control group. The results indicate that the mean arterial pressure was higher in the study group compared to the control group (56.20±40.33 mm Hg vs. 68.51±34.92 mm Hg; p=0.001). Additionally, the mean arterial pressure values at the postoperative 2nd and 6th hours were significantly lower in the control group (p=0.001,p=<0.001, p=<0.001, respectively).

Eighteen (11.5%) of the patients with postpartum hemorrhage received blood transfusions. Three patients (1.9%) underwent arterial ligation after cesarean section. One patient (0.6%) required relaparotomy and peripartum hysterectomy. One patient was referred to the intensive care unit (Table 3).

In the study, the treatment administered significantly affected the difference between the 2-hour and 6-hour hemogram values (p=0.018, p=0.001). Accordingly, delta hemogram values were found to be lower in the control group compared to the study group (0.46±0.96 g/dL vs. 1.02±0.90 g/dL) (Table 4).

Table 4. Comparison of laboratory parameters in study groups			
	Control group (n=73)	Study group (n=83)	P
WBC (10^9/L)			
0. hour[c]	10268.49±2645.06	10444.57±3662.40	.530
2. hour[c]	14371.23±5619.07	16380.84±4994.09	.061
6. hour[c]	14950.68±4981.55	14950.68±4981.55	.817
Hb (g/L)			
0. hour[c]	11.81±1.36	11.60±1.34	.762
2. hour[c]	11.35±1.52	10.88±1.42	.510
6. hour[c]	10.79±1.34	10.48±1.41	.715
Δ 2. hour hb[c]	**0.46±0.96**	**0.71±1.32**	**.018**
Δ 6. Hour hb[c]	**1.02±0.90**	**1.12±1.34**	**.001**
Plt (10^9/L)			
0. hour[c]	232.64±64.42	235.29±68.19	.361
2. hour[c]	216.96±63.04	206.63±59.95	.971
6. hour[c]	210.88±64.74	211.46±64.16	.729
Fibrinogen	380.11±74.89	390.20±74.44	.890

[a]Ki kare analizi, [b]Fisher's Exact Test, [c]Mann Whitney test, WBC (10^9/L): beyaz kan hücresi, Hb (g/L): hemoglobin, Hct: hematokrit, Plt (10^9/L): platelet

4. Discussion

Postpartum hemorrhage, a major cause of maternal mortality and morbidity, affects the lives of millions of women (10). Timely treatment of postpartum hemorrhage, which has numerous negative effects on the mother, is crucial. In this study, we aimed to investigate the impact of tranexamic acid treatment given in addition to the standard protocol on the prognosis of patients. We observed an increase in mean arterial pressure in the patients. In contrast, we found that the change in hemogram values was lower in the control group. This is probably due to the fact that more bleeding occurred in the tranexamic acid- treated group, which necessitated the use of additional agents during treatment. It was also found that the number of blood transfusions was higher in the group of patients receiving this treatment.

Postpartum hemorrhage is usually diagnosed based on the estimated amount of blood observed visually. However, this estimate is often inaccurate. The amount of bleeding can be misleading as it can be mixed with other fluids and can occur in areas that are not visible. Therefore, when making a diagnosis, we should consider not only the 1000 ml of bleeding within 24 hours of delivery, but also the symptoms of hypovolemia associated with postpartum hemorrhage (6). Laboratory values are also unreliable in acute hemorrhage, as it may take some time for hemoglobin and hematocrit levels to drop. It is crucial to treat women with clinically diagnosed postpartum hemorrhage promptly. An estimated blood loss of more than 500 ml after a vaginal delivery or more than 1000 ml after a cesarean section, or a blood loss sufficient to jeopardize hemodynamic stability, is defined as postpartum hemorrhage (11). Women with postpartum hemorrhage receive a fixed dose of 1 g tranexamic acid. This dose, 10 ml (100 mg/ml), is administered intravenously as soon as possible after delivery (1 ml per minute). If bleeding continues after 30 minutes, a second dose of 1 g can be administered intravenously. Tranexamic acid is intended as an adjunct to the usual therapies for the treatment of postpartum hemorrhage.

Tranexamic acid is a safe, effective and cost-effective treatment for postpartum hemorrhage. Current research is focused on interventions to prevent postpartum hemorrhage, particularly in high-risk groups. The TRAAP trial (Tranexamic Acid for the Prevention of Postpartum Hemorrhage Following Vaginal Delivery) was a multicenter, double-blind, placebo-controlled trial in which 4,079 women were randomized to receive either tranexamic acid or placebo. While the trial did not show a reduction in postpartum hemorrhage, it did result in a 25%

reduction in clinically significant postpartum blood loss (12). These results suggest that tranexamic acid has prophylactic potential. In healthy volunteers, intramuscular tranexamic acid reaches therapeutic levels (>10 mg/L) in about 30 minutes. Healthcare professionals are trained in the administration of intramuscular oxytocin, and if proven effective, intramuscular tranexamic acid could be life-saving. Advances in emergency obstetric care, including the use of tranexamic acid as an initial treatment, have resulted in more women surviving postpartum hemorrhage than ever before.

The literature review shows that administration of tranexamic acid (TXA) for prophylaxis of obstetric hemorrhage decreases blood loss after cesarean section and reduce the need for blood transfusions (13). Studies on blood pressure have shown that the additional administration of tranexamic acid leads to favorable results (14,15). Randomized controlled trials have confirmed that maternal mortality and the number of emergency transfusions during surgery are reduced.

This study was not powered to examine the adverse effects of TXA in the treatment of postpartum hemorrhage on the mother. Our review of the results is consistent with previous reports and indicates that more information is needed. Well-designed studies with larger numbers of participants are needed. In addition, the association between this treatment and thromboembolic events is based on assumptions and has not yet been proven.

As shown in various studies, tranexamic acid has been used for almost 50 years but has only recently found its place in the postpartum population. Despite the timeliness of these studies, further research with larger patient series is needed to contribute to the literature. Due to the small number of patients undergoing hysterectomy, curettage, multiple organ dysfunction syndrome (MODS), balloon tamponade and arterial ligation, meaningful results have not been obtained in these groups. Therefore, multicenter prospective studies with larger patient series are required.

Author contribution

Study conception and design: MC and MBB; data collection: MC; analysis and interpretation of results: MC, MBB, and ÖYC; draft manuscript preparation: MC, MBB, and ÖYC. All authors reviewed the results and approved the final version of the manuscript.

Ethical approval

The study was approved by the Non-Interventional Studies Ethics Committee of Etlik Zübeyde Hanım Women's Health Training and Research Hospital (Decision no: 11/23.11.2023).

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Conflict of interest

The authors declare that there is no conflict of interest.

Yazar katkısı

Araştırma fikri ve tasarımı: MC ve MBB; veri toplama: MC; sonuçların analizi ve yorumlanması: MC, MBB ve ÖYC; araştırma metnini hazırlama: MC, MBB ve ÖYC. Tüm yazarlar araştırma sonuçlarını gözden geçirdi ve araştırmanın son halini onayladı.

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Yazarlar herhangi bir çıkar çatışması olmadığını beyan etmiştir.

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Türk Kadın Sağlığı ve Neonatoloji Dergisi

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Original Article

Assessing the Impact of Anthropometric Measurements on Osteoporosis Risk in Postmenopausal Women

Menopoz Sonrası Kadınlarda Osteoporoz Riskini Değerlendirmede Antropometrik Ölçümlerin Etkisi

Büşra Körpe*[1], Caner Köse[1], Samet Kutluay Ergörün[2], Sümeyye Mermi[1], Hüseyin Levent Keskin[1]

[1]Ankara Etlik City Hospital, Obstetrics and Gynecology Hospital, Ankara, Türkiye
[2]Iğdır Dr. Nevruz Erez State Hospital, Iğdır, Türkiye

Abstract

Aim: This study evaluates various anthropometric measurements, including BMI, Waist-to-Hip Ratio (WHR), Waist-to-Height Ratio (WHtR), Conicity Index (C-index), and Visceral Adiposity Index (VAI), to determine their association with osteoporosis in postmenopausal women.

Material and Method: In this cross-sectional study, 304 postmenopausal women aged 45-75 years from a gynecology and menopause clinic participated. Dual-Energy X-ray Absorptiometry (DEXA) was used to assess Bone Mineral Density (BMD). Anthropometric measurements (waist circumference, hip circumference) were recorded, and indices (BMI, WHR, WHtR, C-index, VAI) were calculated. Demographic and medical histories were collected through questionnaires.

