e-ISSN: 2980-0579

Volume: 3 Issue: 1 Year: 2025

JCOGP

Journal of Controversies in Obstetrics & Gynecology and Pediatrics

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It is with great enthusiasm and pride that we present the 2025 issue of the Journal of Controversies in Obstetrics & Gynecology and Pediatrics (JCOGP). Since its inception under the Medihealth Academy, our journal has served as a platform for fostering dialogue, presenting groundbreaking research, and addressing the most compelling and debated topics in the fields of obstetrics, gynecology, and pediatrics.

In an era where the boundaries of medical science are constantly expanding, the need for evidence-based discussions and a multidisciplinary approach has never been greater. Our journal continues to uphold its mission to provide a forum where controversies and innovations can coexist, stimulating critical thinking and inspiring advancements in these essential areas of healthcare.

This year, we remain committed to our goals of improving visibility and accessibility. By maintaining our publication language exclusively in English, we strive to reach a global audience, ensuring that the valuable insights contributed by our authors are accessible to researchers, clinicians, and educators worldwide. Our inclusion in internationally respected indices such as DRJI, ESJI, and OAJI underscores our dedication to academic excellence and impact.

The 2025 issue highlights an array of topics, from innovative approaches in maternal-fetal medicine to emerging treatments in pediatric care and the ongoing discussions around reproductive health. Additionally, we are pleased to feature thought-provoking reviews and case reports that address the complexities and challenges of clinical practice.

We express our gratitude to the authors, reviewers, and editorial team whose tireless efforts make this journal possible. Your commitment to advancing knowledge and improving patient care is the cornerstone of our success.

As we move forward, we invite researchers and practitioners to join us in exploring the controversies that drive progress. Together, let us challenge conventions, inspire breakthroughs, and continue to shape the future of obstetrics, gynecology, and pediatrics.

Thank you for your continued support of the Journal of Controversies in Obstetrics & Gynecology and Pediatrics.

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DOI: 10.51271/JCOGP-0039

The relationship between polycystic ovary syndrome phenotypes and systemic immune inflammation indices

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Cite this article: Gürbüz T, Ayar Madenli A, Çetiner S. The relationship between polycystic ovary syndrome phenotypes and systemic immune inflammation indices. *J Controv Obstetr Gynecol Ped*. 2025;3(1):1-8.

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Received: 27/09/2024 • **Accepted**: 09/10/2024 • **Published**: 09/01/2025

ABSTRACT

Aims: Polycystic ovary syndrome (PCOS) displays chronic, low-grade inflammation characterized by an enhanced release of pro-inflammatory cytokines. However, the extent of systemic inflammation and its variations across different PCOS phenotypes has not been sufficiently characterized. The study aimed to investigate the relationship between the presence and phenotypes of PCOS and systemic immune inflammation (SII) and response (SIRI) indices.

Methods: A total of 310 newly diagnosed PCOS patients and 105 healthy premenopausal women were included in this retrospective study. PCOS were categorized into four distinct phenotypes: phenotype A [hyperandrogenism (HA), oligomenorrhea (OA), and polycystic ovaries (PCO)], phenotype B (HA and OA), phenotype C (HA and PCO), and phenotype D (OA and PCO).

Results: Median SII and SIRI were higher in patients with PCOS than control group. The androgenic phenotypes group, specifically Phenotype A, exhibited elevated levels of SII and SIRI compared to the non-androgenic phenotype group. There was a positive correlation between these indices and hormonal parameters and insulin resistance. These relationships were particularly pronounced in the phenotype A group. Increased SIRI was an independent predictor of PCOS fold (OR=1.08, p<0.001). In distinguishing the androgenic phenotypes from the non-androgenic phenotypes, the threshold value of the SIRI was found to be >1.1 with 67.1% sensitivity and 81.2% specificity. It was incapable of distinguishing phenotype B from Phenotype C, but it was found successful in predicting phenotype A among all phenotypes.

Conclusion: Elevated SII and SIRI levels were associated with the presence of PCOS and its phenotypes, particularly phenotype A. SIRI demonstrated potential as a screening tool for phenotypic discrimination of PCOS, beyond predicting its presence.

Keywords: Polycystic ovary syndrome, systemic immune inflammation, systemic immune inflammation index, phenotype, insulin resistance

INTRODUCTION

Polycystic ovary syndrome (PCOS) is a prevalent endocrine disorder that affects women of reproductive age, and its estimated prevalence ranges from 4% to 20% worldwide.[1] PCOS is characterized by the presence of chronic oligo/anovulation, clinical/biochemical hyperandrogenism, and polycystic ovarian morphology.[2] While the exact pathogenesis of PCOS remains unclear, there is evidence suggesting the involvement of low-grade chronic inflammation, insulin resistance (IR), as well as various genetic and environmental factors.[3] These factors may predispose individuals with PCOS to a variety of unfavorable health outcomes, including metabolic syndrome, cardiovascular diseases, pregnancy complications, and gynecological cancer.[4] Hence, there is a need for further investigation and understanding of the effects of these potential mechanisms.

Human preovulatory follicles have been observed to contain a substantial number of immunocompetent cells, including macrophages, T-cells, and B-cells.[5] It has also been demonstrated that women with PCOS have a chronic low-grade inflammation marked by increased release of pro-inflammatory cytokines such as interferons and interleukins.[6] Furthermore, low-grade inflammation is thought to be a precursor to IR, which is also linked to the development of PCOS.[7,8] These findings indicate a potential link between immune function

and PCOS. However, the extent of systemic inflammation and its variations across different PCOS phenotypes has not been sufficiently characterized.

Considering the potential contribution of low-grade inflammation to the development of PCOS, we postulated an association between PCOS phenotypes and systemic immune inflammation indices derived from leukocytes, which play a role in the production of pro-inflammatory cytokines. Among these indices, we evaluated the systemic immune inflammation index (SII) and systemic inflammation response index (SIRI), which have not yet been investigated in the context of PCOS but are claimed to be associated with metabolic syndrome and cardiovascular diseases.[9,10] The SII, which is an indicator of inflammatory status, is calculated by platelet count×neutrophil count/lymphocyte count, while the SIRI, which is an indicator of the balance between the inflammatory response and immune status, is calculated by neutrophil count×monocyte count/lymphocyte count.[11,12]

In the present study, we aimed to investigate the relationship between the presence and phenotypes of PCOS and SII and SIRI indices. To gain further insight into the relationship of systemic immune inflammation on PCOS phenotypes, we evaluated the association between these indices, hormonal parameters, and IR across phenotypes.

METHODS

This retrospective study conducted at Bakırköy Sadi Konuk Hospital Gynecology and Obstetrics Clinic from June 2015 and June 2020. The study was conducted with the permission of the Clinical Researches Ethics Committee of Bakırköy Dr. Sadi Konuk Training and Research Hospital (Date: 12.09.2022, Decision No: 146/19) and was conducted in compliance with the relevant ethical guidelines and the Declaration of Helsinki (2013 Brazil revision). The local ethics committee waived the requirement of informed consent due to the retrospective nature of the research.

Study Population

A total of 642 woman diagnosed with PCOS who visited the Outpatient Clinic during the study period were evaluated retrospectively. The diagnosis of PCOS was made based on the on the agreed ASRM/ESHRE criteria adopted in Rotterdam, which required the presence of at least two out of the following three criteria: (1) oligo-ovulation and/or anovulation, (2) clinical and/or biochemical hyperandrogenism, and (3) polycystic ovaries observed via ultrasound. The diagnosis of PCOS was confirmed after excluding other potential causes of hyperandrogenemia or ovulation dysfunction, such as thyroid disease, congenital adrenal hyperplasia, Cushing's syndrome, androgen-secreting tumors, 21-hydroxylase deficiency, and hyperprolactinemia.[2] The inclusion criteria in this study were as follows: age between 18 and 40 years old, newly diagnosis of PCOS, fertility requirements within the past year. The following exclusion criteria were then also applied: a history of PCOS or PCOS-related treatment, any systemic inflammatory or autoimmune diseases, history of hypertension or diabetes mellitus, history of coronary artery diseases, liver diseases, active hepatitis, malignancy, renal failure, history of anti-inflammatory or chronic corticosteroid drugs, hormone therapy, early menopause, pregnancy, lactation, use of smoke and alcohol, and missing clinical data. After this exclusion process, 310 patients who had newly diagnosed PCOS were enrolled in this study.

Additionally, the study included a control group consisting of 105 healthy premenopausal women from the general community who met the specific inclusion criteria: (1) consistent regularity in menstrual cycles, (2) absence of observable clinical indications of hyperandrogenemia, including acne, hirsutism, seborrhea or alopecia, and (3) confirmation of normal ovarian morphology as determined through transvaginal ultrasound examination.

Study Protocol

The hospital's electronic information system and patient files were used to gather demographic and clinical data. In accordance with the Rotterdam criteria, the ultrasonographic diagnosis of PCOS necessitates the observation of 12 or more ovarian follicles with a diameter ranging from 2 to 9 mm, and/or a discernible increase in ovarian volume exceeding 10 mL. Regarding the diagnosis of PCOS, the fulfillment of these criteria by at least one ovary has been accepted satisfactory.[2] In accordance with the Rotterdam criteria, women diagnosed with PCOS were categorized into four distinct phenotypes: phenotype A [hyperandrogenism (HA), oligomenorrhea (OA), and polycystic ovaries (PCO)], phenotype B (HA and OA), phenotype C (HA and PCO), and phenotype D (OA and PCO).

Biochemical parameters were analyzed using venous blood samples collected during outpatient evaluations on days 2 to 5 of the menstrual cycle after a 12-hour fasting period then analyzed in a single laboratory using the same methodology as described below.

Laboratory Parameters

A Beckman DxC device (Beckman Diagnostic Corp., CA, ABD) and Hitachi Modular P800 autoanalyzer (Roche Diagnostics Corp., IN, USA) were used to evaluate patients' venous blood samples. Levels of hemoglobin (photometrically), leukocyte count (impedance method), triglycerides and total cholesterol (enzymatic colorimetry), and high-density lipoprotein cholesterol (HDL-C) (homogeneous enzymatic colorimetry) were determined. The Friedewald formula was used to determine low-density lipoprotein cholesterol (LDL-C).[13] Follicle-stimulating hormone (FSH), luteinizing hormone (LH), dehydroepiandrosterone sulfate (DHEA-S), total testosterone (TT), Anti-mullerian hormone (AMH), and fasting insulin levels were determined using the chemiluminescent microparticle immunoassay method (Abbott Architect i2000).

The LH/FSH ratio (LFR) was obtained by dividing the LH by the FSH. Homeostatic Model Assessment for IR (HOMA-IR) was calculated using the following formula: HOMA-IR=[fasting insulin (mU/mL)xfasting glucose (mg/dL)/405]. The inflammation indices were respectively calculated as follows: NLR=neutrophil count/lymphocyte count; PLR=platelet count/lymphocyte count; SII=platelet count×neutrophil count/lymphocyte count; SIRI=neutrophil count×monocyte count/lymphocyte count;[11,12] and MHR=monocyte count/HDL-C.

Statistical Analysis

All data were analyzed with IBM SPSS Statistics for Windows 20.0 (IBM Corp., Armonk, NY, USA). Numerical data

determined to be normally distributed based on the results of Kolmogorov-Smirnov tests are given as mean±standard deviation values while non-normally distributed variables are given as median (25th-75th quartile) values. For comparisons between groups, Student t-test and Mann-Whitney U test or ANOVA test (post-hoc: Bonferroni test) and Kruskall Wallis-H test (post-hoc: Dunn's test) were used in line with the normality of the considered distribution. Categorical variables are given as numbers and percentages, and inter-group comparisons were conducted with Chi-square and Fisher exact tests. Spearman correlation analyses were applied to evaluate the relationships between numerical variables. Multivariable logistic regression analysis with the backward Wald method was subsequently performed to identify any possible independent predictors of PCOS. The components of LFR, HOMA-IR, SII, SIRI and MHR were not included in the multivariable regression model because of their multi-collinearity. The receiver operating characteristic (ROC) curve analysis was applied to assess diagnostic performance. Threshold values were determined by the Youden index method. Significance was accepted at P<0.05 (*) for all statistical analyses.

RESULTS

The PCOS population included 310 patients with a mean age of 28.2±5.5 years and these patients were mostly phenotype A. The characteristic findings of PCOS patients at the time of diagnosis are presented in **Supplementary Table 1**. The levels of LFR, DHEA-S, TT and AMH were higher in the PCOS group compared to control group. The median HOMA-IR level (2.7 vs. 1.6, p<0.001), median SII level (537.6 *vs.* 354.8, p<0.001) and median SIRI level (1.1 vs. 0.4, p<0.001) were higher in the PCOS group than control group (**Supplementary Table 1**).

Demographic findings did not differ significantly according to phenotypes of PCOS. The levels of LFR, DHEA-S, TT and AMH exhibited variations in all PCOS phenotypes when compared to the control group. While the median LFR and mean DHEA-S levels were similar in the hyperandrogenic phenotypes groups, they were higher than the non-hyperandrogenic phenotype group. While The median TT and median AMH levels were higher in the phenotype A group compared to the other PCOS phenotypes groups whereas they exhibited similar levels in the phenotype B, C, and D groups. The median HOMA-IR level was similar in the phenotype A and B groups but it was higher compared to the other PCOS phenotypes groups. The levels of SII and SIRI were higher in all PCOS phenotype groups compared to the control group. The median SII and SIRI levels were higher in phenotype A, comparable in phenotypes B and C, and lower in phenotype D (**Table 1**).

