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Can Inflammatory Indices be Used to Predict Adverse Pregnancy Outcomes in Pregnant Women with Recurrent Urinary Tract Infection?

İnflamatuvar İndeksler Tekrarlayan İdrar Yolu Enfeksiyonu olan Gebelerde Olumsuz Gebelik Sonuçlarını Tahmin Etmek için Kullanılabilir mi?

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ABSTRACT

Aim: This study aimed to investigate the utility of inflammatory indices in predicting adverse maternal and neonatal outcomes in pregnant women with recurrent urinary tract infections.
Material and Methods: This retrospective study was conducted on pregnant women treated for symptomatic urinary tract infection (UTI) between 2017 and 2021. Pregnant women with two or more episodes of symptomatic UTI were included in the study group. Pregnant women with one UTI were included in the control group. The study group consisted of 91 (46.9%) patients and the control group consisted of 103 (53.1%) patients. The groups were compared in terms of clinical characteristics, adverse outcomes, and inflammatory indices.
Results: It was found that more adverse maternal and neonatal outcomes occurred in the study group compared to the control group (p=0.021, and p<0.001, respectively). The cut-off values for platelet-to-lymphocyte ratio (PLR), neutrophil-to-lymphocyte ratio (NLR), and systemic immune-inflammation index (SII) to predict adverse maternal outcomes were found 185.00 (p=0.015, area under the curve (AUC)=0.604, 95% confidence interval (CI)=0.558-0.782,), 4.34 (p=0.051, AUC=0.584, 95% CI=0.514-0.746), and 1210.48 (p=0.008, AUC=0.614, 95% CI=0.547-0.771), respectively. The cut-off values for PLR, NLR, and SII for predicting negative neonatal outcomes were found 192.98 (p=0.001, AUC=0.692, 95% CI=0.572-0.812), 4.67 (p=0.166, AUC=0.583, 95% CI=0.475-0.740), and 1339.47 (p=0.006, AUC=0.666, 95% CI=0.526-0.777), respectively.
Conclusion: Although the success of discrimination is weak, PLR and SII may be useful to predict adverse maternal and neonatal outcomes in pregnant women with recurrent UTI.
Keywords: Adverse pregnancy outcomes; inflammatory indices; recurrent urinary tract infections.

ÖZ

Amaç: Bu çalışmanın amacı tekrarlayan idrar yolu enfeksiyonu olan hamile kadınlarda inflamatuar indekslerin olumsuz maternal ve neonatal sonuçları tahmin etmedeki yararını araştırmaktır.
Gereç ve Yöntemler: Bu geriye dönük çalışma, 2017 ve 2021 yılları arasında semptomatik idrar yolu enfeksiyonu (İYE) nedeniyle tedavi edilen gebeler üzerinde yapılmıştır. İki veya daha fazla semptomatik İYE atağı olan gebeler çalışma grubuna dahil edilmiştir. Kontrol grubuna tek İYE geçiren gebeler dahil edilmiştir. Çalışma grubu 91 (%46,9) hastadan ve kontrol grubu ise 103 (%53,1) hastadan oluşmuştur. Gruplar klinik özellikler, olumsuz sonuçlar ve inflamatuar indeksler açısından karşılaştırıldı.
Bulgular: Kontrol grubu ile karşılaştırıldığında, çalışma grubunda daha fazla olumsuz maternal ve neonatal sonuçların meydana geldiği bulundu (sırasıyla p=0,021 ve p<0,001). Olumsuz maternal sonuçları öngörmek için trombosit-lenfosit oranı (TLR), nötrofil-lenfosit oranı (NLR) ve sistemik immün-inflamasyon indeksi (Sİİ) için kesim değerleri sırasıyla, 185,00 (p=0,015; eğri altında kalan alan (EAA)=0,604; %95 güven aralığı (GA)=0,558-0,782), 4,34 (p=0,051; EAA=0,584; %95 GA=0,514-0,746) ve 1210,48 (p=0,008; EAA=0,614; %95 GA=0,547-0,771) idi. Negatif neonatal sonuçları tahmin etmek için PLR, NLR ve Sİİ için kesim değerleri sırasıyla, 192,98 (p=0,001; EAA=0,692; %95 GA=0,572-0,812), 4,67 (p=0,166; EAA=0,583; %95 GA=0,475-0,740) ve 1339,47 (p=0,006; EAA=0,666; %95 GA=0,526-0,777) idi.
Sonuç: Ayırt etme başarısı zayıf olmakla birlikte, TLR ve Sİİ, tekrarlayan İYE'li gebe kadınlarda olumsuz maternal ve neonatal sonuçları tahmin etmek için faydalı olabilir.
Anahtar kelimeler: Olumsuz gebelik sonuçları; inflamatuar indeksler; tekrarlayan idrar yolu enfeksiyonları.