Results: BMI showed a positive association with lumbar spine ($\beta = 0.503$, $p = 0.001$) and femoral neck T-scores ($\beta = 0.413$, $p = 0.004$). WHR ($\beta = 0.256$, $p = 0.002$) was positively associated with BMD, while C-index ($\beta = -0.455$, $p = 0.001$) was negatively correlated with femoral neck T-scores. Lower BMI and WHtR values were found predictive for osteoporosis according to the ROC curve analysis. While BMI was found as the strongest predictor, VAI did not significantly differentiate between groups ($p > 0.05$).

Conclusion: For assessment of osteoporosis risk in postmenopausal women; anthropometric indices like CI, WHR, and WHtR may be combined with BMI. In populations with different body compositions, these measures in clinical practice can improve osteoporosis screening and management.

Keywords: Anthropometric Indices; Body Fat Distribution; Body Mass Index (BMI); Osteoporosis; Postmenopausal Women

Corresponding author *: Ankara Etlik City Hospital, Obstetrics and Gynecology Hospital, Ankara, Türkiye.
Email: busraejderoglu@yahoo.com
ORCID: 0000-0002-4315-5518
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Öz

Amaç: Bu çalışma, Vücut Kitle İndeksi (VKİ), Bel-Kalça Oranı (WHR), Bel-Yükseklik Oranı (WHtR), Konisite İndeksi (CI) ve Visceral Adipozite İndeksi (VAI) gibi çeşitli antropometrik ölçümlerin postmenopozal kadınlarda osteoporoz ile ilişkisini değerlendirmektedir.

Gereç ve Yöntem: Bu kesitsel çalışmaya, 45-75 yaş arası 304 postmenopozal kadın katılmıştır. Kemik Mineral Yoğunluğu (KMD), İkili Enerji X-Işını Absorpsiyometrisi (DEXA) kullanılarak değerlendirilmiştir. Antropometrik ölçümler (ağırlık, boy, bel çevresi, kalça çevresi) kaydedilmiş ve indeksler (VKI, WHR, WHtR, CI, VAI) hesaplanmıştır. Demografik ve tıbbi veriler toplanmıştır.

Bulgular: VKİ, lomber omurga (β = 0.503, p = 0.001) ve femoral boyun T-skorları (β = 0.413, p = 0.004) ile pozitif ilişki göstermiştir. WHR (β = 0.256, p = 0.002) KMD ile pozitif ilişkilidir, CI (β = -0.455, p = 0.001) ise femoral boyun T-skorları ile negatif korelasyona sahiptir. ROC eğrisi analizleri, düşük VKİ ve WHtR değerlerinin osteoporozu öngördüğünü, VKİ'nin en güçlü öngörücü olduğunu göstermiştir. VAI, osteoporoz risk kategorilerini anlamlı şekilde ayırt edememiştir (p > 0.05).

Sonuç: CI, WHR ve WHtR gibi antropometrik indeksler, VKİ ile birlikte kullanıldığında postmenopozal kadınlarda osteoporoz riskinin değerlendirilmesini artırmaktadır. Bu ölçümlerin klinik pratiğe entegrasyonu, osteoporoz tarama ve yönetimini özellikle çeşitli vücut kompozisyonlarına sahip popülasyonlarda iyileştirebilir.

Anahtar Kelimeler: Antropometrik ölçümler; Osteoporoz; Postmenopozal; Vücut kitle indeksi; Vücut yağ dağılımı

1. Introduction

Osteoporosis is an important health issue has a significant impact on morbidity and mortality worldwide (1). The osteoporosis is defined as a " progressive systemic skeletal disease characterized by low bone mass and microarchitectural deterioration of bone tissue, with a consequent increase in bone fragility and susceptibility to fracture" by World Health Organization. Dual-energy X-ray absorptiometry (DEXA) which assesses bone mineral density (BMD) is the most common diagnostic tool for osteoporosis (2).

Positive correlation between Body Mass Index (BMI) and BMD has been studied. Mechanical loading in obese people potentially explains higher BMD in this population. However, BMD alone may not fully reflect bone health, particularly in obese or diabetic patients (3-5).

BMI is the simple and easy calculation formula for assessing obesity and related health risks in people. However, it has significant limitations which leads to potential misclassifications like; it does not differentiate between fat and muscle mass nor does it provide information on fat distribution (6). For instance, individuals with high muscle mass might be categorized as overweight or obese even if they have low body fat, while those with a normal BMI may still have significant visceral fat, which poses hidden health risks (7). Visceral fat plays an important role for human health. Specific hormones and cytokines that may contribute to osteoporosis are secreted from visceral fat (8). Therefore, it's crucial to utilize more specific anthropometric measurements to assess body fat distribution alongside BMI.

To address these limitations, specific anthropometric measurements have gained attention from researchers and clinicians to understand better body fat distribution and its impact on health. Indices such as the Waist-to-Hip Ratio (WHR), Waist-to-Height Ratio (WHtR), Conicity Index (C-index), and Visceral Adiposity Index (VAI) have gained prominence for their ability to provide a more distinct assessment of body structure and its relationship with health outcomes, including osteoporosis (9-11). Integrating these advanced anthropometric indices into clinical practice may enhance the identification and management of osteoporosis, particularly in populations with diverse body compositions.

This study aims to evaluate the association between various anthropometric measurements of body fat distribution and the risk of osteoporosis in postmenopausal women. By comparing traditional BMI with alternative indices, we seek to determine which measures provide the most accurate and effective assessment of body composition in relation to osteoporosis risk.

2. Materials and Methods

In this cross-sectional study postmenopausal women age between 45 and 75 years old who visited the gynecology and menopause clinics of tertiary hospital for routine gynecological control were planned to include in study. The study approval was taken from Ankara Etlik City Hospital's review board (AEŞH-BADEK-2024-020). Written and verbal informed consent was taken from the women who were volunteer for participation.

There was 450 volunteer postmenopausal women who underwent DEXA for BMD assessment. Demographic information, medical and obstetric history, and medication usage were collected from questionnaires. Women with the absence of menstruation for at least one year, and availability of recent BMD measurements (within the past year), along with concurrent fasting blood glucose and lipid profiles. After an overnight fast blood samples were drawn in the morning after an examination.

Women with fractures, those with a history of bisphosphonates, estrogen replacement therapy, and glucocorticoids, or a history of malignancy, radiotherapy or chemotherapy, renal failure, hyperthyroidism, primary hyperparathyroidism, rheumatic diseases and adrenal conditions were excluded from the study. Flow chart of the study was shown in Figure 1. A total of 304 postmenopausal women were participated in the study. All measurements were conducted by trained researchers following standardized protocols.

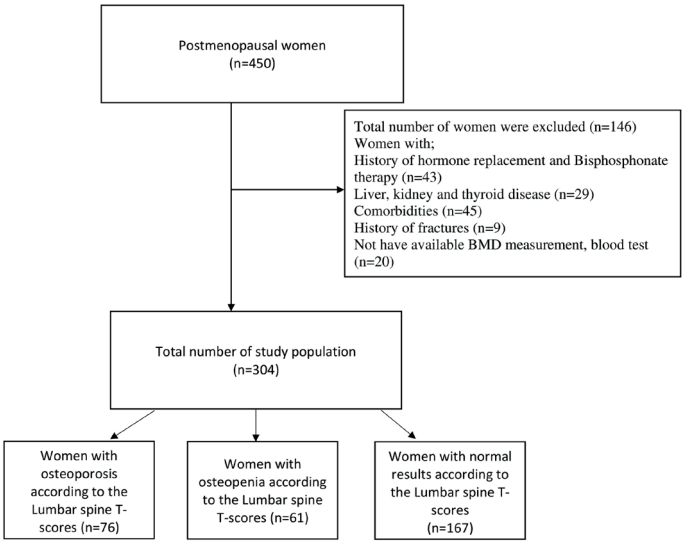

Figure 1. Flow chart of the study

Measurements

1. Anthropometric Measurements:

- **Weight and Height:** Measured using a standard digital scale and stadiometer to the nearest 0.1 kg and 0.1 cm, respectively.
- **Waist Circumference (WC):** Measured at the midpoint between the lowest rib and the iliac crest using a flexible, plastic-coated tape to the nearest 0.1 cm.
- **Hip Circumference (HC):** Measured at the widest part of the hips over the buttocks using the same tape to the nearest 0.5 cm.

2. Body Mass Index (BMI):

- Calculated by dividing weight (kg) by height squared (m^2).

3. Anthropometric Indices:

- **Waist-to-Hip Ratio (WHR):** Calculated by dividing Waist Circumference divided by Hip Circumference.
- **Waist-to-Height Ratio (WHtR):** Calculated by dividing Waist Circumference by height.
- **Conicity Index (C-index):** Calculated as WC (m) divided by [0.109 × body weight (kg) / height (m)] (12).
- **Visceral Adiposity Index (VAI):** Calculated using the formula:
- VAI Female = [36.58+(1.88×BMI) WC (cm)] × (0.81TG) × (HDL-C1.52) where TG is triglycerides, and HDL-C is high-density lipoprotein cholesterol (13).