SII and SIRI were positively correlated with levels of LFR, DHEA-S, TT, AMH, and HOMA-IR (**Supplementary Table 2**). This association was more pronounced in the phenotype A group (**Table 2**).

Among the potential confounding factors associated with PCOS (**Supplementary Table 1**), LFR, DHEA-S, TT, AMH, HOMA-IR, SII, SIRI, MHR and CRP were included in the multivariable logistic regression model. Increased LFR, increased AMH, increased HOMA-IR, and increased SIRI were determined as independent predictors of PCOS. Accordingly, a 1% increase in SIRI increased the risk of PCOS by 1.08-fold

Table 1 (Supplementary). Demographic and clinical findings of PCOS patients

Variables	Control n=105	PCOS n=310	p-value
Demographic findings			
Age, years	27.6±6.4	28.2±5.5	0.355
BMI, kg/m^2	25.8±3.4	26.2±3.1	0.266
WHR	0.7±0.2	0.7±0.2	0.624
Hormonal findings			
LH, mIU/ml	6.4 (5.3-8.0)	8.1 (6.6-10.1)	<0.001*
FSH, mIU/ml	7.5±1.7	6.2±1.8	<0.001*
LFR	0.8 (0.6-0.9)	1.4 (1.1-1.9)	<0.001*
DHEA-S, µg/dl	210.8±53.2	276.8±95.1	<0.001*
TT, ng/ml	0.2 (0.1-0.3)	0.4 (0.3-0.6)	<0.001*
AMH, ng/ml	2.8 (1.9-3.7)	7.0 (5.1-9.8)	<0.001*
Biochemical findings			
Glucose, mg/dl	88.5±6.8	90.1±9.1	0.162
Insulin, µU/ml	7.7 (5.1-10.9)	11.4 (8.3-14.3)	<0.001*
HOMA-IR	1.6 (1.0-2.3)	2.7 (2.0-3.7)	<0.001*
Leukocytes,×10^9/L	6.6±1.7	8.1±2.4	<0.001*
Neutrophils,×10^9/L	3.6±1.1	5.2±1.6	<0.001*
Lymphocytes,×10^9/L	2.5±0.7	2.3±0.7	0.045*
Monocytes,×10^9/L	0.3±0.1	0.6±0.2	<0.001*
Platelets,×10^9/L	242.6±50.0	255.2±52.1	0.032*
NLR	0.5±0.1	0.7±0.2	<0.001*
PLR	103.9±30.1	129.1±33.8	<0.001*
SII	354.8 (270.3-440.4)	537.6 (442.6-690.7)	<0.001*
SIRI	0.4 (0.3-0.7)	1.1 (0.8-1.5)	<0.001*
Cholesterol, mg/dl	180.7±53.8	184.0±48.4	0.765
LDL-C, mg/dl	106.7±41.5	107.1±37.0	0.914
HDL-C, mg/dl	68.0±20.4	55.9±15.7	0.014*
Triglyceride, mg/dl	87.0 (62.0-123.0)	94.5 (68.0-136.0)	0.083
MHR	6.2 (4.7-8)	9.5 (7.2-13.1)	<0.001*
CRP, mg/L	0.3 (0.1-0.9)	1.3 (0.5-2.5)	<0.001*

Data are mean±standard deviation or median (IQR), or number (%). *: p-value <0.05 shows statistical significance. AMH: Anti-müllerian hormone, BMI: Body-mass index, CRP: C-reactive protein, DHEA-S: Dehydroepiandrosterone sulfate, FSH: Follicle stimulating hormone, HDL-C: High-density lipoprotein cholesterol, HOMA-IR: Homeostatic model of insulin resistance, LDL-C: Low-density lipoprotein cholesterol, LH: Luteinizing hormone, LFR: LH to FSH ratio, MHR: Monocyte to HDL-C ratio, NLR: Neutrophil to lymphocyte ratio, PCOS: Polycystic ovary syndrome, PLR: Platelet to lymphocyte ratio, SII: Systemic immune inflammation index, SIRI: Systemic inflammation response index, TT: Total testosterone, WHR: Waist to hip ratio

Table 1. Comparison of demographic and clinical findings by phenotype of PCOS

Variables	Control n=105	Phenotype A n=102	Phenotype B n=66	Phenotype C n=63	Phenotype D n=79	p-value
Demographic findings						
Age, years	27.6±6.4	28.4±4.8	27.9±4.3	28.1±4.5	28.4±4.5	0.550
BMI, kg/m²	25.8±3.4	26.0±3.2	26.4±2.0	26.5±1.8	26.2±2.5	0.197
WHR	0.7±0.2	0.8±0.1	0.7±0.2	0.8±0.1	0.7±0.2	0.562
Hormonal findings						
LH, mIU/ml	**6.4 (5.3-8.0)**	8.9 (6.8-11.7)	9.1 (7.1-10.3)	8.7 (7.1-10.2)	**7.8 (6.5-9.4)**	<0.001*
FSH, mIU/ml	**7.5±1.7**	6.1±1.7	6.0±1.5	6.2±1.7	**6.8±1.8**	<0.001*
LFR	**0.8 (0.6-0.9)**	1.6 (1.2-2.1)	1.4 (1.1-2.0)	1.4 (1.0-2.1)	**1.1 (0.8-1.7)**	<0.001*
DHEA-S, µg/dl	**210.8±53.2**	291.9±91.3	284.6±87.6	302.4±83.5	**232.6±67.0**	<0.001*
TT, ng/ml	**0.2 (0.1-0.3)**	**0.6 (0.4-0.8)**	0.4 (0.3-0.5)	0.4 (0.3-0.5)	0.4 (0.2-0.5)	<0.001*
AMH, ng/ml	**2.8 (1.9-3.7)**	**8.5 (6.0-10.9)**	6.0 (4.9-7.7)	6.6 (5.0-8.3)	6.9 (5.2-9.2)	<0.001*
Biochemical findings						
Glucose, mg/dl	88.5±6.8	91.1±8.7	90.5±8.3	89.4±9.8	88.6±9.1	0.387
Insulin, µU/ml	**7.7 (5.1-10.9)**	12.1 (9.5-16.3)	12.4 (9.8-15.4)	11.7 (8.2-14.1)	**8.9 (6.0-11.2)**	<0.001*
HOMA-IR	**1.6 (1.0-2.3)**	3.1 (2.3-4.5)	3.2 (2.5-4.7)	**2.6 (2.1-3.2)**	**1.9 (1.4-2.6)**	<0.001*
Leukocytes,×10⁹/L	6.6±1.7	8.8±2.5	8.0±2.1	8.3±2.2	6.6±2.0	<0.001*
Neutrophils,×10⁹/L	3.6±1.1	6.0±1.8	5.2±1.7	5.1±1.6	4.2±1.2	<0.001*
Lymphocytes,×10⁹/L	2.5±0.7	2.2±0.7	2.2±0.5	2.4±0.7	2.4±0.6	0.014*
Monocytes,×10⁹/L	0.3±0.1	0.6±0.2	0.5±0.2	0.6±0.1	0.5±0.1	<0.001*
Platelets,×10⁹/L	242.6±50.0	264.8±55.0	251.3±48.4	250.0±50.7	248.6±48.6	0.048*
NLR	0.5±0.1	0.7±0.1	0.7±0.2	0.6±0.1	0.7±0.2	<0.001*
PLR	103.9±30.1	137.4±32.1	133.4±34.1	122.4±26.4	120.4±27.0	<0.001*
SII	354.8 (270.3-440.4)	671.6 (531.0-823.7)	543.1 (457.8-655.8)	526.4 (442.1-628.4)	445.7 (379.0-525.1)	<0.001*
SIRI	0.4 (0.3-0.7)	1.7 (1.2-2.4)	1.2 (1.0-1.5)	1.1 (0.9-1.5)	0.8 (0.6-1.1)	<0.001*
Cholesterol, mg/dl	180.7±53.8	185.1±45.1	176.3±50.7	191.8±55.3	177.1±41.7	0.336
LDL-C, mg/dl	106.7±41.5	110.7±37.4	100.3±42.5	115.4±37.6	101.5±28.9	0.112
HDL-C, mg/dl	68.0±20.4	**53.1±14.4**	**51.0±15.0**	58.5±17.8	62.3±13.4	<0.001*
Triglyceride, mg/dl	87.0 (62.0-123.0)	89.0 (65.4-129.6)	96.3 (73.2-156.4)	97.3 (78.5-126.0)	87.6 (61.1-136.3)	0.165
MHR	**6.2 (4.7-8)**	10.7 (7.5-14.6)	10.2 (7.8-13.3)	**8.2 (7.3-11.1)**	**7.8 (6.2-9.6)**	<0.001*
CRP, mg/L	**0.3 (0.1-0.9)**	**2.0 (0.7-3.8)**	1.5 (0.5-3.3)	1.3 (0.5-2.5)	**0.8 (0.3-1.7)**	<0.001*

Data are mean±standard deviation or median (IQR), or number (%). *: p-value <0.05 shows statistical significance. AMH: Anti-müllerian hormone, BMI: Body-mass index, CRP: C-reactive protein, DHEA-S: Dehydroepiandrosterone sulfate, FSH: Follicle stimulating hormone, HDL-C: High-density lipoprotein cholesterol, HOMA-IR: Homeostatic model of insulin resistance, LDL-C: Low-density lipoprotein cholesterol, LH: Luteinizing hormone, LFR: LH to FSH ratio, MHR: Monocyte to HDL-C ratio, NLR: Neutrophil to lymphocyte ratio, PCOS: Polycystic ovary syndrome, PLR: Platelet to lymphocyte ratio, SII: Systemic immune inflammation index, SIRI: Systemic inflammation response index, TT: Total testosterone, WHR: Waist to hip ratio

Table 2 (Supplementary). Findings related to systemic immune inflammation indices in PCOS patients

Variables	SII		SIRI	
	r	p	r	p
Demographic findings				
Age	0.040	0.479	0.012	0.828
BMI	0.036	0.523	0.143	0.112
Hormonal findings				
LH	0.266	0.048*	0.287	0.030*
FSH	-0.214	0.143	-0.218	0.120
LFR	0.288	0.031*	0.336	<0.001*
DHEA-S	0.280	0.035*	0.327	<0.001*
TT	0.293	0.028*	0.315	<0.001*
AMH	0.284	0.033*	0.320	<0.001*
Biochemical findings				
Glucose	0.127	0.467	0.110	0.487
Insulin	0.263	0.048*	0.289	0.027*
HOMA-IR	0.306	<0.001*	0.337	<0.001*
NLR	0.565	<0.001*	0.446	<0.001*
PLR	0.386	<0.001*	0.186	0.480
SIRI	0.523	<0.001*	-	-
Cholesterol	0.139	0.491	0.103	0.663
LDL-C	0.102	0.669	0.119	0.545
HDL-C	-0.189	0.496	-0.196	0.452
Triglyceride	0.164	0.461	0.188	0.400
MHR	0.311	<0.001*	0.415	<0.001*
CRP	0.305	<0.001*	0.321	<0.001*

*: p-value <0.05 shows statistical significance. AMH: Anti-müllerian hormone, BMI: Body-mass index, CRP: C-reactive protein, DHEA-S: Dehydroepiandrosterone sulfate, FSH: Follicle stimulating hormone, HDL-C: High-density lipoprotein cholesterol, HOMA-IR: Homeostatic model of insulin resistance, LDL-C: Low-density lipoprotein cholesterol, LH: Luteinizing hormone, LFR: LH to FSH ratio, MHR: Monocyte to HDL-C ratio, NLR: Neutrophil to lymphocyte ratio, PCOS: Polycystic ovary syndrome, PLR: Platelet to lymphocyte ratio, SII: Systemic immune inflammation index, SIRI: Systemic inflammation response index, WHR: Waist to hip ratio

Table 2. The relationship between hormonal parameters, insulin resistance, and systemic immune inflammation indices based on phenotype of PCOS

	Variables	SII		SIRI	
		r	p	r	p
Phenotype A	LFR	0.364	<0.001*	0.389	<0.001*
	DHEA-S	0.321	<0.001*	0.366	<0.001*
	TT	0.315	<0.001*	0.341	<0.001*
	AMH	0.317	<0.001*	0.354	<0.001*
	HOMA-IR	0.322	<0.001*	0.381	<0.001*
Phenotype B	LFR	0.314	<0.001*	0.337	<0.001*
	DHEA-S	0.305	0.018*	0.320	0.004*
	TT	0.306	<0.001*	0.315	<0.001*
	AMH	0.291	0.025*	0.318	<0.001*
	HOMA-IR	0.310	<0.001*	0.342	<0.001*
Phenotype C	LFR	0.305	<0.001*	0.310	<0.001*
	DHEA-S	0.311	<0.001*	0.310	<0.001*
	TT	0.296	0.010*	0.309	0.001*
	AMH	0.278	0.046*	0.281	0.036*
	HOMA-IR	0.290	0.027*	0.317	<0.001*
Phenotype D	LFR	0.285	0.030*	0.290	0.027*
	DHEA-S	0.292	0.022*	0.283	0.032*
	TT	0.280	0.041*	0.289	0.026*
	AMH	0.283	0.044*	0.297	0.019*
	HOMA-IR	0.276	0.050*	0.288	0.029*

*: p-value <0.05 shows statistical significance. AMH: Anti-müllerian hormone, DHEA-S: Dehydroepiandrosterone sulfate, HOMA-IR: Homeostatic model of insulin resistance, LFR: Luteinizing hormone to follicle stimulating hormone ratio, TT: Total testosterone

(OR=1.08, p<0.001) (**Supplementary Table 3**). The threshold value of the SIRI was found to be >0.6 with 87.2% sensitivity and 74.8% specificity and it showed superior diagnostic performance compared to the other inflammation indices in predicting PCOS (**Supplementary Table 4**) (**Figure 1A**). When the diagnostic performance of SIRI compared to other independent predictors of PCOS, it was lower than AMH, and superior to LFR and HOMA-IR (**Figure 1B**).