INTRODUCTION

Urinary tract infection (UTI) is the most common bacterial infection during pregnancy due to anatomical, hormonal, and immune changes (1,2). UTI is classified as asymptomatic and symptomatic UTI. Asymptomatic bacteriuria is defined as the presence of at least 105/ml bacterial colonies in the urine culture without any symptoms or signs. Symptomatic UTI is defined as the presence of bacteriuria accompanied by symptoms related to the localization of the infection in the urinary tract. Cystitis, which is a lower UTI, causes dysuria, frequency, urgency, and suprapubic pain and occurs in 1-2% of pregnant women. Pyelonephritis, an upper UTI, is characterized by symptoms, such as malaise, fever, nausea, vomiting, flank pain, and costovertebral angle tenderness, and its incidence is 0.5-1% (3).

Regardless of whether UTIs are symptomatic or asymptomatic, they have been associated with many adverse pregnancy outcomes, such as preterm birth, fetal growth restriction (FGR), low birth weight, and preeclampsia (4,5). Adverse pregnancy outcomes are more common in pyelonephritis that is characterized by renal parenchymal inflammation (6).

Recurrent urinary tract infection (RUTI) is the occurrence of two or more UTI episodes during pregnancy. Patients who have had UTI once are more likely to suffer from colonization of the urinary tract by the same or similar agents. UTI recurs in 4-5% of pregnancies (7,8). It has been demonstrated that continuous or postcoital antibiotic therapy in RUTI, which causes an increase in adverse pregnancy outcomes, reduces adverse outcomes (1,9,10).

Systemic inflammation is associated with changes in the number and function of blood cell components, and this underlies the inflammatory response. While clinical inflammation is characterized by symptoms, such as fever, pain, and redness, there is infiltration of the tissue by neutrophils, macrophages, and lymphocytes in subclinical inflammation (11). The level of inflammation can be evaluated by indices derived from full blood count (FBC) parameters. In recent years, the use of inflammatory indices obtained from FBC components to evaluate inflammation and predict adverse maternal and neonatal outcomes has become one of the research areas with increasing popularity. The mean platelet volume (MPV), red cell distribution width (RDW), neutrophil-to-lymphocyte ratio (NLR), and platelet-to-lymphocyte ratio (PLR) are among the frequently used indices. The systemic immune-inflammation index (SII) is a new inflammatory index that has been developed in recent years and incorporates more FBC parameters, and a growing number of studies in the field of obstetrics have used SII (12-16).

The primary aim of this study is to calculate the cut-off values for inflammatory indices in predicting adverse maternal and neonatal outcomes in pregnant women with RUTI. The secondary aim is to analyze the outcomes of pregnancies treated for RUTI at our center.

MATERIAL AND METHODS

The study was conducted on pregnant women with recurrent, symptomatic UTI who were treated at Ankara Etlik Zübeyde Hanım Gynecology Training and Research Hospital between January 2017 and January 2021. The study was approved by the hospital's local ethics committee with a decision number 2021-03/6. Patient consent was renounced due to the retrospective nature of the study.