4. Bone Mineral Density (BMD):

- DEXA scan was used to determine bone mineral density at the lumbar spine and femoral neck. Osteoporosis was defined by a T-score of less than -2.5 SD, osteopenia by a T-score between -1 and -2.5 SD, and normal bone density by a T-score between -1 SD and +1 SD (2).

Statistical analysis

SPSS software version 25.0 (IBM Corp., Armonk, NY) was used for statistical analysis. Descriptive statistics were used to summarize the general characteristics, anthropometric measurement, and laboratory findings of the study population. Continuous variables were presented as means ± standard deviations. To compare the general characteristics, measurements, and laboratory findings among the three groups (normal, osteopenia, and osteoporosis), one-way ANOVA was performed for continuous variables, followed by post hoc Tukey tests for pairwise comparisons. Correlation analysis was used to evaluate the correlation between lumbar spine and femoral neck T-scores and various anthropometric indices, including BMI, WHR, WHtR, and C-index. Pearson correlation coefficients were calculated. To further explore the associations between anthropometric measurements and BMD, multivariate linear regression analyses were performed. Different models were used for lumbar spine and femoral neck T-scores as dependent variables. Receiver Operating Characteristic (ROC) curve analyses were used to assess the predictive ability of different anthropometric indices for identifying osteoporosis. Area under the curve (AUC) values with 95% confidence intervals (CI) were calculated to determine the diagnostic performance of each index. A p-value of <0.05 was considered statistically significant for all tests.

Table 1. General characteristics, measurements and laboratory results of the patients	
	(N=304)
Age (y)	56.35±5.03
Parity (median,min-max)	2 (0-7)
Fasting Glucose (mg/dL)	110.68±39.8
Triglyceride (mg/dL)	148.62±56.05
Total cholesterol (mg/dL)	199.88±41.74
HDL-cholesterol (mg/dL)	53.99±13.15
LDL- cholesterol (mg/dL)	123.84±34.6
Hip circumference (cm)	110.53±13.85
Waist circumference (cm)	98.64±13.85
BMI (kg/m^2)	30.78±6.38
WHR	0.89±0.08
WHtR	0.63±0.09
Conicity index	0.19±0.02
VAI	5.52±2.93
Lumbar Spine T-score	-0.132±2.99
Femoral Neck T-score	1.24±3.06
BMI: Body mass index, WHR: Waist to hip ratio, WHtR: weight to height ratio, VAI: visceral adipocity index	

3. Results

Table 1 presents the general characteristics, anthropometric measurements, and laboratory findings of the study population. Women were categorized into three groups based on their lumbar spine BMD results: normal, osteopenia, and osteoporosis.

Table 2 provides a detailed comparison of general characteristics, anthropometric measurements, and laboratory findings across the three BMD categories. The VAI values were similar among the three groups ($p > 0.005$). Correlation analysis revealed a positive and moderate correlation between T-scores of lumbar spine ($r = 0.350$, $p < 0.001$) and T-scores of femoral neck ($r = 0.347$, $p < 0.001$) with BMI. A negative and weak correlation was found between lumbar spine ($r = -0.261$, $p < 0.001$) and femoral neck T-scores ($r = -0.307$, $p < 0.001$) with the C-index.

ROC analyses were performed to assess the predictive ability of various indices for identifying osteoporosis. A higher C-index demonstrated predictive ability for determining women with osteoporosis according to lumbar spine T-scores (AUC = 0.722, 95% CI 0.660-0.783) and femoral neck T-scores (AUC = 0.679,

Table 2. Comparison of the groups according to the lumbar spine T-scores				
	Osteoporosis group	Osteopenia group	Normal group	
	(n=76)	(n=61)	(n=167)	p
Age (y)	57.89±4.63^a	57.67±4.7^{a,b}	55.16±5.04^c	<0.001
Parity (median, min-max)	2(0-6)	2(0-7)	2(0-7)	0.797
Fasting Glucose (mg/dL)	116.97±49.06^a	119.9±40.2^{a,b}	104.44±33.64^c	0.025
Triglyceride (mg/dL)	156.61±61.93^a	160.68±54.12^{a,b}	140.57±52.86^c	0.042
Total cholesterol (mg/dL)	205.19±36.61	191.49±40.64	196.89±44.01	0.136
HDL- cholesterol (mg/dL)	57.03±14.14^a	50.24±10.83^b	53.98±13.18^{a,b}	0.007
LDL- cholesterol (mg/dL)	128.9±32.28^a	134.16±36.11^{a,b}	117.6±33.99^c	0.004
Hip circumference (cm)	105±10.68^a	115.14±16.65^b	111.36±12.17^{b,c}	<0.001
Waist circumference (cm)	92.78±11.15^a	102.57±16.37^b	99.86±13.2^{b,c}	<0.001
BMI (kg/m^2)	27.24±4.83^a	33.03±8.12^b	31.57±5.64^{b,c}	<0.001
WHR	0.88±0.07	0.89±0.08	0.89±0.08	0.829
WHtR	0.59±0.07^a	0.66±0.1^b	0.63±0.08^{b,c}	<0.001
Conicity index	0.2±0.01^a	0.18±0.01^b	0.18±0.01^{b,c}	<0.001
VAI	5.24±2.82	6±3.42	5.48±2.79	0.295
Lumbar Spine T-score	-3.77±0.65^a	-1.71±0.34^b	2.1±2.03^c	<0.001
Femoral Neck T-score	-1.9±0.95^a	-0.31±0.59^b	3.24±2.67^c	<0.001
^{a,b,c} groups with different letters are significantly different from each other. BMI: Body mass index, WHR: Waist to hip ratio, WHtR: weight to height ratio, VAI: visceral adipocity index.				

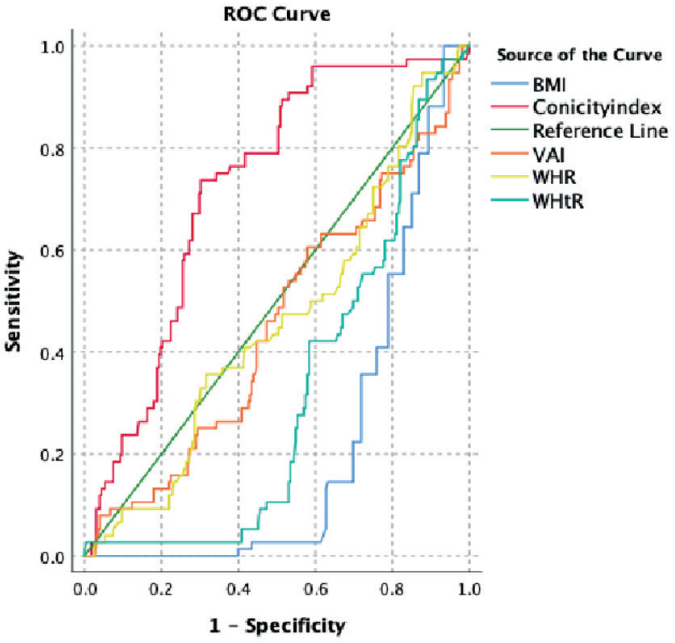

Figure 2. ROC analysis of the anthropometric measurements and osteoporosis according to the Lumbar spine T-scores

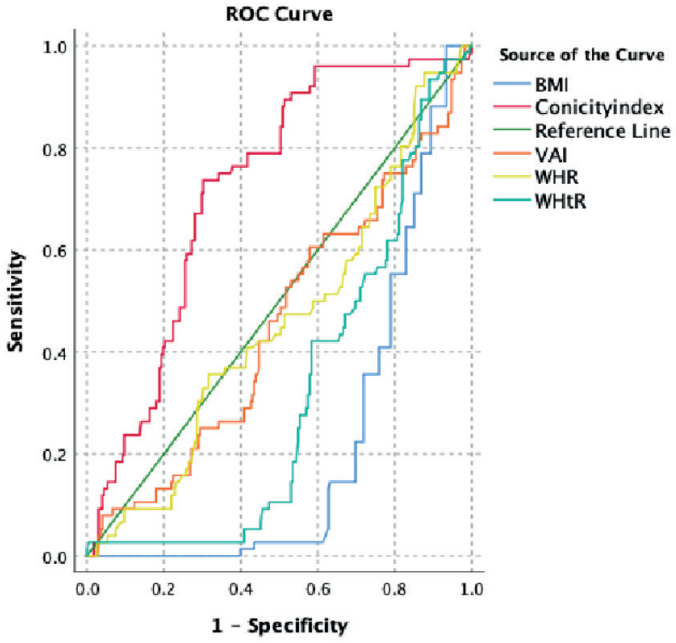

Figure 3. ROC analysis of the anthropometric measurements and osteoporosis according to the femoral neck T-scores

Table 3. Multivariate Linear Regression Analysis of the Measurements and T-Scores

	Lumbar spine T-score				Femoral neck T-score			
			95% CI				95% CI	
	Beta	p	Lower Bound	Upper Bound	Beta	p	Lower Bound	Upper Bound
BMI	.503	.001	3.558	15.403	.413	.004	.075	.380
Weight	-.193	.202	.118	.425	-.298	.044	-.119	-.002
WHtR	-.236	.104	-16.736	1.575	-.189	.182	-15.320	2.929
WHR	.256	.002	-77.454	4.732	.343	.000	7.049	18.854
Conicity index	-.245	.083	-.041	.186	-.455	.001	-110.019	-28.110
VAI	.071	.211	-.097	.021	.092	.096	-.017	.209

BMI: Body mass index, WHR: Waist to hip ratio, WHtR: weight to height ratio, VAI: visceral adipocity index.