In distinguishing the non-androgenic phenotypes of PCOS from the control group, the threshold value of the SIRI was found to be >0.6 with 92.4% sensitivity and 61.0% specificity (**Figure 2A**). In distinguishing the androgenic phenotypes from the non-androgenic phenotypes, the threshold value of the SIRI was found to be >1.1 with 67.1% sensitivity and 81.2% specificity (**Figure 2B**). SIRI showed superior diagnostic performance compared to SII in the phenotypic differentiation

Table 3 (Supplementary). Independent predictors of PCOS

Variables	Univariable regression				Multivariable regression			
	OR	95% CI		p-value	OR	95% CI		p-value
		Lower	Upper			Lower	Upper	
LFR, %	1.04	1.03	1.05	<0.001*	1.03	1.01	1.04	0.004*
DHEA-S	1.11	1.07	1.15	<0.001*	-	-	-	-
TT, $\times 10^2$	1.06	1.04	1.08	<0.001*	-	-	-	-
AMH	3.10	2.42	3.98	<0.001*	4.88	2.83	8.42	<0.001*
HOMA-IR	3.18	2.33	4.35	<0.001*	2.98	1.53	5.84	0.001*
SII	1.10	1.08	1.12	<0.001*	-	-	-	-
SIRI, $\times 10^2$	1.06	1.05	1.07	<0.001*	1.08	1.04	1.11	<0.001*
MHR	1.40	1.28	1.54	<0.001*	-	-	-	-
CRP	3.23	2.25	4.64	<0.001*	-	-	-	-
					Nagelkerke R^2 = 0.872; p< 0.001*			

The components of LH/FSH ratio, HOMA-IR, SII, SIRI and MHR were not included in the multivariable regression model because of their multi-collinearity. The effects of age, BMI, and waist to hip ratio were adjusted for multivariable regression analysis. * p-value <0.05 shows statistical significance. AMH: Anti-müllerian hormone, CI: Confidence interval; CRP; C-reactive protein, DHEA-S: Dehydroepiandrosterone sulfate, FSH: Follicle stimulating hormone, HOMA-IR: Homeostatic model of insulin resistance, LH: Luteinizing hormone, LFR: LH to FSH ratio, MHR: Monocyte count to HDL-C ratio, OR: Odds ratio, PCOS: Polycystic ovary syndrome, SII: Systemic immune inflammation index, SIRI: Systemic inflammation response index, TT: Total testosterone

Table 4 (Supplementary). The diagnostic performance of SII and SIRI compared to leukocyte-based inflammatory indices and other independent predictors of PCOS

Variables	AUC±SE	95% CI	Sensitivity	Specificity	Threshold value	p-value
SII	0.83±0.02	0.79-0.87	81.3%	72.4%	>421.2	<0.001
SIRI	0.89±0.02	0.86-0.92	87.2%	74.8%	>0.6	<0.001
NLR	0.78±0.02	0.74-0.83	81.0%	67.6%	>0.5	<0.001
PLR	0.72±0.03	0.58-0.66	77.1%	61.9%	>106.5	<0.001
MHR	0.78±0.03	0.74-0.82	75.8%	69.5%	>7.2	<0.001
LFR	0.83±0.02	0.79-0.87	82.6%	75.2%	>1.0	<0.001
AMH	0.94±0.02	0.91-0.96	84.2%	89.5%	>5.7	<0.001
HOMA-IR	0.79±0.03	0.75-0.83	77.4%	70.5%	>1.9	<0.001

AMH: Anti-müllerian hormone, AUC: Area under the curve, CI: Confidence interval, HOMA-IR: Homeostatic model of insulin resistance, LFR: Luteinizing hormone to follicle stimulating hormone ratio, MHR: Monocyte to HDL-C ratio, NLR: Neutrophil to lymphocyte ratio, PLR: Platelet to lymphocyte ratio, SE: Standard error, SII: Systemic immune inflammation index, SIRI: Systemic inflammation response index

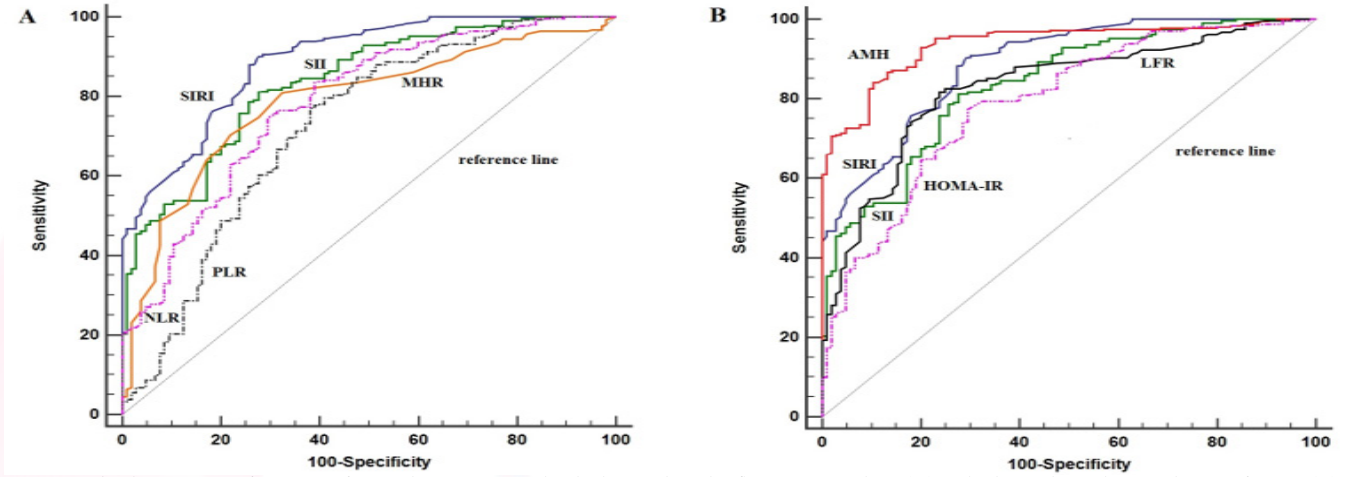

Figure 1. The diagnostic performance of SII and SIRI compared to leukocyte-based inflammatory indices (**A**) and other independent predictors of PCOS (**B**).
AMH: Anti-müllerian hormone, HOMA-IR: Homeostatic model of insulin resistance, LFR: Luteinizing hormone to follicle stimulating hormone ratio, MHR: Monocyte to HDL-C ratio, NLR: Neutrophil to lymphocyte ratio, PLR: Platelet to lymphocyte ratio, SE: Standard error, SII: Systemic immune inflammation index, SIRI: Systemic inflammation response index

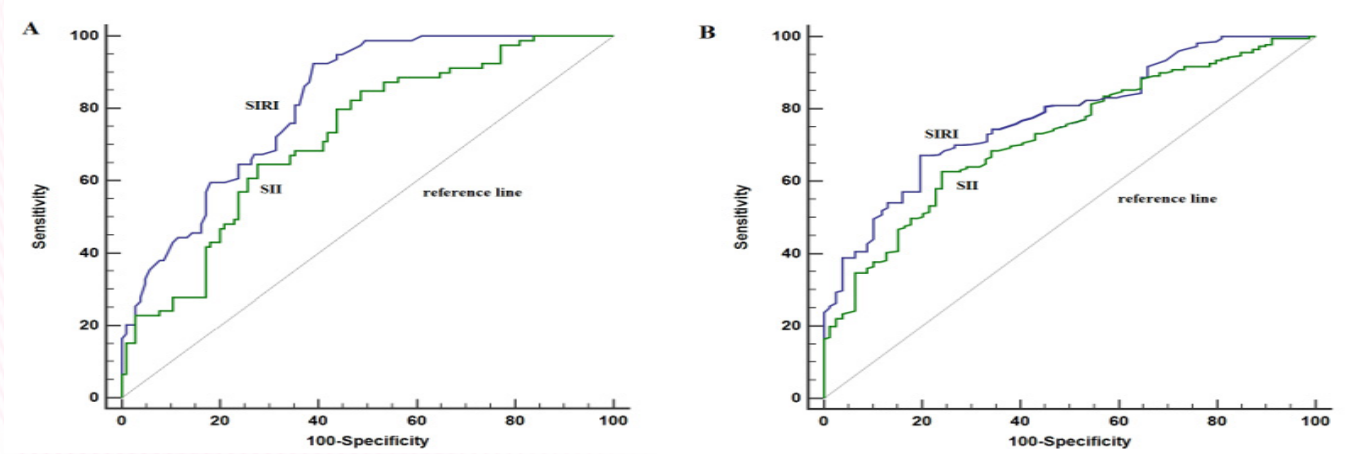

Figure 2. The diagnostic performance of SII and SIRI in distinguishing the non-androgenic phenotypes (vs. the control group) (**A**) and the androgenic phenotypes (vs. the non-androgenic phenotypes) (**B**)
SII: Systemic immune inflammation index, SIRI: Systemic inflammation response index

of PCOS. The diagnostic performance of SII and SIRI in predicting PCOS phenotypes is shown in **Table 3**. Although SII and SIRI were incapable of distinguishing phenotype B from phenotype C, they were found successful in predicting phenotype A among all the phenotypes.

DISCUSSION

To our knowledge, this is the first study in the literature to report the association between the immune inflammation indices and the phenotypes of PCOS. The associations between PCOS and high SII and SIRI indices are not surprising, as previous limited studies found that increased levels of the NLR, PLR, or leukocyte components, as well as the MHR, were predictive of PCOS.[14,16] However, to obtain a more comprehensive assessment of immune inflammation in PCOS, it may be necessary to consider a broader range of immune cell subsets. While a few case-control studies have demonstrated elevated levels of SII in PCOS patients,[17,18] current findings suggest that SIRI may be a more significant indicator.

SIRI exhibited not only a more pronounced correlation with hormonal parameters but also served as an independent marker of PCOS. During the inflammatory process in PCOS, neutrophils, acting as the frontline immune defenders, initiate the induction of macrophages through the activation of the nuclear factor (NF)-κB pathway.[19] Macrophages secrete migration inhibitory factor (MIF), a pro-inflammatory cytokine, which triggers cytokinesis through the

Table 3. The diagnostic performance of SII and SIRI in distinguishing between phenotypes of PCOS

Variables	SII	SIRI
Phenotype D vs. control		
AUC±SE	0.72±0.04	0.82±0.03
95% CI	0.65-0.79	0.75-0.87
Sensitivity	64.6%	92.4%
Specificity	72.4%	61.0%
Threshold value	>421.2	>0.6
P-value	<0.001	<0.001
Phenotype C vs. phenotype D		
AUC±SE	0.67±0.05	0.72±0.04
95% CI	0.58-0.75	0.64-0.79
Sensitivity	71.4%	%75.7
Specificity	68.2%	%73.4
Threshold value	>480.6	>1.0
p-value	<0.001	<0.001
Phenotype B vs. phenotype C		
AUC±SE	0.50±0.05	0.52±0.04
95% CI	0.41-0.59	0.44-0.63
Sensitivity	56.3%	59.1%
Specificity	34.9%	30.2%
Threshold value	>530.9	>1.1
p-value	0.941	0.904
Phenotype A vs. phenotype B/C		
AUC±SE	0.66±0.04	0.72±0.04
95% CI	0.61-0.72	0.64-0.80
Sensitivity	69.6%	76.5%
Specificity	62.5%	70.2%
Threshold value	>586.3	>1.4
p-value	<0.001	<0.001

AUC: Area under the curve, CI: Confidence interval, SE: Standard error, SII: Systemic immune inflammation index, SIRI: Systemic inflammation response index, vs: Versus

mitogen-activated protein kinase (MAPK) signaling pathway,[20] and MIF stimulates the NF-κB pathway, leading to increased levels of testosterone and LH.[21] Previous studies demonstrated that in the blood of women with PCOS, abnormal activation of T cells, the main component of lymphocytes, and macrophages leads to the production of cytokines such as and interferon (IFN)- alpha (α),- gamma (γ) and interleukin (IL) -2, -4, -5, -10.[6] Hence, immune system-initiated leukocyte activation may be a key player in the pathogenesis and phenotype of PCOS.