The diagnosis of UTI was based on the urine culture with a bacterial count $\geq 10^3$ colony-forming unit (CFU)/ml in pregnant women with symptoms, such as dysuria, frequency, urgency, suprapubic pain, fever, flank pain, and costovertebral angle tenderness. Cases of asymptomatic bacteriuria, defined as the presence of $\geq 10^5$ CFU/ml in the urine without any clinical symptoms, were not included in the study. The study group comprised singleton pregnant women with two or more episodes of symptomatic UTIs during pregnancy. The control group comprised pregnant women who had symptomatic UTI once at similar gestational weeks during pregnancy. Pregnant women with pregestational diabetes mellitus, chronic hypertension, collagen tissue disease, autoimmune disease, and smokers were excluded from the study. Multiple pregnancies were not included in the study. The data of the patients were obtained from the hospital's electronic archive and patient files.

The laboratory parameters included leukocyte, lymphocyte, neutrophil, and platelet counts, MPV, and RDW. While calculating inflammatory indices, absolute lymphocyte, neutrophil, and platelet counts in the FBC at the time of admission to the hospital and prior to the start of antibiotic therapy were used. The NLR was calculated by dividing the neutrophil count by the lymphocyte count. The PLR was calculated by dividing the platelet count by the lymphocyte count. The following formula was used to calculate the SII: neutrophil x platelet/lymphocyte. In the study group, FBC values at the time of admission to the hospital in the last symptomatic UTI during pregnancy were used. In the control group, FBC values at the time of admission to the hospital due to UTI were used.

In the study, clinical data such as maternal age, gravida, parity, number of miscarriages, gestational week at diagnosis, gestational week at birth, mode of delivery, and adverse pregnancy outcomes, such as preterm birth, preeclampsia, FGR, small for gestational age (SGA), gestational diabetes mellitus (GDM), preterm premature rupture of membranes (PPROM), were evaluated. Birth weight, 1-minute, and 5-minute Apgar scores, and the need for neonatal intensive care were analyzed as newborn parameters. The diagnoses of preterm birth, FGR, SGA, preeclampsia, GDM, and PPROM were established according to the current guidelines (17-21).

An adverse maternal outcome was defined as the presence of any of the following conditions: preterm birth, FGR, SGA, preeclampsia, and PPROM. Adverse neonatal outcome was defined as the presence of any of the following findings: 1-minute Apgar score of <7, 5-minute Apgar score of <7, and the need for neonatal intensive care unit (NICU). The cut-off values for inflammatory indices were calculated for the prediction of composite adverse maternal and neonatal outcomes in the study group.

Statistical Analysis

Statistical analysis was performed using SPSS software version 26 (Armonk, NY: IBM Corp). Normality distribution was evaluated with the Kolmogorov-Smirnov test. Continuous data without normal distribution were expressed as median and interquartile range, and the

comparisons between the groups were made using the Mann-Whitney U test. Categorical data were expressed as number and percentage and analyzed using the chi-square and Fisher's exact tests. The performances of inflammatory indices in predicting adverse maternal and neonatal outcomes were evaluated using receiver operating characteristic (ROC) curve analysis. A p-value less than 0.05 was considered significant.

RESULTS

During the study period, 106 pregnant women were treated for RUTI. Seven patients were excluded from the study because of the presence of a concurrent disease during pregnancy (2 had familial Mediterranean fever, 1 had systemic lupus erythematosus, 3 had diabetes mellitus, and 1 had chronic hypertension). Four pregnant women with multiple pregnancies were excluded from the study. Pre-treatment laboratory parameters of four patients could not be accessed. The final study group included 91 patients. The control group comprised 103 patients who had had symptomatic UTI once during pregnancy and were matched for maternal age and gestational week. Demographic and clinical characteristics and laboratory parameters of the groups are presented in Table 1. The median gestational age at diagnosis was similar between the two groups (p=0.498). The median number of UTI episodes was 2 (range, 2-6) in the study group. 44 (48.4%) of the pregnant women in the study group and 66 (64.1%) of the pregnant women in the control group were nulliparous (p=0.027). Gravida and parity were significantly higher in the study group than in the control group (p=0.010, and p=0.008, respectively). Preterm birth and composite adverse maternal outcomes were more common in the study group than in the control group (p=0.001, and p=0.021, respectively). The need for admission to NICU and composite adverse neonatal outcomes were significantly more common in the study group (both p<0.001).