95% CI 0.592-0.766). Lower BMI and lower WHtR values were predictive of osteoporosis based on lumbar spine T-scores (BMI AUC = 0.783, 95% CI 0.733-0.833; WHtR AUC = 0.682, 95% CI 0.620-0.743) and femoral neck T-scores (BMI AUC = 0.699, 95% CI 0.630-0.768; WHtR AUC = 0.612, 95% CI 0.518-0.706) (Figure 2 and 3).

In the multivariate linear regression analysis for the lumbar spine T-score model, a positive and significant association was found with BMI (Beta = 0.503, p = 0.001) and WHR (Beta = 0.256, p = 0.002). Similarly, in the femoral neck T-score model, both BMI (Beta = 0.413, p = 0.004) and WHR (Beta = 0.343, p < 0.001) showed positive and significant associations. Additionally, a negative and significant association was observed with the C-index (Beta = -0.455, p = 0.001) (Table 3).

4. Discussion

To evaluate the association between various anthropometric measurements and osteoporosis in postmenopausal women was the primary aim of the study. By comparing traditional BMI with alternative indices such as WHR, WHtR, CI, and VAI, we sought to determine which measures provide the most accurate reflection of bone health. Our results indicated that BMI, C-index, and WHtR are significant predictors of osteoporosis.

While BMI and WHR showed a positive association with both lumbar spine and femoral neck T-scores, C-index showed a negative association with femoral neck T-scores.

Fan et al. (14) found that both lean mass (LM) and fat mass (FM) positively correlated with BMD in postmenopausal women, with FM maintaining its positive association even after adjusting for age, height, and years of post-menopause. Their study did not find a significant association between the android-to-gynoid fat ratio (AOI) and BMD, except for the head region. Our results confirm the positive association between WHR and BMD. However, unlike Fan et al., we did not measure AOI, highlighting a difference in our assessment of fat distribution's impact on BMD.

Yaman et al. (15) found that lower weight and BMI were linked to lower T-scores at the lumbar spine and femur in postmenopausal women. They also noted a positive correlation between thigh circumference, skeletal mass index (SMI), and femur T-scores. Our findings align with theirs, showing a positive correlation between BMI and T-scores at the lumbar spine and femoral neck. This supports the idea that higher body weight, often comprising more lean and fat mass, benefits bone health.

Murat et al. (16) found significant correlations between lumbar spine T-scores and skeletal muscle mass index (SMI), weight, BMI, and waist circumference (WC). The correlations between femur neck T-scores and fat percentage, SMI, weight, BMI, WC, and hip circumference were noted in this study. These similar findings with our study highlight the importance of considering multiple anthropometric indices in assessing osteoporosis risk.

The effect of anthropometric factors on osteoporosis which is diagnosed by using different tools was not found association with body weight, BMI, or DXA anteroposterior spine thickness (17). In our study BMI showed a significant positive association with both lumbar spine and femoral neck T-scores. Li et al. (18) found a positive correlation between lean mass and total BMD and a negative correlation with visceral fat mass. These studies support that it is benefical for bone health maintaining an appropriate balance of body composition.

VAI was found independently linked to a higher prevalence of osteoporosis in older people of US (19). Sun et al. (19) found that with each one-unit increase in the VAI, the prevalence of osteoporosis decreased by 1.2%. In contrast, our study found that VAI values did not significantly differ among normal, osteopenia, and osteoporosis groups. This suggests that while VAI is useful for assessing visceral fat and related metabolic risks, it may not be an indicator of osteoporosis risk. This aligns with the understanding that osteoporosis is multifactorial and requires consideration of other factors such as age, hormonal status, and overall nutritional status.

Strengths and limitations

This study has several strengths like a well-defined study population, string inclusion and exclusion criteria. However, there are several limitations. Firstly, the cross-sectional design limits causal inferences, and the study population may not be representative of the general population due to the single center design. Additionally, other factors influencing bone health, such as dietary intake, physical activity, and genetic predispositions, were not controlled for in this study.

5. Conclusion

In conclusion, this study emphasizes the importance of using anthropometric indices with BMI to assess osteoporosis risk in postmenopausal women. The indices such as the C-index, WHR and WHtR provide valuable insights into bone health. This has an importanance for postmenopausal women, who often present with different body compositions that are not adequately captured by BMI alone. Integrating these measurements into clinical practice can improve the identification and prevention of osteoporosis, ultimately reducing morbidity and mortality associated with this condition.

Author contribution

Study conception and design: BK and CK; data collection: BK, CK, SM, and SKE; analysis and interpretation of results: BK, CK, SM, and SKE; draft manuscript preparation: BK, CK, and HLK. All authors reviewed the results and approved the final version of the manuscript.

Ethical approval

The study was approved by the Ankara Etlik City Hospital Scientific Research Evaluation and Ethics Committee (Protocol no. AEŞH-BADEK-2024-020/14.02.2024).

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Conflict of interest

The authors declare that there is no conflict of interest.

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Araştırma fikri ve tasarımı: BK ve CK; veri toplama: BK, CK, SM ve SKE; sonuçların analizi ve yorumlanması: BK, CK, SM ve SKE; araştırma metnini hazırlama: BK, CK ve HLK. Tüm yazarlar araştırma sonuçlarını gözden geçirdi ve araştırmanın son halini onayladı.

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Türk Kadın Sağlığı ve Neonatoloji Dergisi

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Case Report

Transient Fetal Non-Immune Second-Degree 2:1 Atrioventricular Block: A Case Report

Geçici Fetal İmmün Olmayan Atriyoventriküler Blok 2:1 Atriyoventriküler Blok: Olgu Sunumu

Zornitsa Vassileva*[1], Elena Pavlova[2], Dimiter Markov[2], Petya Radulova[3]

[1]Department of Pediatric Cardiology, Medicinski University, Sofia, Bulgaria
[2]Department of Obstetrics and Gynecology, Medicinski University, Sofia, Bulgaria
[3]Department of Neonatology, Universitetska Akusero Ginekologicna Bolnica Majcin Dom EAD, Sofia, Bulgaria

Abstract

We present a case of a transient second-degree 2:1 conduction atrioventricular (AV) block in a fetus with a structurally normal heart and fetal heart rate of 74 bpm at 21 weeks of gestation (WG). The maternal medical history was unremarkable and the autoantibody screening was negative. The subsequent follow-up documented complete resolution of the AV block at 25 WG. The fetal heart rate and AV conduction remained normal until delivery. The postnatal electrocardiogram (ECG) demonstrated normal sinus rhythm and duration of corrected QT (QTc)-intervals. These observations remained normal upon follow-up. Although uncommon, second-degree AV block can be one of the underlying causes of fetal bradycardia.

Keywords: fetal; atrioventricular block; second-degree; transient

Öz

Biz yapısal olarak normal kalp ve 21. gebelik haftasında (w.g.) fetal kalp hızı 74 bpm olan bir fetüste geçici ikinci derece 2:1 iletim AV bloğu olgusunu sunuyoruz. Annenin tıbbi öyküsünde özellik yoktu ve otoantikor taraması negatifti. Sonraki takip, AV bloğunun 25 w.g'de tam çözünürlüğünü belgeledi. Fetal kalp hızı ve AV iletimi doğuma kadar normal kaldı. Doğum sonrası EKG normal sinüs ritmini ve QTc aralıklarının süresini gösterdi. Takip sonrasında bu gözlemler normal kaldı. Nadir de olsa ikinci derece AV blok, fetal bradikardinin altında yatan nedenlerden biri olabilir.