The present study findings revealed that hyperandrogenic phenotypes of PCOS, particularly phenotype A, have higher levels of SII and SIRI. Hormone levels can exert an influence on both the endocrine and immune systems, leading to variations in the inflammatory environment among different phenotypes of PCOS. An elevated androgen level in PCOS patients has been linked to a significant reduction in T cell count.[8] Lipid metabolism, which contributes to the differentiation of monocytes into macrophages, tends to be more impaired in hyperandrogenic phenotypes of PCOS compared to non-hyperandrogenic phenotype.[22] It has also been reported that the risk of metabolic dysfunction is higher in patients with the full-blown PCOS (phenotype A).[23] MHR levels were higher in phenotype A but lower in phenotype D, similar to the findings of a previous study.[24] On the other hand, pro-inflammatory cytokines produced by immune cells have the potential to stimulate androgen production, induce IR, and disrupt the secretion of the hypothalamic-pituitary-ovarian axis.[8] Thus, chronic inflammation and hyperinsulinemia can contribute to anovulation by affecting the hypothalamic-pituitary-ovarian axis and increasing the LFR.[25,26] Consistent with these mechanisms, phenotype A, which is associated with increased IR and greater severity of hyperandrogenism,[27] may exhibit a higher inflammatory milieu. In the phenotype A, correlations between systemic immune-inflammation indices, especially SIRI, and levels of LFR, AMH, androgen blood serum, and HOMA-IR were more pronounced.

To the best of our knowledge, this is the first study to compare the diagnostic performance of SII and SIRI with other leukocyte-based inflammatory indices and hormonal parameters for identifying PCOS patients. SIRI exhibited superior diagnostic performance compared to other parameters, with the exception of AMH. It has been reported that AMH levels, which serve as direct indicator of the follicular pool, are elevated in instances of oligo-anovulation and hyperandrogenism. This could elucidate the superior diagnostic performance exhibited by AMH.[28,29] On the other hand, it has been demonstrated that elevated cytokine release associated with PCOS can lead to a rise in AMH levels.[30] In clinical practice, the SII and SIRI indices, which can be easily obtained in a simple and cost-effective manner, may serve as valuable biomarkers for a more comprehensive evaluation of the inflammatory status in different PCOS phenotypes. This multifaceted approach could provide a more accurate representation of the immune-inflammatory processes involved in PCOS and potentially enhance the predictive power of such assessments. This hypothesis is strengthened by the identification of SII and SIRI as superior prognostic indicators compared to NLR and PLR in diverse cancer types.[31,32] Furthermore, these indices serve as significant indicators for the metabolic syndrome and cardiovascular diseases that patients with PCOS are predisposed to.[9,10] This study revealed that SIRI demonstrated superior diagnostic performance, as compared to SII, in distinguishing among various PCOS phenotypes. SIRI exhibited high sensitivity in distinguishing non-androgenic phenotypes compared to the control group, while demonstrating high specificity in differentiating these phenotypes from androgenic ones. Besides, SIRI has acceptable diagnostic performance in predicting phenotype A among androgenic phenotypes.

Limitations

This study is subject to several limitations. Firstly, its single-center retrospective design precludes the establishment of a cause-effect relationship. Another important limitation is that cytokines that play a role in the inflammatory response have not been analyzed. Finally, subtypes of lymphocytes and monocytes were not evaluated. These may provide a better understanding of the role of inflammation in the phenotypes of PCOS.

CONCLUSION

Each of the PCOS phenotypes had higher SII and SIRI levels compared to healthy controls. The androgenic phenotypes, specifically Phenotype A, exhibited elevated levels of SII and SIRI compared to the non-androgenic phenotype. Additionally, there was a positive correlation between SII and SIRI indices and IR and hormonal parameters. These relationships were particularly pronounced in the phenotype A of PCOS. Increased SIRI levels were an independent predictor of PCOS and it showed superior diagnostic performance compared to the other inflammation indices. Furthermore, SIRI had the potential to differentiate between phenotypes A and D of PCOS. Therefore, SIRI could potentially be a useful screening tool in the phenotypic discrimination of PCOS, beyond merely predicting the presence of the syndrome.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was conducted with the permission of the Clinical Researches Ethics Committee of Bakırköy Dr. Sadi Konuk Training and Research Hospital (Date: 12.09.2022, Decision No: 146/19).

Informed Consent

Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

The authors declared that this study has received no financial support.

Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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Journal of
Controversies in Obstetrics & Gynecology and Pediatrics

Original Article

DOI: 10.51271/JCOGP-0040

Prediction of preoperative and postoperative FIGO grade concordance in patients with endometrial cancer

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Cite this article: Öztürk UK, Akis S, Keleş E, et al. Prediction of preoperative and postoperative FIGO grade concordance in patients with endometrial cancer. *J Controv Obstetr Gynecol Ped.* 2025;3(1):9-13.

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Received: 19/09/2024 • **Accepted**: 17/10/2024 • **Published**: 09/01/2025

ABSTRACT

Aims: To determine the factors leading to upgrading in the final pathology result in cases with endometrial cancer.

Methods: We retrospectively analyzed the records of patients with endometrioid endometrial adenocarcinoma to evaluate the concordance between FIGO grade in preoperative endometrial sampling and postoperative final pathology grade. As a result of endometrial sampling, FIGO grade was reported as up-grading if it was lower than final pathology report, and as down-grading, if it was higher than final pathology report. The effects of tumor size, degree of myometrial invasion, lymphovascular invasion, FIGO stage, tumor localization, and additional uterine/endometrial pathologies on up-grading were evaluated.

Results: A total of 151 patients remained eligible for final analysis. The overall down-grading percentage was 8.6%, and the up-grading percentage was 25.2%. In preoperative endometrial sampling, the up-grading rates for FIGO grades 1 and 2 were analyzed as 30.5% and 20.0%. The concordance rates between preoperative endometrial sampling results and postoperative definitive pathology results were calculated as 69.5%, 55.6%, and 81.8% for FIGO grade 1,2,3, respectively.It was found that patients with more than 50% myometrial invasion (p=0.048), and those with advanced FIGO stages were more up-grading than those with earlier stages (p=0.005).

Conclusion: There is a substantial difference between the grade of preoperative endometrial sampling material and the postoperative final pathology grade in patients with endometrioid-type endometrial cancer.In the preoperative evaluation, assessment of additional markers in combination with magnetic resonance imaging may reduce misconceptions in the diagnosis, given that 25% of the patients were up-grading.

Keywords: Endometrial adenocarcinoma, endometrial sampling, FIGO grade, preoperative pathology, up-grading

INTRODUCTION

Endometrial cancer is the most prevalent malignancy of the reproductive system, accounting for 417.367 new cases and 97.370 deaths in 2020 in the World.[1] The most common histopathological type is endometrioid adenocarcinoma.[2] The management of this disease begins with the endometrial sampling result before the operation. Patients with early-stage endometrioid adenocarcinoma treated with total hysterectomy and bilateral salpingo-oophorectomy, while other patients undergo comprehensive surgical staging. Afterward, the stage of the disease is determined as a result of the histopathological evaluation of the surgical sample obtained, and the patients are evaluated in terms of the need for adjuvant treatment.[3]

The most common system used to grade endometrioid endometrial cancers is the International Federation of Gynecology and Obstetrics (FIGO) ternary grading system.[4] Ascending grade is associated with deep myometrial invasion and presence of lymph node metastasis. Furthermore, survival is lower in grade 3 tumors.[5]

Recent studies have shown that tumor grade in the preoperative endometrial sampling and tumor grade in the final histopathological result may differ.[6] Therefore, managing the operation based on the preoperative pathology may lead to incomplete surgery, as well as an increase in the morbidity of the patient with unnecessary lymphadenectomy.[7] The purpose

of the study to determine the factors leading to "up-grading" by comparing the tumor grade before and after the operation.

METHODS

This was a retrospective study conducted on 276 patients with pure endometrioid endometrial adenocarcinoma who were admitted to the gynecological oncology department at a tertiary healthcare center and evaluated for FIGO grade of preoperative endometrial sampling and postoperative final pathology grade between 2014 and 2020. This study was approved by the Research Ethics Committee of the Zeynep Kamil Women's and Children's Disease Training and Research Hospital (Date: 07.04.2021, Decision No: 87/2021). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

The pathological tissues of all patients were obtained by dilatation and curettage (D&C) biopsy and examined by specialist gynecopathologists. FIGO grading was used to assess tumor grade. If the FIGO grade in the endometrial sampling report is lower than final histological report, it was recorded as up-grading; if the FIGO grade in the endometrial sampling report is higher than final histological report, it was recorded as down-grading. The possible effect of some factors on the up-grading was investigated including, maximum tumor diameter (MTD), degree of myometrial invasion (MI [≤1/2, >1/2]), lymphovascular invasion (LVSI), FIGO stage, tumor localization (fundus, corpus, lower segment, entire endometrium), and additional uterine/endometrial pathologies (endometrial polyp, adenomyosis, and leiomyomas). Lymph node dissection requirement was designed according to Mayo criteria. It was determined that tumor size ≤2 cm, myometrial invasion ≤1/2, and conditions that meet low-grade endometrioid endometrial cancer characteristics do not require lymph node dissection.[8] When staging was required, patients treated with adequate lymph node dissection were included, and lymph node dissection regarded as satisfactory when at least 15 pelvic and/or paraaortic lymph nodes removed.[9]One hundred twenty-four patients without FIGO grading on pre-operative endometrial sampling slides, and one patient with inadequate surgical staging were excluded. Flow diagram of the studyis shown in **Figure 1**.

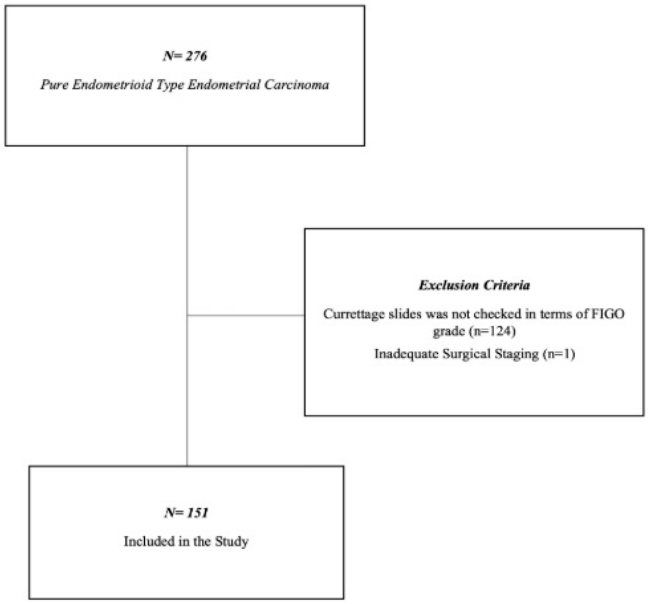

Figure 1. Flowchart of the study

RESULTS

A total of 151 patients were included in the study. The mean age of patients was 57.3 ± 0.8 years. The distribution ratio of FIGO grade 1 in preoperative endometrial sampling (62.9%) and final pathology (51.0%) was higher than FIGO grades 2 and 3. All detailed pathology-related data are given in **Table 1**.

Table 1. Pathology-related characteristics (n=151)

	n (%)
Preoperative endometrial sampling FIGO grade	
1	95 (62.9)
2	45 (29.8)
3	11 (7.3)
Final FIGO grade	
1	77 (51.0)
2	55 (36.4)
3	19 (12.6)
MI	
≤½	103 (68.2)
>½	48 (31.8)
LVSI	
No	98 (64.9)
Yes	53 (35.1)
FIGO stage	
1	125 (82.8)
2	4 (2.7)
3	16 (10.6)
4	6 (3.9)
Tumor localization	
Fundus	32 (21.2)
Corpus	78 (51.7)
Lower segment	9 (5.9)
Entire endemetrium	32 (21.2)
Additional uterine pathology	
None	93 (61.6)
Polyp	11 (7.3)
Adenomyozis	20 (13.2)
Myoma uteri	27 (17.9)

n: Number, %: Percent, PC: Probe curettage, MI: Myometrial invasion, LVSI: Lymphovascular space invasion

The overall down-grading percentage was 8.6%, and the up-grading percentage was 25.2%. According to the results of preoperative endometrial sampling, the up-grading rates for FIGO grades 1 and 2 were analyzed as 30.5% and 20.0%, respectively. The concordance rates between preoperative endometrial sampling results and postoperative definitive pathology results were calculated as 69.5%, 55.6%, and 81.8% for FIGO grade 1,2,3, respectively (**Figure 2**). There was no statistical difference between these rates (p=0.140). All detailed down/up-grading and concordance percentages are given in **Table 2**.

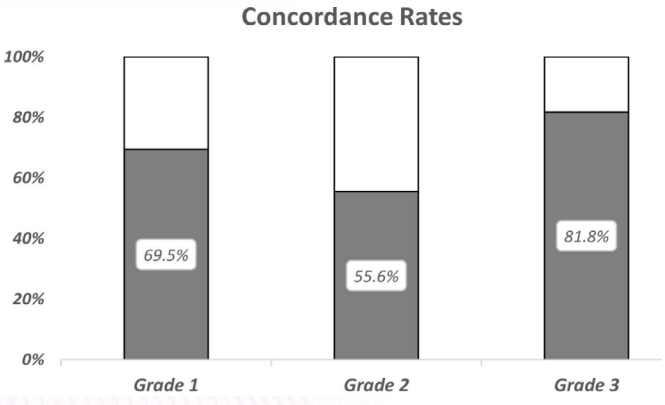

Figure 2. Concordance rates between preoperative endometrial sampling results and postoperative definitive pathology resultsfor FIGO grades

Table 2. Detailed up-staging and concordance analysis according to probe curettage and final pathology FIGO grade data (n= 151)

		Final FIGO grade			Down-grading (%)	Up-grading (%)	Concordance (%) (p= 0.140)*	Total
		1	2	3				
Pre Op E.S FIGO grade	1	**66**	28	1	-	30.5	69.5	95
	2	11	**25**	9	24.4	20.0	55.6	45
	3	-	2	**9**	18.2	-	81.8	11
Total		77	55	19	**8.6**	**25.2**	**66.2**	151

Pre Op E.S: Preoperative endometrial sampling
-Down-grading was defined as FIGO grade on probe curettage more than FIGO grade on final pathology.
-Up-grading was defined as FIGO grade on probe curettage less than FIGO grade on final pathology.
* Statistical analysis of concordance rates for preoperative FIGO grade 1,2,3.