In the study, 196 urine cultures in the RUTI group and 103 urine cultures in the control group were analyzed. *E. coli* was the most commonly reproduced pathological agent in urine culture in both groups (n=141, 71.9% cases vs. n=73, 70.9% cases). *Klebsiella* spp., *S. aureus*, group B streptococci, and *Proteus* spp. were other common agents. The results of antimicrobial susceptibility tests were similar between the groups. In the entire population, the rate of drug resistance in *E. coli* isolates was 56.2% (n=168) for ampicillin, 23.1% (n=69) for ampicillin-sulbactam, 21.1% (n=63) for amoxicillin-clavulanic acid, and 25.1% (n=75) for trimethoprim/sulfamethoxazole. Mixed infection was detected in 5 (2.6%) cases in the RUTI group and 1 (0.97%) case in the control group.

FBC parameters and inflammatory indices in the groups are presented in Table 2. The platelet count was higher in the study group (p<0.001). SII and PLR were found to be significantly higher in the study group than in the control group (p=0.002, and p<0.001, respectively). The performances of inflammatory indices in predicting composite adverse maternal and neonatal outcomes were analyzed using the ROC curve (Table 3, Figure 1). The cut-off values in the ROC curves with the most ideal sensitivity and specificity balance that can be used to predict adverse maternal and neonatal outcomes were obtained using the Youden index.

Table 1. Comparison of demographic and clinical characteristics between pregnant women with and without recurrent UTI

	Recurrent UTI (n=91)	**Non-recurrent UTI (n=103)**	**p**
Age (years)	25 (7) [17-41]	25 (7) [17-45]	0.359
Gravida	2 (2) [1-11]	1 (1) [1-5]	**0.010**
Parity	1 (2) [0-6]	0 (1) [0-4]	**0.008**
Nulliparity, n (%)	44 (48.4%)	66 (64.1%)	**0.027**
Miscarriages	0 (0) [0-5]	0 (0) [0-2]	0.108
Gestational age at diagnosis (weeks)	28 (7) [20-37]	28 (8) [13-39]	0.498
Number of UTIs in pregnancy	2 (0) [2-6]	1 (0) [1-1]	**<0.001**
Hydronephrosis, n (%)	9 (9.9%)	2 (1.9%)	**0.017**
Preeclampsia, n (%)	10 (11.0%)	7 (6.8%)	0.303
Fetal growth restriction, n (%)	7 (7.7%)	5 (4.9%)	0.413
Small for gestational age, n (%)	11 (12.1%)	11 (10.7%)	0.758
Gestational diabetes mellitus, n (%)	4 (4.4%)	4 (3.9%)	1.000
Preterm premature rupture of membranes, n (%)	4 (4.4%)	3 (2.9%)	0.708
Preterm birth, n (%)	35 (38.5%)	17 (16.5%)	**0.001**
Composite adverse maternal outcomes, n (%)	42 (46.2%)	31 (30.1%)	**0.021**
Gestational age at delivery (week)	38 (3) [24-41]	38 (3) [26-41]	**0.004**
Route of delivery, n (%)			
Cesarean section	45 (49.5%)	46 (44.7%)	0.505
Vaginal delivery	46 (50.5%)	57 (55.3%)	
Birth weight (gram)	3000 (680) [565-4120]	3050 (515) [915-4100]	0.065
1st minute Apgar	9 (0) [2-9]	9 (0) [6-9]	**0.020**
5th minute Apgar	10 (1) [2-10]	10 (0) [7-10]	**0.019**
Neonatal intensive care unit admission, n (%)	21 (23.1%)	4 (3.9%)	**<0.001**
Composite adverse neonatal outcomes, n (%)	22 (24.2%)	5 (4.9%)	**<0.001**

UTI: urinary tract infection, descriptive statistics were presented as median (interquartile range) [min-max] for numerical variables, and n (%) for categorical variables

Table 2. Comparison of full blood count parameters and inflammatory indices in the groups