Anahtar Kelimeler: fetal; atriyoventriküler blok; ikinci derece; geçici

Corresponding author *: Department of Pediatric Cardiology, Medicinski University, Sofia, Bulgaria.
Email: drvass@abv.bg
ORCID: 0000-0002-9947-0242
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1. Introduction

The atrioventricular (AV) block represents an abnormal conduction between the atria and the ventricles. It can be first-degree (prolonged AV conduction), second-degree (intermittent AV conduction), or third-degree with complete interruption of AV conduction (complete AV block - CAVB). About 45% of cases with CAVB are associated with congenital heart defects (CHD) – left isomerism, congenitally corrected transposition of the great arteries, etc. Other 50% are immune-mediated - maternal anti-Sjögren's syndrome-related antigen A autoantibodies (anti-SSA) and anti-Sjögren's syndrome type B antibodies (anti-SSB) and only about 5% of cases are isolated (1-3). Most often the impairment of the AV node is permanent and the AV conduction is irreversibly disrupted (4). Rarely, an isolated transient non-immune second-degree AV block can be observed (5-6).

2. Case Presentation

A 33-year-old, gravida 2 para 1 (G2P1) was referred for fetal echocardiography at 21 WG due to fetal bradycardia (fetal heart rate (FHR) = 70 beats per minute (bpm)) detected during a routine second-trimester scan. The patient medical and obstetric history was unremarkable. No previous medication use, nor any suspicion of past maternal infection was reported. The fetal echocardiogram demonstrated a structurally normal heart with normal systolic function. However, the fetal heart rate was 74 bpm. M-mode (Figure 1) and Pulsed wave Doppler (Figure 2) examination revealed a second-degree 2:1 conduction AV block. The atrial rate was 149 bpm, while the ventricular rate - 74 bpm. The fetal cardiovascular function was normal.

ECG of both parents demonstrated a regular sinus rhythm with normal QTc-intervals. The maternal laboratory tests including complete blood count, electrolytes, renal, hepatic, thyroid function, and anti-SSA and anti-SSB antibodies were within normal range. The follow-up examination repeated one week later revealed the persistence of the 2:1 AV block with normal fetal cardiac function. The patient was re-scanned again one week later. This time a normal fetal heart rate of 130-145 bpm was documented. The third fetal echocardiography at 25 WG demonstrated a fetal heart rate of 134-144 bpm with normal AV conduction (Figure 3).

The patient was followed up regularly and the fetal heart rate, as well as the AV conduction, remained normal until delivery. A female neonate was delivered transvaginally, with a birth weight of 3010 g, 48 cm in length. The APGAR score in the first and fifth minute was 7 and 9, respectively. The adaptation period was unremarkable with neonatal heart rate between 95 and 130 bpm in the first seven days of life. The postnatal echocardiography revealed a structurally and functionally normal heart. The serial ECGs on the first, third, and fifth days demonstrated regular sinus rhythm, normal AV-conduction and QTc-intervals. The complete blood count, blood culture, and blood gas analysis were within reference ranges. The newborn was discharged home on the eight day postpartum, weighing 3370 g.

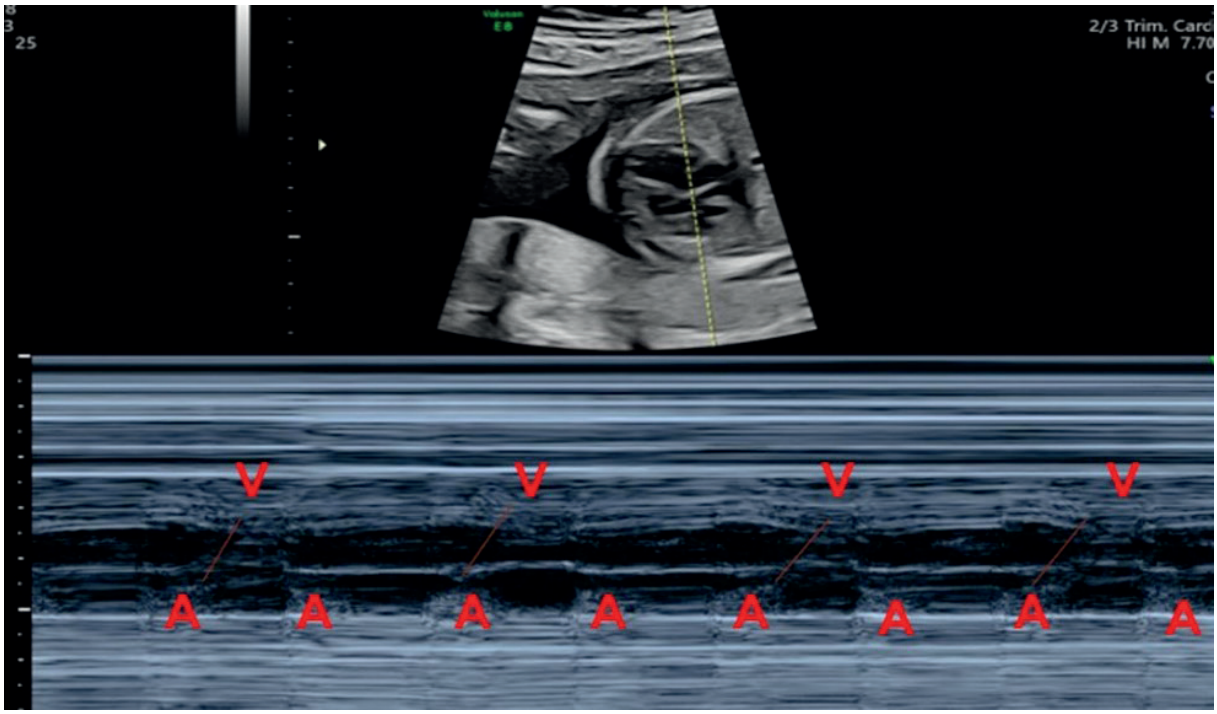

Figure 1. M-mode tracing through the right atrium and the left ventricle revealing 2:1 atrioventricular conduction at 21 WG

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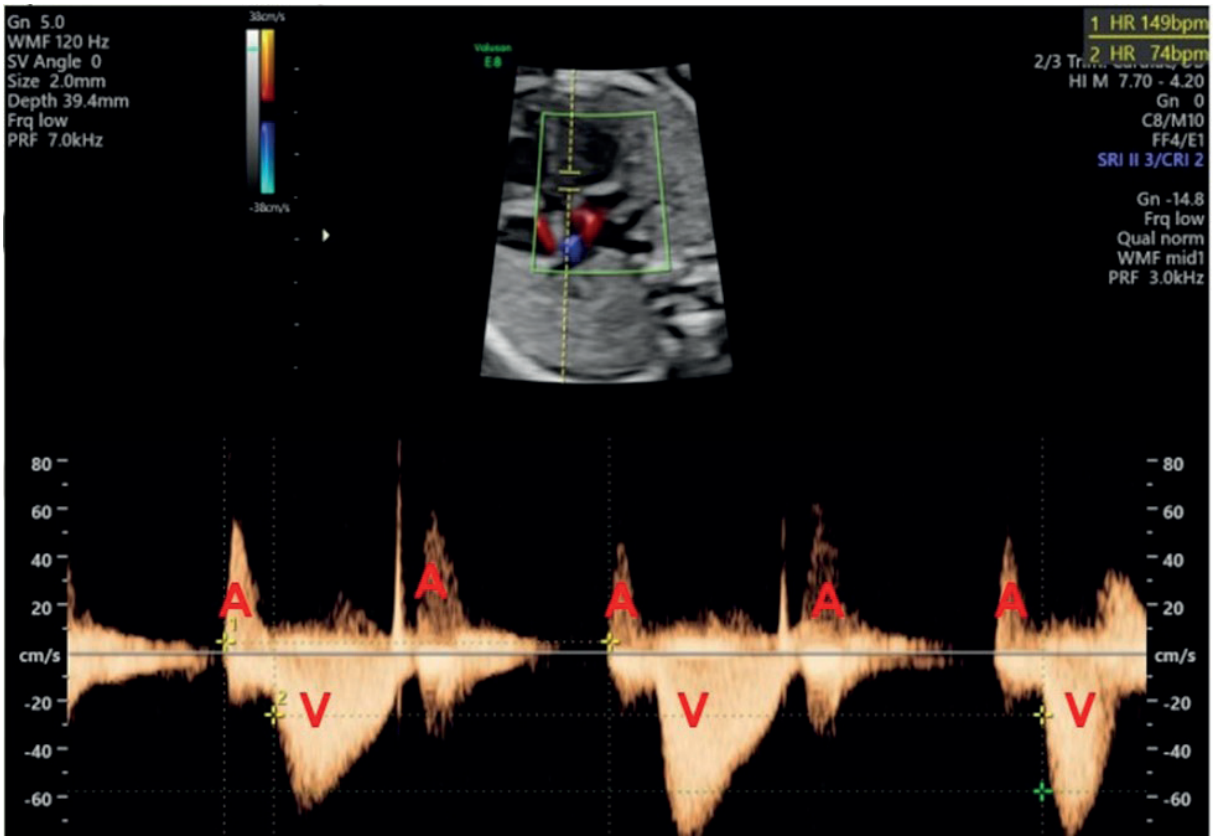