When possible factors that might have an effect on up-grading were analyzed; 35.4% of patients with more than 50% myometrial invasion (p=0.048) and patients with advanced FIGO stage had more up-grading than those with earlier stages (p=0.005). Analysis of factors associated with up-grading are presented in **Table 3**.

DISCUSSION

Management of endometrial canceris usually made according to the results of the preoperative endometrial sampling. However, the question of how compatible these endometrial sampling results are with the final pathology is controversial.[10] Therefore, the present study aimed to evaluate the concordance between preoperative and final histological pathologies in patients with endometrial cancer.

Francis et al.[10] reported that the concordance rates of preoperative endometrial sampling with final pathology were 73%, 52%, and 53% for grades 1, 2, and 3, respectively. Petersen et al.[8] foundthese rates as 60%, 71%, and 84% for grade 1, grade 2, and grade 3, respectively.Wang et al.[9] showed in their study that with 52 women, concordancy rates were 20%,61.5%, and 77.8% for grade 1, 2, and 3, respectively. In our study, similar to the studies of Francis et al.[10] the concordance rate was 69.5% in grade 1 tumors and 55.6% in grade 2 tumors. The percentage of concordancy in grade 3 tumors was 81.8%, similar to the studies of Petersen[8] and Wang.[9]

There are publications in the literature recommending surgical staging for all endometrial cancer patients, including those diagnosed with preoperative grade 1 endometrial cancer.[11,12] Although it is known that extra-uterine spread is low in grade 1 disease, Francis et al.[10] drew attention to the importance of the upgrading percentage, which they found as 27% in grade 1 patients. They stated that it is controversial to make a surgical decision based on this solely in patients with preoperative grade 1. In our study, an upgrading rate of 30.5% in preoperative grade 1 patients supports this view.

The study by Eltabbakh et al.[13] indicated that approximately 30% of the patients with grade 1 endometrial adenocarcinoma as a result of preoperative endometrial sampling were found to be grade 2 or grade 3 in the hysterectomy specimen, and advanced surgical stage (stage III or IV) was found in 12.6%. Similarly, in our study, 30.5% up-grading was found in grade 1 tumors and 20% in grade 2 tumors. Considering that our total up-grading rate is 25.2%, the grade elevation

Table 3. Analysis of the factors in terms of up-grading (n= 151)

	FIGO grade*		
	No-upgrading (n=113)	Up-grading (n=38)	p value
Age	57.8±0.9	56.1±1.7	0.346[a]
Tumor size	38.2±2.5	44.5±4.2	0.203[a]
MI			**0.048**[b]
≤ ½	82 (79.6)	21 (20.4)	
> ½	31 (64.6)	17 (35.4)	
LVSI			0.067[b]
No	78 (79.6)	20 (20.4)	
Yes	35 (66.0)	18 (34.0)	
FIGO stage			**0.005**[c]
1	99 (79.2)	26 (20.8)	
2	4 (100.0)	0 (0.0)	
3	8 (50.0)	8 (50.0)	
4	2 (33.3)	4 (66.7)	
Tumor localization			0.300[b]
Fundus	22 (68.8)	10 (31.3)	
Corpus	58 (74.4)	20 (25.6)	
Lower segment	9 (100.0)	0 (0.0)	
Entire endometrium	24 (75.0)	8 (25.0)	
Additional uterine pathology			0.868[b]
None	68 (73.3)	25 (26.7)	
Endometrial polyp	9 (81.8)	2 (18.2)	
Adenomyozis	16 (80.0)	4 (20.0)	
Myoma uteri	20 (74.1)	7 (25.9)	

MI: Myometrial invasion, LVSI: Lymphovascular space invasion, * Upgrading was defined as FIGO grade on probe curettage less than FIGO grade on final pathology. a Statistical analysis were based on the independent sample T Test. b Statistical analysis were based on the Pearson Chi-Square test. c Statistical analysis were based on the Fisher Exact test

seen in one out of every four patients suggests that only preoperative endometrial sampling may not be sufficient for the operation management in patients planned for endometrial cancer surgery. Additionally, the advanced surgical stage (Stage III or IV) draws attention in 31.5% of our up-grading patients. This finding shows that patients with preoperative endometrial sampling results of grade 1 and 2 may have an advanced stage after surgical staging, and the need for adjuvant treatment may arise.

There are publications in the literature showing that increasing grade in endometrial cancers is associated with increased myometrial invasion, positive lymph node count, and extra-uterine disease spread.[14] Prior studies showed that deep myometrial invasion was associated with an increased risk of recurrence of disease.[15] In our study, the fact that patients with more than 50% myometrial invasion and those with advanced FIGO stage showed higher up-grading compared to the early stages, showing the importance of the role of grade in preoperative pathology in determining the final pathology. Because the patients' need for adjuvant treatment is carried out according to the final pathology.

There are publications stating that other factors besides preoperative pathology are important for the surgical staging decision in endometrial cancer. Recently, new methods have been proposed to determine tumor grade in the preoperative period using magnetic resonance imaging.[16] Preoperative magnetic resonance imaging has a sensitivity of approximately 84% in detecting deep myometrial invasion.[17] There are publications showing that high preoperative CA125 levels can predict lymph node metastases with high accuracy.[18] In addition, a prediction model using serum CA125 has recently been published.[19] Intraoperative frozen applications provide information in the confidence interval of 67% to 91% for myometrial invasion, and in the confidence interval of 40% to 100% in determining the final pathology.[20,21] Considering these rates, it is controversial how much to trust the intraoperative frozen result. Moreover, frozen applications cannot be performed in every center. Considering these situations, the importance of a strong preoperative evaluation emerges.

Limitations

A limitation of this study was that it was a retrospective, single-centerstudy. The information on whether the pathologists evaluating the hysterectomy material knew the preoperative endometrial sampling results were not included in our study. On the other hand, the main strengths are the high number of patients, and evaluation of the cases by expert gynecological oncologistsand pathologists.

CONCLUSION

There is a substantial difference between the grade of the preoperative endometrial sampling material and the postoperative final pathology grade in patients with endometrioid-type endometrial cancer. Considering that 25% of the patients are upgrading, it is aimed to reduce the misconceptions in the diagnosis with the combined evaluation of other markers and magnetic resonance imaging results in the preoperative evaluation. There is a need for prospective randomized controlled studies in which many preoperative markers are evaluated together in this regard.

ETHICAL DECLARATIONS

Ethics Committee Approval

This study was approved by the Research Ethics Committee of the Zeynep Kamil Women's and Children's Disease Training and Research Hospital (Date: 07.04.2021, Decision No: 87/2021).

Informed Consent

Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

The authors declared that this study has received no financial support.

Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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Uğur Kemal Öztürk

Associate Professor Ugur Kemal Öztürk is a distinguished expert in gynecologic oncology, particularly in the molecular profiling of endometrial cancer. He earned his medical degree from Ankara University Faculty of Medicine and completed his PhD at Zeynep Kamil Women's and Children Training and Research Hospital. His research focuses on the molecular mechanisms underlying endometrial cancer, aiming to identify biomarkers for early detection and targeted therapies. Dr. Öztürk has published extensively in peer-reviewed journals, contributing valuable insights into the genetic and epigenetic alterations associated with endometrial malignancies. He is actively involved in clinical practice, translating his research findings into improved patient management strategies. As a dedicated educator, he mentors future medical professionals, promoting a thorough understanding of both the clinical and research aspects of gynecologic oncology. His contributions have solidified his reputation as a leading figure in the field.

Journal of
Controversies in Obstetrics & Gynecology and Pediatrics

Original Article

DOI: 10.51271/JCOGP-0041

Relationship between the use of an intrauterine device and ASC-US

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Cite this article: Esercan A, Civelek M, Demir İ, Ay Haldız G, Özyürek ŞE. Relationship between the use of an intrauterine device and ASC-US. *J Controv Obstetr Gynecol Ped*. 2025;3(1):14-18.

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Received: 07/09/2024 ◆ **Accepted**: 03/01/2025 ◆ **Published**: 09/01/2025

ABSTRACT

Aims: Cervical cancer is one of the most common gynecological cancers and has poor outcomes. Although it is more easily detected through cervical cancer screening programs, studies on the interpretation of precancerous lesions and their future consequences are among the controversial issues in literature. Atypical squamous cells of undetermined significance (ASC-US) is a category of cervical epithelial cell abnormalities described by the Bethesda system for reporting cervical cytology. It refers to abnormal cytologic changes that suggest the squamous intraepithelial lesion (SIL) but are qualitatively and quantitatively less than those of a definitive SIL diagnosis. Only some studies about intrauterine devices (IUDs), a frequently used family planning method, and causality with ASC-US have been found in the literature. Although it is known that ASC-US may be caused by inflammation, it is not clear whether an IUD can cause it. Our study aimed to evaluate the prevalence of ASC-US in women who used or did not use IUDs and to determine the risk factors associated with IUD use.

Methods: Pregnant and lactating women, women with malignancies, hormonal intrauterine devices, vaginal infections, and patients whose cervical screening data were unavailable or diagnosis of inflammation were excluded. Cervical cancer screening results of ASC-US and normal cytologic results were included in the study.

Results: At our gynecological oncology reference center, cervical cancer screening (smear + human papillomavirus [HPV]) was performed on 6452 patients between 2021 and 2022, and the smear result was interpreted as ASC-US in 306 (4.7%) of these patients. In patients without IUDs, the percentage of patients with negative ASC-US cytology was significantly greater (p:0.002) than that in patients with IUDs. The odds ratio was 1.75, as IUD-positive patients had a 1.75-fold risk of having positive ASC-US results.

Conclusion: IUDs cause inflammation, which results in ASC-US. In addition to preventing ASC-US formation, this risk can be reduced by 1.75 times by not using an IUD. Even if an IUD is used, the results of colposcopic examinations do not extend beyond the findings of inflammation.

Keywords: Atypical squamous cells of undetermined significance, colposcopy, inflammation, IUD

INTRODUCTION

Cervical cancer is the third most common gynecological cancer. The mortality and morbidity associated with cervical cancer have decreased in countries in which early diagnosis and screening are performed.

Human papillomavirus (HPV) is responsible for 99.7% of cervical pathologies and cervical cancers after eliminating non-HPV risk factors, low socioeconomic status, oral contraceptive use, smoking, and genetic predisposition. A meta-analysis in which 16 studies, including those considering nonhormonal intrauterine devices (IUDs), were evaluated revealed that cervical cancer was 30% less common in women who used IUDs (summary odds ratio [OR] 0.64, 95% confidence interval [CI] 0.53–0.77). The authors interpreted the results to indicate that cervical cancer is often less likely to be an altered immune response.[1]

IUD is one of the most commonly used family planning methods, and the device can remain in the body for a long time. Nevertheless, it is not known whether this device can cause precancerous cervical lesions. Routine smear tests are essential for detecting cervical cancer and precursor lesions, and some cervical smear results can identify abnormal cells of unknown significance (ASC-US). ASC-US results show that

cells exhibit abnormalities that are more pronounced than simple reactive changes but not squamous lesions; in some cases, these lesions are associated with cervical intraepithelial neoplasia. Colposcopy can confirm such a result and usually reveals a low-grade intraepithelial lesion (LGSIL) or cervical intraepithelial neoplasia grade 1 (CIN1), normal cytology, and inflammation (infection). No publications in the literature addressing how an IUD (which is a foreign body) can cause inflammation and ASC-US are available.

ASC-US is an intermediate diagnosis named as a finding of abnormal cells in the tissue that lines the outer part of the cervix. ASC-US is the most common abnormal finding in a Pap test. It may be a sign of infection with certain types of human papillomavirus (HPV) or other types of infection, such as a yeast infection. It may also be a sign of inflammation, low hormone levels (in menopausal women), or a benign (not cancer) growth, such as a cyst or polyp. More testing, such as an HPV test or another Pap test, may be needed. Also called ASC-US and ASC-US.

In a review, changes of cervical cytology in IUD users was discussed and defined as cellular changes reflect reactive changes in endometrial and/or endocervical cells due to chronic irritation.[2] A study by M. Fornari[3] in 1974 was one of the early investigations that described the cellular changes associated with IUDs on cytology and was particularly notable for describing the atypical changes in glandular cells in which cytoplasmic vacuolization and some variation in nuclear size and shape could mimic adenocarcinoma. Later, a 1978 study by P. Gupta et al.[4] described cases with squamous atypia in addition to glandular atypia as well as an indeterminate type of case that included cells with high nuclear-cytoplasmic ratios, hyperchromasia, and at times, prominent nucleoli and multinucleation. They proposed at the time that these changes could be IUD-related, but that the findings were diagnostically worrisome as they could be difficult to differentiate from in situ carcinoma. In addition, in this study, IUDs are associated with two distinct cell types, vacuolated cells and small dark cells, and each pose their own diagnostic challenges given their overlap with distinct neoplastic processes.