	Recurrent UTI (n=91)	Non-recurrent UTI (n=103)	p
Leukocytes (10^3/μL)	9.03 (4.5) [4.3-22.8]	8.2 (4.5) [3.9-21.6]	0.211
Neutrophils (10^3/μL)	7.4 (4) [3.6-21.7]	6.8 (4.1) [1.5-20.2]	0.224
Lymphocytes (10^3/μL)	1.5 (0.7) [0.3-2.9]	1.6 (0.6) [0.5-3.5]	0.489
Platelet (10^3/mm^3)	293 (92) [136-448]	251 (76) [104-504]	**<0.001**
Mean platelet volume (fL)	8.7 (1.6) [5.6-12.2]	8.8 (1.5) [5.2-11.5]	0.817
Red cell distribution width (%)	14.1 (1.5) [12.3-31.5]	14.5 (1.7) [12.4-19.9]	0.109
Neutrophil-to-lymphocyte ratio	4.5 (5) [1.7-25.3]	4.2 (3.4) [0.4-24.6]	0.158
Platelet-to-lymphocyte ratio	201.5 (91.7) [78.5-725.9]	166.9 (81.2) [82.4-494.1]	**<0.001**
Systemic immune-inflammation index (10^3/mm^3)	1402.3 (1611.5) [455.9-7615.3]	1111.4 (896.1) [181.9-6201.2]	**0.002**

UTI: urinary tract infection, descriptive statistics were presented as median (interquartile range) [min-max] for numerical variables, and n (%) for categorical variables

Table 3. ROC curve analysis for assessing the performance of NLR, PLR, and SII values in predicting composite adverse maternal and neonatal outcomes for RUTI

	AUC	95% CI	p	Cut-off	Sensitivity	Specificity
Maternal outcomes						
NLR	0.584	0.514 - 0.746	0.051	4.34	60.3	53.7
PLR	0.604	0.558 - 0.782	**0.015**	185.00	60.3	60.3
SII	0.614	0.547 - 0.771	**0.008**	1210.48	67.1	58.7
Neonatal outcomes						
NLR	0.583	0.475 - 0.740	0.166	4.67	59.3	58.3
PLR	0.692	0.572 - 0.812	**0.001**	192.98	74.1	60.1
SII	0.666	0.526 - 0.777	**0.006**	1339.47	70.4	60.1

ROC: receiver operating characteristic, NLR: neutrophil-to-lymphocyte ratio, PLR: platelet-to-lymphocyte ratio, SII: systemic immune-inflammatory index, RUTI: recurrent urinary tract infections, AUC: area under the curve, CI: confidence interval.