Figure 2. Doppler tracing of the left ventricular inflow/outflow demonstrating 2:1 atrioventricular conduction

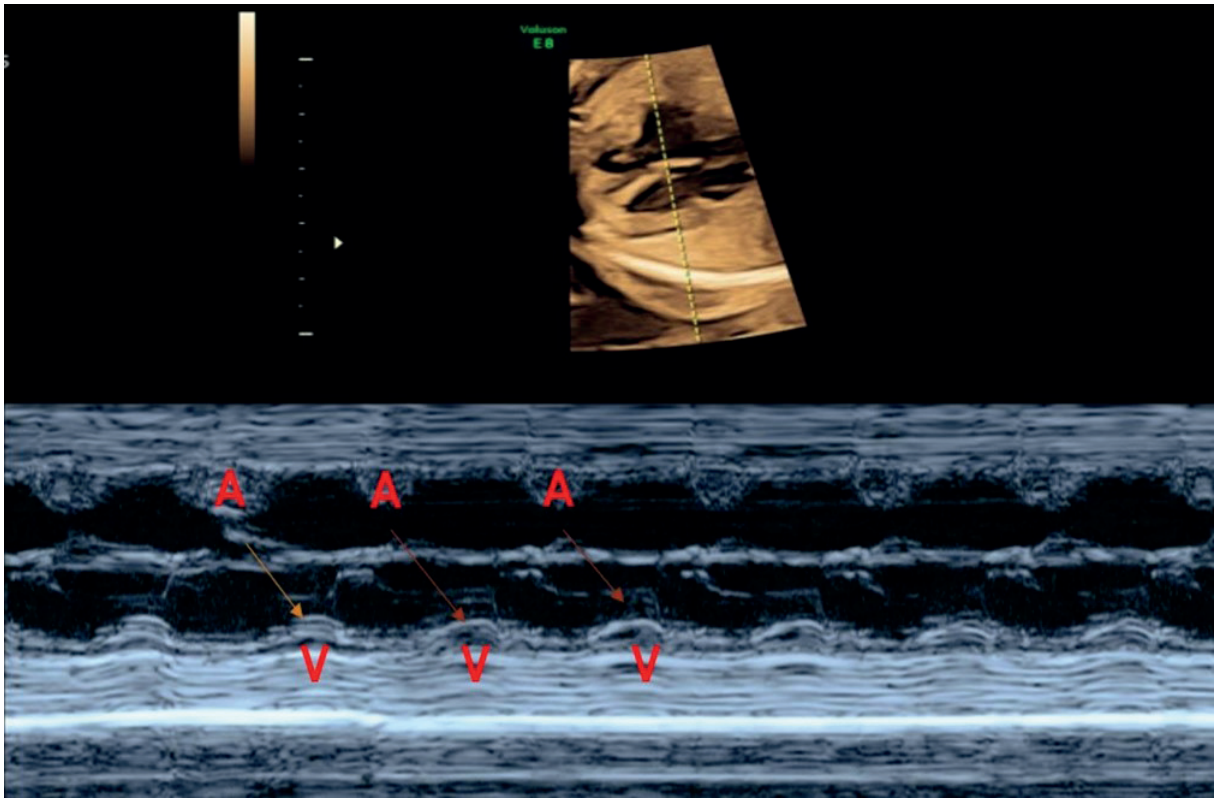

Figure 3. M-mode tracing through the right atrium and the left ventricle revealing 1:1 atrioventricular conduction at 25 WG

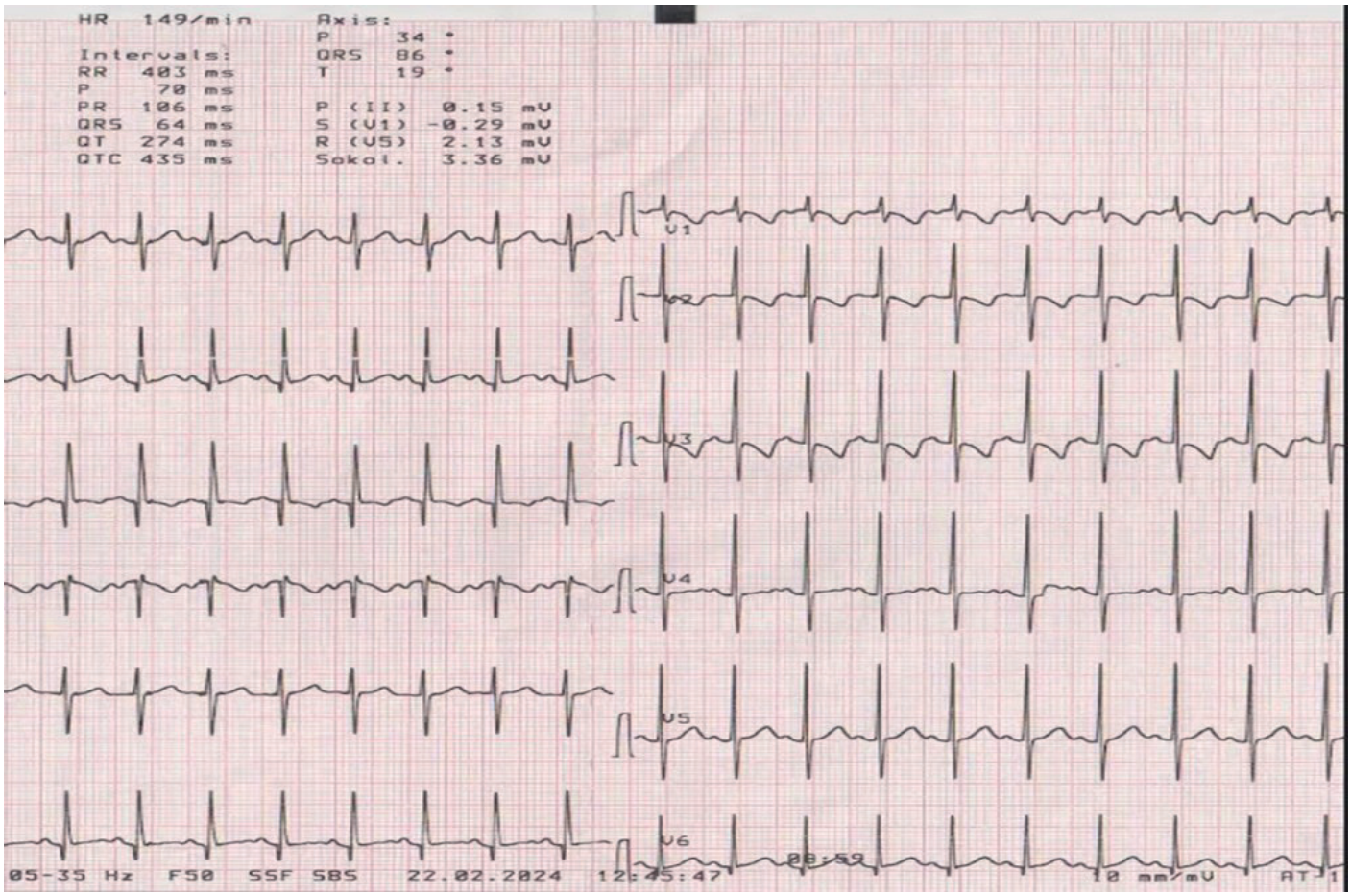

Figure 4. ECG of the newborn at one month of age demonstrating normal sinus rhythm and QTc-interval

At the end of the first and third months of age the baby was in good condition, with normal weight gain, regular heart rate of 120-149 bpm, normal ECG (Figure 4) and echocardiogram.

3. Discussion

We present an unusual case of transient non-immune fetal 2:1 AV block observed in the mid-trimester. Evidence suggests that second-degree AV-block can progress to complete AV block (CAVB) (1,2). Consequently, the differential diagnosis of CAVB should be thoroughly investigated in all affected cases - structural heart abnormalities (left atrial isomerism, discordant atrioventricular connections), immune-mediated AV block, and long-QT syndrome (LQTS). All these were excluded based on the findings of a normal fetal echocardiogram, negative maternal serology, and normal ECG of both parents.