As a result of these studies, our study aimed to define the relationship between ASC-US and IUD.

METHODS

Ethics

The study was conducted with the permission of Harran University Clinical Researches Ethics Committee (Date: 21.08.2023, Decision No: HRU/23.15.16). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

General Data

In our hospital, a gynecological oncology reference center, cervical cancer screening (smear+HPV cotest) was performed on 6452 patients between 2021 and 2022. The smear result was interpreted as ASCUS in 306 (4.7%) of these patients. Three hundred and six patients diagnosed with ASCUS were included in this retrospective study. Pregnant and lactating women, women with malignancies, hormonal intrauterine devices, vaginal infections, and patients whose cervical screening data were unavailable were excluded. Only cervical cancer screening results of ASC-US were included in the study.

Liquid-Based Cytological Examination

The exfoliated cells of the cervical canal and external ostium of the cervix were collected with a special brush designed for liquid-based cell tests (TCTs). The specimens were prepared with a Liqun technology centrifuge and stained with Pap. Two professional pathologists agreed on the cytological diagnosis. According to the TBS (2004) classification criteria, the TCT results were described based on specific classifications: (1) no intraepithelial lesions or malignant lesions (NILM), (2) ASC-US, (3) LGSIL, (4) atypical squamous cells without excluding high-grade intraepithelial lesions (ASC-H), and (5) high-grade squamous intraepithelial lesions (HGSIL).

HPV mRNA Detection

According to the specific steps of the Aptima HPV test kit (capture hybridization), the preservative solution of 1 ml of exfoliated cervical cells was added to the sample delivery medium (STM). Finally, the result was determined by the ratio of the signal to the threshold (s/C0). The HPV E6/E7 mRNA-positive cases were further typed and identified according to the Aptima HPV16, 18/45 genotype detection kit (capture hybridization).

This method could detect HPV 16 and HPV 18/45 E6/E7 mRNA but could not distinguish between HPV18 and HPV45. We defined HPV types as 16, 18, and others; a joint finding of ASCUS and HPV 16 or 18 will require further examination via colposcopy.

Colposcopic Evaluation

A gynecological oncologist usually performs a colposcopic examination when needed using an electronic colposcopy system (Shenzhen Jinkewei Industrial Co., Ltd.) to selectively obtain multiple biopsies in the acetic acid white and iodine test abnormally indicated areas. The biopsy tissue was fixed and preserved in 4% neutral formalin, and two professional pathologists made a diagnosis based on the routine paraffin sections.

The pathological grades included several findings:

(1) Changes in regular or chronic inflammatory responses,

(2) LGSIL;

(3) HGSIL; and

(4) Invasive carcinoma of the cervix (Ca); LGSILs and lower lesions referred to as LGSILs–, HGSILs and higher lesions referred to as HGSILs+, including HGSILs and invasive cancer.

Statistical Analysis

The data were evaluated using the SPSS 26.0 statistical program, and the percentages were calculated for the means, standard deviations, and categorical data. The normal distribution of values was examined using visual (histogram and probability graphs) and analytical methods (Kolmogorov–Smirnov test). Student t-tests were used to evaluate the statistical significance between two independent groups for variables with a normal distribution. The t-test was used to compare means between groups, and the chi-squared test was used for categorical data. If the values were not normally distributed, nonparametric tests were applied. For comparisons of more than two group averages, a single one-way analysis of variance (ANOVA) was used. Correlation analysis was performed for the significant means. For the level of statistical significance, $p<0.05$ was accepted.

RESULTS

Three hundred and six patients were diagnosed with ASC-US. The mean age of these patients was 43.92±10.33 (20-76) years. Less than half (45.1%) of the patients were postmenopausal. Less than one-quarter (16.3%) of patients had IUDs. Only 8% were cigarette smokers. Thirty-seven (12.1%) patients had positive human papillomavirus (HPV) tests (**Figure**, **Table 1**), and thirteen patients (4.3%) had colposcopic examination. Eleven out of thirteen patients (3.6% of total) patients were diagnosed with chronic inflammation, and two out of thirteen (0.7% of total) were diagnosed with CIN1. No statistically significant difference according to smoking status between the IUD-positive and IUD-negative groups in the ASC-US group was noted (p: 0.26).

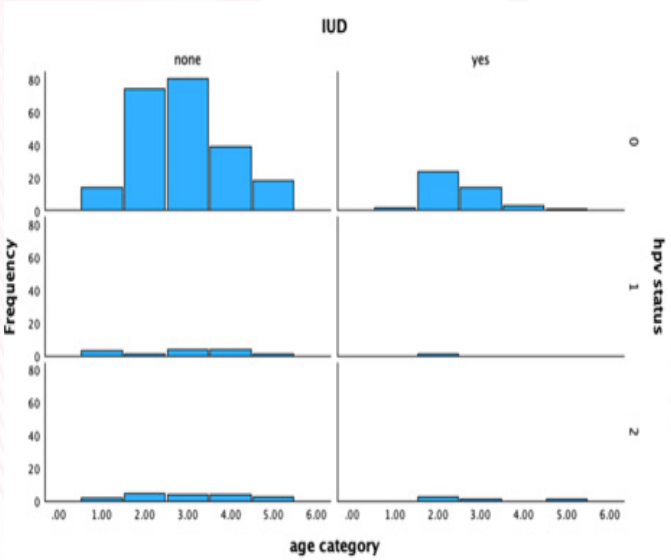

Figure. Intrauterine device and human papillomavirus (IUD and HPV, respectively) status according to age in abnormal cells of unknown significance (ASC-US) patients
Age categories: (1) ≤30, (2) 31–40, (3) 41–50, (4) 51–60, (5) >60 years
HPV status 0: none, 1: HPV16/18 positive, 2: HPV other types (non-16/18) positive

According to HPV status and categorized age, HPV positivity for 16/18 positive and other types (non-16/18) was statistically significant in ASC-US positive but IUD negative patients (p:0.04) (**Table 1, Figure**).

Out of the total 6452 cervical cancer screening patients, a group of patients with normal cytological results was chosen and divided by IUD status. This group was named the control group, ASC-US negative, normal cytological results without infection or inflammation diagnosis.

According to the Chi-Squared test results (p: 0.002), ASC-US cytology negativity was statistically significant in patients without an IUD (**Table 2**).

The odds ratio was 1.75, as IUD-positive patients had a 1.75-fold lower risk of having positive ASC-US results (p:0.018).

DISCUSSION

An IUD is one of the most commonly used family planning methods in Turkey; however, few studies addressing its relationship with HPV colonization and ASC-US are available. ASC-US is an undefined definition of squamous intraepithelial lesions. In a study by Durmus et al.[5] ASC-US prevalence was 2.1% in patients using IUDs. In our study, this percentage was 4.2%. In a study from the southeastern Turkey-Mardin region, where patients lived under similar socioeconomic conditions, the rate was reported to be 6%.[6]

In the same study[6], the rate of ASC-US was greater in the IUD-positive group than in the IUD-negative group (p = 0.02). In our study, the IUD negative group (4344/6452) had statistically significant ASC-US negative results (p:0026).

The main effect of IUDs occurs in endocervical and endometrial epithelial cells. Due to local inflammatory effects created by an IUD, edema in the endometrium, vascular congestion, necrosis, and pseudo-decidualization, especially in cells exposed to

Table 1. Distribution of different human papillomavirus (HPV) genotypes at different ages, n (%) of patients with abnormal cells of unknown significance (ASC-US) cytology

		Total number	Age				
			≤30	31–40	41–50	51–60	>60
		10	3	0	4	2	1
IUD +	HPV 16 +	0	0	0	0	0	0
IUD -		*10	3	0	4	2	1
		4	0	2	0	2	0
IUD+	HPV 18 +	1	0	1	0	0	0
IUD-		*3	0	1	0	2	0
		23	2	8	5	4	4
IUD+	Non 16/18 +	5	0	3	1	0	1
IUD-		18	2	5	4	4	3
		269	16	98	94	42	19
IUD+	HPV negative	44	2	24	14	3	1
IUD-		225	14	74	80	39	18
	Total	306	21	108	103	50	24

*Chi-square test; HPV positivity for 16/18 positive and other types (non-16/18) was statistically significant in ASC-US positive but IUD negative patients (p: 0.04), IUD: Intrauterine device

Table 2. The relationship between intrauterine device (IUD) and ASC-US cytology results

	ASC-US positive	ASC-US negative (normal cytological results and no infection/inflammation)	Total	p
IUD positive	50	512	562	
IUD negative	256	4344	4600	0.002, OR:1.75
Total	306	4856	5162	

ASC-US: Abnormal cells of unknown significance

copper IUDs, are among the observed findings.[7] These results are similar to the local inflammatory effects of ASC-US. The IUD strings consist of monofilaments and synthetic materials in contact with the cervix; such contact may trigger a chronic inflammatory response. In a study conducted with LNG and copper IUDs, inflammation was greater in these groups than in the control group without IUDs.[8] In our ASC-US positive and HPV 16/18 + group in the IUD+ group, thirteen patients had colposcopic examination. Eleven out of thirteen patients' colposcopy results were chronic inflammation.

In addition, Gupta et al.[4] reported that patients with this atypical cytology type recovered within an average of 1 to 13 months following IUD removal.

This increase in inflammation may also be due to increased infection or changes in the vaginal microbiota. In studies on this subject, Donders et al.[9] reported a greater frequency of vaginal candidiasis among LNG-IUD (IUD with levonorgestrel) users. Copper IUD is associated with bacterial vaginosis and the presence of actinomyces. Moreover, the LNG-IUD is associated with inflammatory infiltration with no specific pathogen, cytolysis, or candidiasis.[10] In our study, we exclude patients with vaginal infection and inflammation. Despite this, eleven patients had chronic inflammation result by colposcopic examination. So, this finding supported the IUD-inflammation theory.

The cytologic features of IUD cells may overlap with and thus pose diagnostic challenges concerning two main neoplastic processes: a high-grade squamous intraepithelial lesion (HGSIL) or endometrial adenocarcinoma.[11] This is only a false result because a study found that neither the LNG-IUS nor the copper IUD affects the incidence of cellular atypia.[8] In our study, no cellular atypia was found in the patients with IUD and HPV positivity in colposcopic examination.

In our study, 12.1% of patients had positive human papillomavirus (HPV) tests. It is similar with Turkey's HPV prevalence about reported between 2.0% and 46.0% in some regional studies.[12] No significant difference among IUD-positive patients according to HPV type was found ($p>0.05$). For high-risk HPV in conjunction with ASC-US findings, colposcopy was performed, but only 0.7% of patients were classified as cervical intraepithelial neoplasia grade 1 (CIN1). No patients with more advanced cervical precancerous lesions (high-grade lesions or carcinoma) were found. Our findings suggest that the cervical cytological finding of ASC-US in the presence of an IUD is more likely to indicate inflammation rather than a precancerous lesion. In a study comparing IUD and oral contraceptives (OC), the risk of CIN 3 and cervical cancer was found to be greater in the OC group.[13]

Limitations

The strengths of our study are the large population of 6452 people, the large number of patients with IUDs, the exclusion of patients with infection, and the fact that the patients were followed and accessible. The limitation of this study is that it was retrospective. However, from a result-oriented perspective, since the IUD is a contributing factor to the leading cause of inflammation, the presence of an IUD can be interpreted as such. No other studies in the literature have examined HPV, IUD, and ASC-US together.

CONCLUSION

IUDs cause inflammation, which results in ASC-US. IUD-positive patients had a 1.75 risk for ASC-US diagnosis. Even if an IUD is used, the results of colposcopic examinations do not extend beyond the findings of inflammation.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was conducted with the permission of Harran University Clinical Researches Ethics Committee (Date: 21.08.2023, Decision No: HRU/23.15.16).

Informed Consent

Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

The authors declared that this study has received no financial support.

Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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Journal of
Controversies in Obstetrics & Gynecology and Pediatrics

Review

DOI: 10.51271/JCOGP-0042

Effects of yoga exercise in the postpartum period on physical and psychological health

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Cite this article: Aydemir G, Döner Şİ, Uğurlu M. Effects of yoga exercise in the postpartum period on physical and psychological health. *J Controv Obstetr Gynecol Ped*. 2025;3(1):19-23.

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Received: 16/11/2024 ◆ **Accepted**: 03/01/2025 ◆ **Published**: 09/01/2025

ABSTRACT

Women may experience many physical and psychological problems in the postpartum period. She prefers non-pharmacological interventions in solving problems, thinking that pharmacological interventions may harm her and her babies' health. Since physical and psychological problems affect each other, it is important to provide holistic interventions to solve problems. Yoga stands out as an adaptable, comfortable and accessible method that can provide women with a holistic physical, mental and spiritual recovery in the postpartum period. Increased blood flow and strengthening of the muscles with yoga in the postpartum period improves abdominal strength, muscle endurance, coordination and also provides flexibility and balance. Blood flow to the pelvic floor and strengthening of the muscles accelerate the healing and involution of the perineum. Exercises stimulate the hormones oxytocin and prolactin, increase breast milk production and reduce breastfeeding problems. In addition to its physical effects, such as reducing postpartum weight by increasing basal metabolic rate, yoga provides psychological healing and increases bonding. Yoga is in the category of moderate-intensity exercises recommended in the postpartum period and can be practiced safely by women. This review aims to guide health professionals and mothers by examining the benefits of yoga practices started in the postpartum period. In addition, it aims to evaluate existing studies on yoga practices in the postpartum period and to contribute to the literature by compiling information.

Keywords: Postpartum period, postpartum care, postpartum yoga

INTRODUCTION

The postpartum period is a process that begins with the delivery of the placenta and continues for approximately 6 weeks.[1,2] In this special period when a new member joins the life of the woman and her family, many changes occur in the mother that require anatomical, physical, psychological and social adaptation.[2,3] In the postpartum period, women face many problems including decreased pelvic floor muscle strength, depression, stress, anxiety, sleep quality, fatigue, pain, urinary incontinence and sexual dysfunction. When these problems are not intervened, the complaints may persist for up to one year and may even impair the woman's quality of life for a lifetime.[1] Women prefer nonpharmacological methods in solving the problems they experience because of the side effects of pharmacological interventions and the thought that they may harm themselves or the baby.[2] In the postpartum period, women prefer many methods such as education, traditional and complementary alternative medicine treatment methods, meditation and exercise.[1,4]

Exercise is one of the non-pharmacologic interventions frequently recommended as part of maternal care in the postpartum period. In the postpartum period, exercise is recommended 4-6 weeks after vaginal delivery, 6-8 weeks after cesarean delivery and 150 minutes per week at moderate intensity.[5] Many types of exercise such as walking, light brisk running, pilates and yoga can be practiced during this period. Since there is a bidirectional relationship between physical and mental problems in the postpartum period, it is important to include non-pharmacological interventions such as yoga that can intervene simultaneously in both physical and mental health in health promotion.[6]

Yoga in the postpartum period is a mind-body based practice that can be adapted to the living conditions, physical and psychological needs of women. By focusing on the body and breath, yoga promotes muscular strengthening and psychological well-being.[7] When the literature is examined, in addition to the positive effects of yoga practice during pregnancy on the birth process, such as low cesarean section rates[8], shortened labor duration[9] and reduced labor pain[10], it also provides many benefits on the postpartum period, such as rapid recovery[8] and reduced risk of depression.[11] The findings of studies conducted during pregnancy show that yoga practiced during this period positively affects the birth process

and postpartum recovery. However, the effects of yoga on women's physical and psychological health in the postpartum period need to be examined in more detail. In this context, it is observed that studies on the benefits of yoga practices in the postpartum period have increased in the literature. This review aims to comprehensively evaluate the effects of yoga on women's physical and psychological health in the postpartum period. Within the scope of the review, studies conducted between 2015 and 2024 and conducted with women who had recently started practicing yoga in the postpartum period were examined; studies conducted with women who started practicing yoga during pregnancy were not included in the evaluation.

YOGA

Yoga originates from Indian culture and is a mind-body based complementary medicine practice.[2] Yoga, derived from the Sankskrit root "yuj", means "to unite, to bring together and wholeness". The unity referred to is the unity of mind-body-spirit.[12] Yoga, one of the oldest traditions in the world, has crossed the borders of India and started to be adopted in Western culture. Yoga, which has increased in popularity in recent years, is one of the most widely used complementary and alternative medicine treatments in the United States.[13] Yoga has become an increasingly popular practice, utilizing its health-enhancing properties in immunological, neuromuscular, psychological and pain conditions.[14] There are many types of yoga such as bhakti, raja, vinyasa, jnana, asthanga and hatha. Yoga practices in the postpartum period are based on Hatha yoga.[9]

The fact that yoga postures (asana) have modifications and variations suitable for the needs of the person allows them to be adapted to the postpartum period.[12] At the same time, it is a convenient method for women in the postpartum period as it is a convenient, comfortable and accessible method that does not require high costs.[15]

The success of interventions involving physical activity depends on four factors: how often you exercise, how hard you exercise, how long you exercise, and the type of exercise you choose.[15] The centers for disease control and prevention (CDC) recommends at least 150 minutes of moderate-intensity walking, water aerobics, cycling and some forms of yoga per week for women in the postpartum period.[17] The UK Chief Medical Officer's emphasizes that there are many benefits for women up to 12 months postpartum, including at least 150 minutes a week of moderate-intensity activity, including yoga. Their recommendations include starting pelvic floor exercises as soon as possible and continuing them daily.[18] The American College of Obstetricians and Gynecologists (ACOG) recommends at least 150 minutes of moderate-intensity aerobic activity per week. Muscle strengthening activities, including yoga, are recommended at least 2 days a week in addition to your aerobic activity.[19]

EFFECTS OF YOGA EXERCISE ON PHYSICAL HEALTH IN THE POSTPARTUM PERIOD

When we look at the physical benefits of yoga, muscle stretching occurs through asanas performed standing, sitting, supine and prone. It increases muscle strength and coordination. In the postpartum period, yoga is practiced to improve the woman's abdominal strength, muscular endurance, coordination and also to improve flexibility and balance.[5]

During pregnancy and the postpartum period, women become prone to a sedentary lifestyle. During childbirth, loss of strength in the pelvic floor may occur. In addition to urinary incontinence and sexual dysfunction, many physiological problems such as diastasis recti abdominis due to weakness in abdominal muscles arise. Yoga practiced in the postpartum period increases blood flow to the muscles and strengthens them.[5] Strengthening the pelvic floor and abdominal muscles allows the perineum to heal, accelerate the involution process and improve the quality of life of the mother.[3,20]

Breastfeeding and breast problems, back pain and weight problems are among the other ailments seen in the postpartum period. By stimulating the hormones oxytocin and prolactin with yoga, breastfeeding problems are reduced and pain is relieved by providing spinal mobility. However, yoga increases basal metabolic rate and helps to reduce postpartum weight, body fat percentage and fat mass.[3,5]

As a result of the literature review, the effects of yoga on physical health in the postpartum period were examined under 3 titles (effects on uterine involution, abdominal muscles, pelvic floor and breastfeeding).

Effects of Yoga on Uterine Involution

Postpartum hemorrhage is the leading cause of maternal mortality. Postpartum hemorrhage, especially in the first days, is the cause of more than half of all maternal deaths. The causes of postpartum hemorrhage are tonus (uterine subinvolution), tissue (placental retention), trauma (vaginal and cervical lacerations) and thrombin. Failure to maintain uterine tone, especially in the first hours postpartum, is the major cause of bleeding. Physical activities can prevent uterine subinvolution by contracting uterine muscles. As long as the stimulation continues with exercise, oxytocin continues to be produced by the pituitary. With the circulation, oxytocin is transported to the alveoli and causes myoepithelial cells to contract, thus making the process of involution more rapid.[7,21] In a quasi-experimental study by Anggraeni et al.[7] examining the effect of yoga on uterine involution in the postpartum period, women were divided into yoga (n=19) and general postpartum exercise group (n=38). Both groups were practiced for 30 minutes every day for 7 days postpartum. As a result of the study, yoga was reported to be very effective in accelerating uterine involution with a Cohen effect size of 1.63.[7]

Effects of Yoga on Abdominal Muscles and Pelvic Floor

Diastasis recti abdominis (DRA) can be seen in 30-70% of women in the postpartum period as a result of increased intra-abdominal pressure caused by the growing uterus during pregnancy. Diastasis occurs when the white line connecting the rectus abdominis is stretched and thinned. If the rectus are not connected and persist for a long time, it causes problems such as displacement of organs, decreased spinal stability, hernia and obesity. DRA is also closely related to pelvic floor dysfunction and the development of chronic back pain.[22] Yoga increases blood flow to the muscles and strengthens them.[5] DRA can be prevented by providing recovery of abdominal muscles in the postpartum period with yoga.[3,20] The randomized control study by Li et al.[22] in China investigating the effects of a yoga exercise program on reducing the recti distance (IRD) included

mothers who gave birth vaginally between 1 and 12 weeks postpartum. The intervention group (n=63) received a two-stage yoga exercise program for 12 weeks, while the control group (n=53) did not receive any intervention. The results of the study were analyzed by measuring the inter-recti distance using high frequency ultrasound at 6 and 12 weeks. After a 12-week progressive yoga exercise intervention, supraumbilical, umbilical and sub-umbilical IRD were significantly reduced in the yoga exercise group.[22]

Due to the many physical, hormonal, psychological and social changes in the postpartum period, women are prone to weight gain. Especially in this period, there is an increase in body-mass index (BMI) due to weight gain due to weakening of abdominal muscles and sedentary life.[5,23] In a study conducted in India, it was reported that yoga practiced in the postpartum period decreased the BMI of women.[23]

The pelvic floor system consists of the pelvic floor muscles and connective tissue. The levator ani, the main pelvic floor muscle, covers the lower part of the pelvic floor. Supporting the organs in the pelvic cavity plays a role in maintaining the processes of excretion, sexuality, pregnancy and childbirth.[24] Coordinated contraction and relaxation of the levator ani muscle is important to support the pelvic floor organs. Changes in the function and position of organs can occur in situations that cause morphological changes in this area, such as pregnancy and childbirth. Pelvic floor dysfunctions may develop as a result of conditions that weaken the levator ani muscle hiatus (LAH) area, such as uterine enlargement during pregnancy, relaxin secretion, lacerations at birth and episiotomy. Pelvic floor dysfunctions include pelvic organ prolapse, pelvic pain, urinary/fecal incontinence, and sexual dysfunction. If symptoms are not addressed early postpartum, they may lead to irreversible decompensation. This situation negatively affects the quality of life of women physically and psychologically.[24] In a study examining the effects of yoga intervention applied to early postpartum women in China on the recovery of the LAH area, the yoga group practiced 60 minutes of yoga once a week from postpartum week 1 to week 12. Improvement in the LAH area was measured during pelvic ultrasound examination at 6 and 12 weeks during rest, contraction and valsalva maneuver. As a result of the study, there was no difference in the measurements at week 6, while a significant improvement was reported in the measurements made at week 12.[24] When the studies in the literature are examined, it is seen that yoga practiced in the postpartum period strengthens the abdominal and pelvic muscles.

Effects of Yoga on Breastfeeding

Yoga has many positive effects on breastfeeding women.[25] Yoga and meditation in the postpartum period play a role in maintaining hormonal balance. Yoga gives the body a sense of physical relaxation and the mind a sense of psychological relaxation, which improves a woman's thoughts about breastfeeding in a positive way and facilitates the release of the hormone endorphins. Thus, the pituitary is stimulated and oxytocin and prolactin are secreted.[15,26] In addition, asana and pranayama techniques that stimulate the muscles around the chest and in the breasts of lactating women are also important in increasing milk secretion.[15] In a study investigating the effect of yoga on breastfeeding self-efficacy and maternal attachment in primiparous women (n=124) in Turkey, it was reported that breastfeeding self-efficacy increased and maternal attachment improved in the intervention group (n=62).[27] In a single-group experimental study in Indonesia examining the effect of yoga on breast milk quantity, it was reported that breastfeeding women (n=30) with infants aged 1-6 months had an average increase of 110.97 ml (82.4 ml-195.17 ml) after 6 days of yoga practice.[15] The results of the studies show that yoga exercise has both physiological and psychological effects on breastfeeding.

THE EFFECTS OF YOGA EXERCISE ON PSYCHOLOGICAL HEALTH IN THE POSTPARTUM PERIOD

In addition to physical changes in the postpartum period, many psychological changes cause women to experience problems. The imposition of new roles and responsibilities with the transition to motherhood predisposes women to psychological problems.[4] Psychological changes in the postpartum period are not diagnosed because they are often neglected and ignored.[20] Postpartum psychological problems may start from pregnancy and may also be caused by the sudden and rapid decrease in placental estrogen and progesterone and the disruption in the pituitary-adrenal axis.[28] Various symptoms such as anxiety, maternal sadness, depression and psychosis can be observed.[13] Especially postpartum depression affects approximately 25% of women in this period.[9] Psychological problems experienced in the postpartum period may cause mild symptoms to severe side effects such as inability to care for the baby and even severe depression, psychosis and suicide.[13,29]

Anxiety and stress experienced by the woman may lead to increased incidence of perinatal complications in the newborn[30], decreased mother-infant attachment[28,30], and cognitive and psychosocial developmental problems for the infant.[6] Effective and feasible strategies are needed to improve the psychological health and well-being of the mother in the postpartum period.[31] Evidence-based interventions such as selective serotonin reuptake inhibitors (SSRIs) are known to be effective in postpartum anxiety and depression. However, in this period, women do not want to use drugs because of the possibility of transmission to the baby with breast milk during breastfeeding, side effects and stigmatization by the society[9] and turn to non-pharmacological alternative methods.[31,32]

Yoga is one of the recommended approaches to reduce psychological problems as well as physical problems.[28,31] In yoga practices, especially pranayama and meditation techniques are utilized to improve psychological health. Breath control with pranayama is effective in activating the parasympathetic system. In addition, breathing exercises and meditation increase the ability to concentrate.[12] Meditation is a type of mental practice designed to improve concentration and mindfulness.[5] When practiced together, yoga and meditation help to alleviate the effects of the fight-or-flight response by giving the body a chance to rest.[23] Yoga is effective in increasing serotonin, dopamine levels and endorphin release by helping to regulate the hypothalamic-pituitary-adrenal (HPA) axis, which plays a role in how people respond to stressors.[6] The hormones released reduce psychological problems. Yoga is a preventive method that prevents the development of psychological problems by providing mental well-being as well as improving existing problems.[28] In a randomized controlled trial by Buttner et al.[9] the effect of yoga on women with postpartum depression was examined. In the study, measurements were made at the 2nd, 4th, 6th and 8th weeks after the practice. It

was reported that 78% of the women in the yoga group had reduced depression symptoms, while 59% of the women in the control group had reduced depression symptoms.[9] In a randomized controlled study examining the effect of yoga on posttraumatic quality of life in women with 2-6 month old babies (yoga=80; control=80) in Turkey, it was reported that yoga improved psychological recovery and quality of life.[3] In a randomized controlled trial conducted in Egypt with women with moderate depression at least one month after childbirth, one group received antidepressant treatment (n=20) and the other group received antidepressant treatment and yoga (n=20). As a result of the study, it was reported that while there was a decrease in depression levels in both groups, the decrease was greater in the group in which antidepressants and yoga were used.[29] In a randomized controlled trial examining the effect of Dru yoga intervention in primiparous mothers, it was reported that there was a decrease in stress, negative affect and dysfunctional coping and an increase in problem-focused coping after the intervention.[4] When the studies in the literature are examined, it shows that yoga is a method that can be used in psychological problems experienced or may be experienced in the postpartum period.