There was a negative history of maternal infection throughout pregnancy in our case. Nevertheless, it can be hypothesized that the mother could have had a subclinical viral infection causing a transient impairment of the fetal AV node which spontaneously resolved later in gestation. Another presumption might be that this transitory fetal AV block could have been the result of a relative immaturity of the fetal conduction system. This hypothesis has been suggested by other authors, as well (5,6).

To the best of our knowledge, only a few cases of transient non-immune self-resolving 2:1 fetal AV block have been described in the literature. Breur et al. report four cases of transient non-immune fetal AV-block over a 14-year observation period in a single center (5). In half of them, the AV block was complete, and in the rest - it was second-degree. The fetal heart appeared to be structurally normal and negative maternal serology was observed. In all reported cases, the fetal heart rate was 70-85 bpm and the AV block resolved spontaneously until delivery. Postnatal ECG patterns revealed regular sinus rhythm. Kikano et al. also describe four cases of transient non-immune AV block with spontaneous resolution (6).

Second-degree AV block with intermittent AV conduction can be a possible cause of fetal bradyarrhythmia. A thorough investigation for underlying pathology should be performed in all affected cases. When structural cardiac abnormalities, maternal autoimmune disease, and hereditary channelopathy

are excluded, a favorable perinatal outcome with spontaneous resolution and normal sinus rhythm is expected to occur in most patients.

Author contribution

Study conception and design: ZV; draft manuscript preparation: ZV, EP, and PR; revision and supervision: DM. All authors reviewed the results and approved the final version of the manuscript.

Ethical approval

Written and verbal consent was obtained for this case report.

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Conflict of interest

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Etik kurul onayı

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Çıkar çatışması

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Türk Kadın Sağlığı ve Neonatoloji Dergisi

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Case Report

A Case of Spontaneous Uterine Fundus Rupture in Term Pregnancy: As A Risk Factor of Septum Resection Operation

Term Gebelikte Spontan Uterus Fundus Rüptürü Olgusu: Bir Risk Faktörü Olarak Septum Rezeksiyonu Operasyonu

Ayşe Gizem Yıldız*[1], Kübra Dilbaz[1]

[1]Department of Obstetrics and Gynecology, University of Health Sciences Etlik Zübeyde Hanım Women's Health Training and Research Hospital, Ankara, Türkiye

Abstract

Uterine septum is the most common Mullerian anomaly. Hysteroscopic surgeries offer increased fertility rates caused by Mullerian anomalies. Uterine rupture after hysteroscopic septum resection is a rare complication with a reported incidence of approximately 1-2,7%. Uterine rupture in pregnancy is a life-threatening complication. The primary risk factors for uterine rupture after a previous cesarean birth are previous uterine rupture. Also hysteroscopic surgeries such as septum resection are known risk factors for uterine rupture in pregnancy following the operation. In this report, a patient with a history of hysteroscopic septum resection due to uterine septum presented to our hospital at 37 weeks of gestation due to spontaneous premature rupture of membranes. After the procedure, the patient, who had her first pregnancy, but she had a history of previous cesarean section, was taken to emergency cesarean section. On observation, uterine rupture at the fundus level, which can be considered as a late complication of septum resection, was detected. In this case, we aimed to emphasize uterine rupture, which is an important complication that may occur in pregnancies after a history of septum resection. In rarely, uterine rupture may occur in pregnancies after hysteroscopic resection of the uterine septum. But there is no consensus on the management of pregnancies after hysteroscopic operations. Until more reliable methods are available, patients should be informed about the possible symptoms of uterine rupture and the physician should be aware of fetal and maternal well-being.

Keywords: uterin rupture; hysteroscopy; septum resection

Corresponding author *: Department of Obstetrics and Gynecology, University of Health Sciences Etlik Zübeyde Hanım Women's Health Training and Research Hospital, Ankara, Türkiye.
Email: drgizem.yildiz3@gmail.com
ORCID: 0009-0001-6332-6724
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Öz

Uterin septum en sık görülen Müllerian anomalidir. Histeroskopik ameliyatlar Müllerian anomalilerin neden olduğu fertilite oranlarında artış sağlar. Histeroskopik septum rezeksiyonu sonrası uterus rüptürü nadir görülen bir komplikasyondur ve insidansı yaklaşık %1-2,7 olarak bildirilmiştir. Gebelikte uterus rüptürü hayatı tehdit eden bir komplikasyondur. Geçirilmiş sezaryen doğum sonrası uterus rüptürü için primer risk faktörü ise geçirilmiş uterin rüptürdür. Ayrıca septum rezeksiyonu gibi histeroskopik cerrahiler de operasyon sonrası gebelikte uterus rüptürü için bilinen risk faktörleridir. Bu olgu raporunda, uterin septum nedeniyle histeroskopik septum rezeksiyonu öyküsü olan bir hasta 37. gebelik haftasında spontan erken membran rüptürü nedeniyle hastanemize başvurdu. İşlem sonrası ilk gebeliği olan ancak daha önce sezaryen öyküsü bulunan hasta acil sezaryene alındı. Gözlemde septum rezeksiyonunun geç bir komplikasyonu olarak değerlendirilebilecek fundus seviyesinde uterus rüptürü tespit edildi. Bu olguda, septum rezeksiyonu öyküsü olan gebeliklerde ortaya çıkabilecek önemli bir komplikasyon olan uterus rüptürünü vurgulamayı amaçladık. Uterin septumun histeroskopik rezeksiyonu sonrası gebeliklerde uterin rüptür nadir de olsa görülebilir. Ancak histeroskopik operasyonlardan sonra gebeliklerin yönetimi konusunda bir fikir birliği yoktur. Daha güvenilir yöntemler bulunana kadar, hastalar uterus rüptürünün olası semptomları hakkında bilgilendirilmelidir ve uzman fetal ve maternal iyilik halini gözeterek karar vermelidir.

Anahtar Kelimeler: uterin rüptür; histeroskopi; septum rezeksiyonu

1. Introduction

The uterine septum represents the most common Mullerian anomaly and is associated with recurrent pregnancy loss and infertility (1). Spontaneous abortion is the most common complication with uterine septum and 60% of these cases are associated with pregnancy-related complications (2). Although outcomes during pregnancy vary due to the morphology of the septum, hysteroscopic resection of the intrauterine septum has been reported to reduce the miscarriage rate. Hysteroscopic surgery offers higher fertility rates while avoiding the risks of open surgery. Rupture of the uterus after septal resection is a rare complication with a reported incidence of about 1-2,7%. Damage to the myometrium is thought to be a predisposing factor for uterine rupture. Uterine rupture in a subsequent pregnancy may be considered a late complication due to myometrial damage (3). Uterine rupture is a life-threatening pregnancy complication for the mother and the fetus. The primary risk factors for uterine rupture are previous uterin rupture, previous fundal or high vertical hysterotomy, patients with a previous low vertical hysterotomy and induction of labour. After a previous classical hysterotomy with cesarean section, the reported risk of rupture varies widely in the literature, from 1 to 12 percent (4).

The incidence of rupture is higher in patients with a previous cesarean delivery who undergo induction of labour spontaneously (NIH statement 2010) 1.5 versus 0.8 percent (5).

Factors that are inconsistently associated with an increased risk of rupture include older maternal age, gestational age >40 weeks, birth weight >4000 grams, delivery interval less than approximately 18 months (especially<6 months), single-layer closure, especially if locked and more than one previous cesarean delivery (6). Hysteroscopic procedures such as septal resection are also known risk factors for rupture of membranes in pregnancy following surgery.

In this case report, we wanted to emphasize uterine rupture, which is an important late complication that can occur in pregnancies following hysteroscopic septal resections.

2. Case Report

A 31-year-old female patient applied to us in June,2024 with a complaint of rupture of membranes. She was 37 weeks pregnant, had normal pregnancy tests, no known comorbidities.

Ultrasound measurements were consistent with 36 weeks of gestation with a weight of 2765 grams and a positive fetal heartbeat with oligohydroamnion. In 2015, she had a cesarean section at 32 weeks. In 2021, the patient turned to an external center for secondary infertility.

Diagnostic laparoscopy and hysteroscopy were scheduled in the same session to make a differential diagnosis of bicornuate uterus and deep septum in the hysterosalpingography made during the examinations performed. We do not know if there are any complications during hysteroscopy. Preoperative hysterosalpingography image is available (Figure 1). 2 years after this operation, the patient became spontaneously pregnant.

The patient came to the emergency department with a complaint of amnion retention. An emergency cesarean section was planned because cervical dilatation progressed two centimeter in an hour on digital examination.