YOGA IN THE POSTPARTUM PERIOD: STRATEGIES FOR INITIATION AND MAINTENANCE

In the postpartum period, yoga offers a holistic approach to improve the physical and psychological health of women.[6] Starting early[22], continuing consistently[27] and working with the guide[22] are important in maximizing the benefits of yoga practice. ACOG recommends starting exercise again as soon as possible postpartum if a healthy pregnancy results in vaginal delivery. A few days after delivery, if the woman feels ready, she can start yoga practices.[19] In the early weeks after vaginal delivery, a structured program that starts with simple yoga practices that will help the main muscle groups at low intensity and increases the intensity in the following weeks is recommended.[22,27] It is important to consult with the physician when it is safe to start exercise if cesarean delivery and complications developed as a result.[19]

Regular yoga practices will contribute significantly to both physical and psychological health.[27] The practice, which started as 20-30 minutes in the first lessons, can be increased up to 60 minutes in the future.[19] The CDC, UK Chief Medical Officer's and ACOG emphasize that there are many benefits for women to engage in moderate-intensity activity, including yoga for at least 150 minutes per week.[17-19] During yoga practices, mothers are advised to wear cool and loose-fitting clothes so that they can move comfortably. For breastfeeding women, it should be emphasized that they should breastfeed or express milk before the class. In addition, wearing bras with thick straps that will provide appropriate support to the breasts is important for comfort. In order to prevent fluid loss during the application, it is recommended to have water with them.[19] Practicing yoga with a health professional who is an expert in the postpartum period and yoga will maximize the benefits and minimize the risks by ensuring that it is done correctly and safely.[22]

CONCLUSION

Yoga practiced in the postpartum period has many physiological and psychological benefits. Yoga is a viable, acceptable and accessible complementary treatment option for women during this period. When the studies in the literature are examined, it is seen that the focus is on the psychological effects of yoga applied for the first time in the postpartum period; there are few studies examining its physiological effects. In this period, randomized controlled studies are needed to evaluate the physical and psychological benefits of yoga and to determine the standards that will ensure that appropriate effects are achieved. In addition, in order to benefit more from the positive effects of yoga practice, women should be initiated into yoga practices starting from the gestational period and studies should be conducted to examine the long-term postpartum effects of yoga started in this period and continued in the postpartum period.

ETHICAL DECLARATIONS

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

The authors declared that this study has received no financial support.

Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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Journal of
Controversies in Obstetrics & Gynecology and Pediatrics

Case Report

DOI: 10.51271/JCOGP-0043

A rare cause of unimproved respiratory distress syndrome in a preterm infant: congenital hypothyroidism

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Cite this article: Gürkan M, Tandırcıoğlu ÜA, Alan S. A rare cause of unimproved respiratory distress syndrome in a preterm infant: congenital hypothyroidism. *J Controv Obstetr Gynecol Ped.* 2025;3(1):24-26.

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Received: 16/12/2024 • **Accepted**: 03/01/2025 • **Published**: 09/01/2025

ABSTRACT

In our country, congenital hypothyroidism (CH) is screened in all centres' within the scope of the national screening program. Because early diagnosis and treatment of CH prevents not only mental retardation but also the lots of morbidities. The findings of respiratory distress syndrome (RDS) and thyroid dysfunction of prematurity have a bidirectional relationship. Here we discuss the regression of RDS findings in a preterm infant with CH with hypothyroidism treatment. A 910 g female infant, born at 28 weeks' gestation from the twin pregnancy of a 27-year-old mother, was admitted to the neonatal intensive care unit (NICU) with a diagnosis of prematurity and RDS. The RDS resolved with treatment in the infant's first days. On postnatal day 7, the newborn's respiratory symptoms worsened and RDS symptoms developed again. Respiratory distress syndrome signs and symptoms did not improve despite treatment until CH was detected on postnatal day 14 and thyroid replacement therapy (levotiroksin [L-T4]) was initiated. Thyroid function improved with L-T4 treatment and the unexplained RDS findings improved without the need for additional treatment within 48 hours of L-T4 treatment.

Keywords: Respiratory distress syndrome, congenital hypothyroidism, thyroid replacement

INTRODUCTION

Thyroid hormone abnormalities in preterm infants can have several causes, including transient or permanent congenital hypothyroidism (CH), transient hypothyroxinemia of prematurity and transient hyperthyrotropinemia.[1] The findings of respiratory distress syndrome (RDS) and thyroid dysfunction of prematurity have a bidirectional relationship.[1-3] Previous studies have shown that free thyroxine (fT4) remains low during the first 5 days of life in late preterm and term infants with RDS.[1] However, it is also known that hypothyroxinemia of prematurity is associated with pulmonary dysfunction (particularly surfactant deficiency).[2]

Here we discuss the regression of RDS findings in a preterm infant with CH with hypothyroidism treatment.

CASE

A 910 g female infant, born at 28 weeks' gestation from the twin pregnancy of a 27-year-old mother, was admitted to the neonatal intensive care unit (NICU) with a diagnosis of prematurity and RDS. The infant, who received surfactant treatment for RDS on the first day of life, was referred to our hospital because of persistent respiratory distress on the 6th day of life. The history at the previous centre showed that he was extubated after surfactant treatment, his oxygen requirement decreased to 21%, but tachypnea and retractions resumed on day 5 and his oxygen requirement increased. During follow-up in our NICU, echocardiography revealed first-degree tricuspid regurgitation and mild pericardial effusion. Chest radiography showed mild reticulogranular pattern and air bronchograms (Figure 1). The patient was not administered surfactant treatment again.

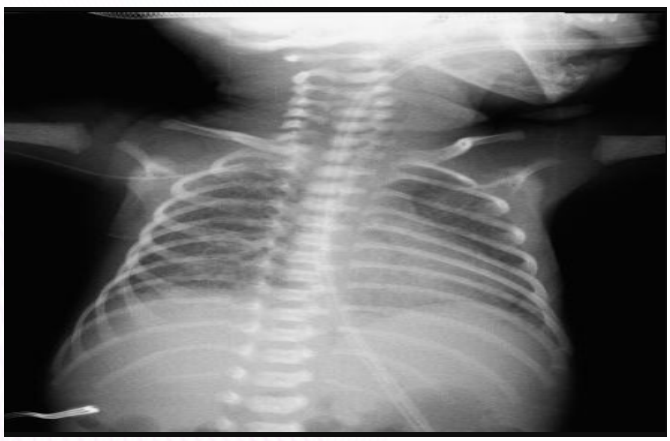

Figure 1. Reticulogranular pattern and air bronchograms

On postnatal 7th day, Thyroid stimulating hormone (TSH): 13.8 uIU/ml (0.7-7.9 uIU/ml) and fT4: 0.83 (0.84-1.76 ng/dl), the reference interval was obtained from literature data according to the gestational age of the infant.[3] On postnatal 14th day, the patient was supported by non-invasive mechanical ventilation (NIV) due to increased tachypnoea and retractions. Acute phase reactants were negative in concurrent investigations. Hemoglobin was 12.9 g/dl. Lung ultrasound showed that diffuse B-lines in the basal and apex of the right lung with no hepatisation. Control TSH value increased to 84.1 uIU/ml and fT4 value decreased to 0.57 ng/dl after seven days. CH was diagnosed and L-T4 treatment was started at a dose of 10 mcg/kg/day. This patient did not improve at the desired rate after all supportive treatments such as appropriate respiratory support, fluid electrolyte support, nutritional support, cardiac support were provided appropriately. The symptoms of respiratory distress resolved within 48 hours after L-T4 treatment without surfactant or antibiotic treatment, and the patient was weaned from NIV.

The radiological findings resolved within 72 hours (**Figure 2**). Thyroid hormone values 1 week later were as follow, TSH: 1.09 uIU/ml (0.27- 4.2), fT4: 2.43 ng/dl (0.93-1.7). The administration of oxygen was discontinued on the 62nd day, and the infant was discharged with L-T4 treatment on the 70th day. The patient, who had reached the expected developmental milestones for his age, is currently 21 months old and continues to receive L-T4 treatment at a dose of 8 mcg/kg/day.

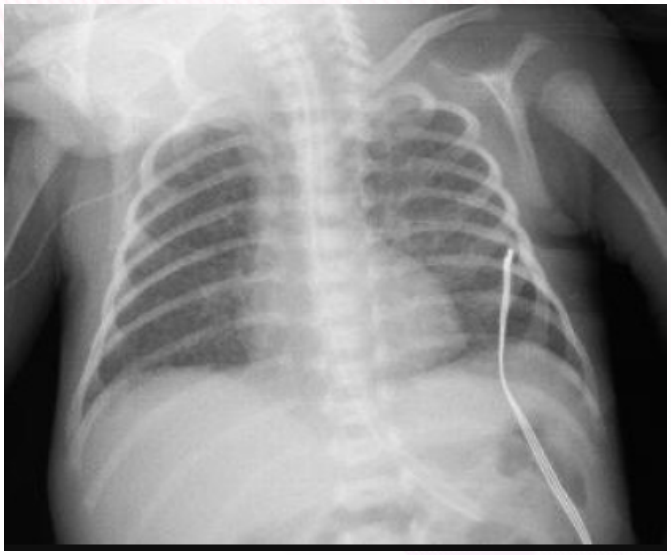

Figure 2. Resolved radiological findings

DISCUSSION

CH is one of the most important endocrine and metabolic causes of mental retardation in the neonatal period if diagnosis or treatment is delayed, and CH is diagnosed in 3500-4000 infants each year and the incidence is even higher in premature infants.[3] Although their underlying pathophysiology is multifactorial, RDS and CH have been shown to have a bidirectional clinical relationship.[1-3]

In a study by Val Abbassi et al. using fetal cord blood, preterm infants with low cord blood free T3 levels were found to be more at risk for RDS. Contrary to our case, the same study reported no difference in fT4 levels.[4]

Some studies have found TSH levels to be relatively higher in preterm infants diagnosed with RDS than in non-RDS preterm infants.[5,6] In a study conducted by Hye Rim Chung et al.[8] in premature infants with similar other characteristics, the rate of RDS was found to be 62% in the group with hypothyroidism, while this rate was found to be 40% in premature infants without hypothyroidism with statistical significance. This supports the improvement of RDS signs of the present case just after L-T4 treatment.

These studies have investigated the relationship between low thyroxine levels and short-term clinical outcomes; however, it is thought that clinical conditions such as disease severity, respiratory distress syndrome, and heart disease may alter thyroid function alone and that low thyroxine levels do not cause or predispose to such adverse outcomes.[7-10] In our case, L-T4 treatment was initiated after CH was detected in a neonate who was followed up for RDS, and the respiratory distress findings resolved within 48 hours.

In addition, a mutation in the NK2 homeobox-1 (NKX2.1) gene encoding thyroid transcription factor-1 (TTF-1), which is important for the morphogenesis and function of the lungs, thyroid, and central nervous system, causes a rare clinic for respiratory failure called brain-lung-thyroid syndrome.[11] In this case, this diagnosis was excluded because no neurological findings were observed.

According to the results of a group of patients consisting of term and late preterm infants in besides the early preterm case we presented, it has been reported that low fT4 levels are associated with increased RDS similar to our case.[12]

CONCLUSION

Our patient with RDS signs that did not improve despite surfactant treatment was diagnosed as CH and RDS signs improved dramatically with L-T4 treatment. CH should be considered in cases of recurrent and/or unresolving RDS in neonates, even if they are premature.

Also, in our country, CH is screened in all centres' within the scope of the national screening program. Because early diagnosis and treatment of CH prevents not only mental retardation but also the lots of morbidities. We would like to emphasize this with this case.

ETHICAL DECLARATIONS

Informed Consent
The patient signed a free and informed consent form.

Referee Evaluation Process
Externally peer-reviewed.

Conflict of Interest Statement
The authors have no conflicts of interest to declare.

Financial Disclosure
The authors declared that this study has received no financial support.

Author Contributions
All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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