Under spinal anesthesia, the abdomen was opened through a Pfannenstiel incision. The uterus was introduced through

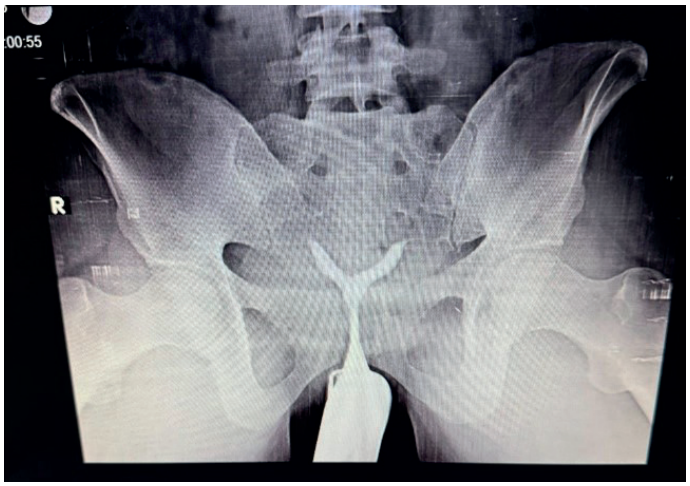

Figure 1. Preoperative hysterosalfingography image

a transverse incision in the lower segment and a single fetus weighing 2805 grams was born.

When the uterus was taken out of the abdomen, complete ruptured area of about three centimeters in length was noted, originating from the fundus (Figure 2). There was no free fluid in the abdomen. The incision was quickly closed with a single layer locked and the fundal perforated area was closed with a double layer without skipping (Figure 3).

However, after this procedure, the uterus was atonic, so rapid medical treatment was performed. 40 units of oxytocin, 1 ampoule of methylergonovine, 1 gram of transamine were administered. But there is no response to medical treatment. Therefore, further treatments were planned.

Compression sutures were not attempted as the fundus was extremely fragile. Therefore, an intrauterine tamponade was applied. No problems occurred postoperatively. The patient was discharged on the third postoperative day.

3. Discussion

Rupture of uterus during pregnancy poses significant risks to both the fetus and mother, with high mortality and morbidity rates. Hysteroscopic procedures such as septal resection are also known risk factors for uterine rupture in subsequent pregnancy. The 2010 statement from the National Institutes of Health (NIH) Consensus Development Conference reported no maternal deaths due to uterine rupture (7) but a 10-year review of severe maternal outcomes in Canada reported four maternal deaths among 1879 cases of uterine rupture in patients with no major preexisting medical conditions (8). While awareness of the prevention of uterine rupture following cesarean section has increased, not enough attention has been paid to cases caused by pregnancy following hysteroscopy. Complications

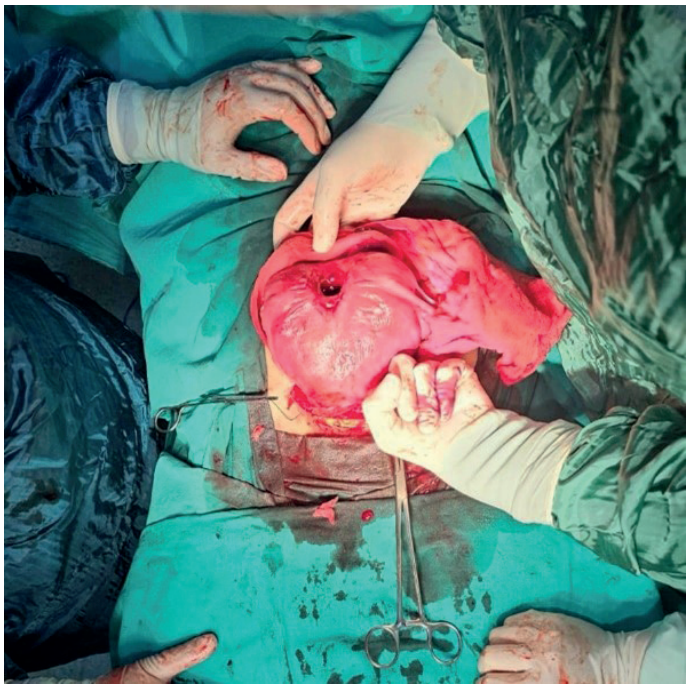

Figure 2. Image of the rupture area before repair

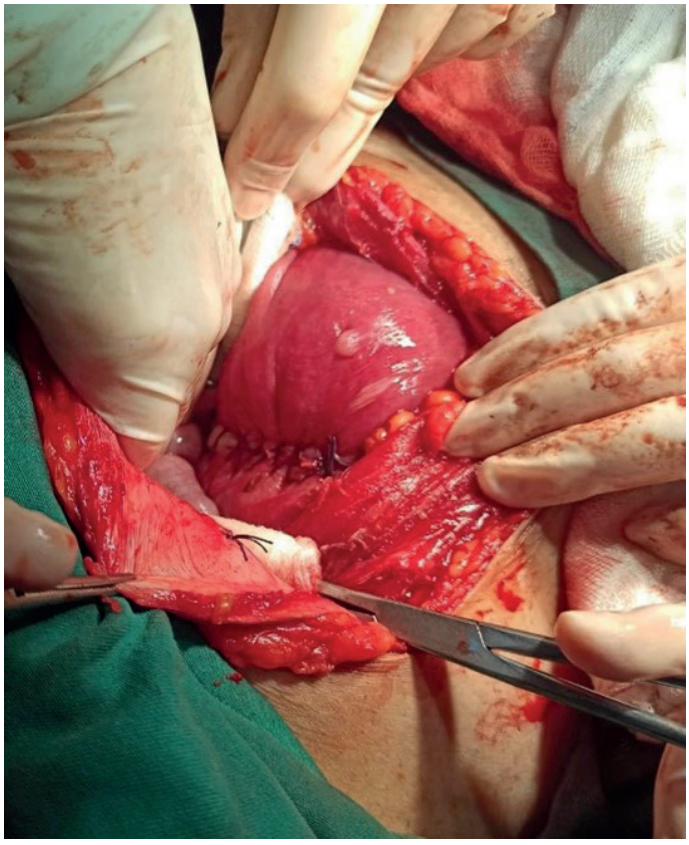

Figure 3. Image of the ruptured area after repair

can include uterine perforation during surgery, hemorrhages, development of intrauterine adhesions after surgery and uterine rupture in subsequent pregnancies. Although rare, uterine rupture can be fatal if not recognized in time.

Jansa et al. performed retrospective data analysis over 20 years and found 4 cases of rupture after hysteroscopy. In this article, which is similar to our case (case 4), there was a period of 2 years between hysteroscopy and pregnancy and there were no known complications during hysteroscopic surgery. When the patient was brought for elective cesarean section due to fetal macrosomia at 40 weeks' gestation, an approximately 4-cm-long perforation area was noted originating from the fundus, but no intra-abdominal hemorrhage was observed, similar to our case. The tear was reconstructed with sutures in a single layer. In contrast, in case 2, vaginal delivery was unsuccessful despite the administration of oxytocin and a cesarean section was performed at 38 weeks' gestation. The perforated area extending from the fundus to the left parametrium was observed intraoperatively. Although a uterine ligation was performed due to the heavy bleeding, followed by ligation of the hypogastric artery, the patient could not be stabilized and a hysterectomy was performed. The remarkable thing was that the patient became pregnant one month after the operation (9). The time between surgery and pregnancy therefore also influences pregnancy complications.

After the treatment of Asherman's syndrome, Deaton et al. reported a case of uterine rupture that was not due to uterine contractions but to dilation of the uterus during pregnancy. The patient underwent two hysteroscopic adhesiolysis procedures. After becoming pregnant, she had to be admitted to hospital at 25 weeks of pregnancy due to vaginal bleeding without contractions. She was hospitalized for 40 days with no signs of labor, but then an acute uterine rupture occurred, necessitating an emergency cesarean hysterectomy. The fundus was described as "paper thin from cornu to cornu" (10).

In our case, the myometrial tissue in fundal area was thinned and too friable to allow compression sutures as it was paper thin from cornu to cornu. Although the bleeding in our patient was not heavy, the lack of contraction of the uterus, especially in the fundus area, can be explained in this way.

4. Conclusion

A review of the literature indicates that cases of uterine rupture following hysteroscopic septum resection are solely documented in case reports.

The frequency and intensity of uterine contractions during pregnancy after septal resection is an important factor. In our case, premature rupture of membranes occurred. In addition, uterine contractions were present and cervical dilatation progressed rapidly on vaginal examination. All this shows that our patient was at high risk of uterine rupture.

Until more reliable methods are available, it is important to inform patients about the possible symptoms of uterine rupture, and physicians should keep the well-being of the fetus and mother in mind.

Author contribution

Study conception and design: AGY; draft manuscript preparation: AGY and KD; revision and supervision: AGY and KD. All authors reviewed the results and approved the final version of the manuscript.

Ethical approval

Written and verbal consent was obtained for this case report.

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Conflict of interest

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