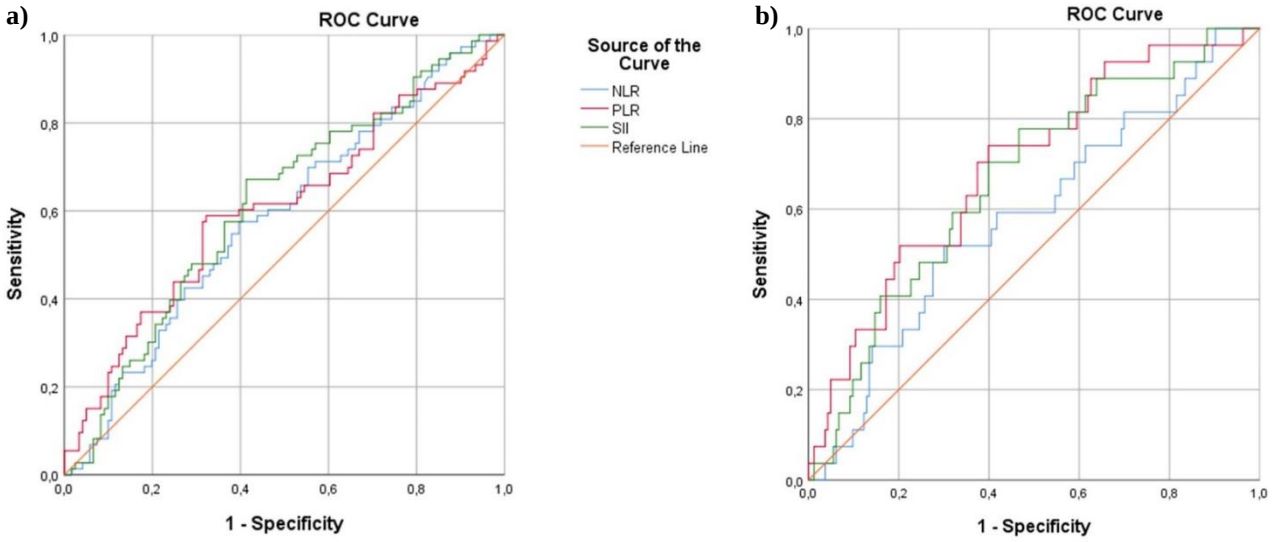

Figure 1. Receiver operating characteristic curve for **a)** composite adverse maternal outcomes, and **b)** composite adverse neonatal outcomes in pregnant women with recurrent urinary tract infection

DISCUSSION

The main finding of this study is that inflammatory indices are elevated in pregnancies with symptomatic RUTI, especially the high platelet count draws attention. There was no significant difference in leukocyte components between the groups. The present findings suggest that inflammatory indices could be used to predict composite adverse maternal and neonatal outcomes in pregnancies with RUTI.

The alterations in the urogenital system associated with pregnancy cause more frequent occurrence of UTIs, easy dissemination, and more frequent recurrence of the infection (22). Previous studies have shown that bacteriuria, whether symptomatic or asymptomatic, is associated with adverse maternal and neonatal outcomes (23-25). RUTIs are associated with an increased incidence of adverse outcomes as bacteriuria persists for a longer period of time

during pregnancy (9,26). In this study, preterm birth, which was seen at a rate of 37.5%, was the most prominent adverse pregnancy outcome caused by RUTIs. Adverse outcomes such as FGR, SGA, preeclampsia, and PPROM were also observed more frequently, but this difference did not gain statistical significance. Upon review of the literature, it is noteworthy that the prevalence of preterm birth and low birth weight is high, although the treatment of UTIs with antibiotics causes a decrease in negative outcomes (27). Inflammation caused by bacterial colonization in the urinary tract plays a role in the etiology of preterm birth. Inflammation leads to the production of cytokines by the leukocytes, resulting in cervical ripening and disrupting myometrial silence (28). Maternal inflammation also affects fetoplacental tissues, disrupting vascular structure and circulation, leading to an increase in adverse neonatal outcomes (4). Consistent with this information, this study shows that composite adverse maternal and neonatal outcomes are more common in RUTIs.

The immune system changes occurring during pregnancy are necessary for normal maternal-neonatal interaction. This change plays an active role in the development and regulation of the fetoplacental component (4). The effects of inflammation during pregnancy on adverse outcomes have been extensively investigated in the field of obstetrics, and its relationship with maternal and neonatal prognosis has been evaluated. NLR, PLR, and SII are inflammatory indices obtained by the combination of FBC components (12-14). When the FBC components were analyzed in pregnancies with RUTI, a significant increase in platelet count was noted in the study group than in the control group. No significant difference was observed in other components. The role of leukocytes in inflammation has been mentioned in previous sections. Along with their hemostatic functions, platelets also play a role in chemotaxis, tissue regeneration, and inflammatory reactions. They are also involved in implantation and vascular development and remodeling in pregnancy (29).

This study shows that inflammatory indices incorporating platelet count in the calculation can be used to predict adverse maternal and neonatal outcomes in pregnant women with RUTI. The cut-off values for PLR and SII in predicting the composite adverse maternal outcomes were found 185.00, and 1210.48, respectively. In the prediction of composite adverse neonatal outcomes, the cut-off values for PLR and SII were found 192.98, and 1339.47, respectively.

Adverse pregnancy outcomes can be reduced by appropriate and effective antibiotic therapy for UTI. In the presence of recurrent infections, preventing bacteriuria is important in reducing morbidity. It has been demonstrated that complications are reduced with continuous or postcoital antibiotic therapy in these pregnant women (1,30). The effects of antibiotic therapy during pregnancy on the fetus, and the infant in the neonatal and childhood periods are still the subject of research (31-33). The concerns of parents regarding drug use during pregnancy reduce adherence to treatment. Therefore, we believe that inflammatory indices can be used to predict adverse pregnancy outcomes in pregnant women with RUTI, as well as to guide prophylactic antibiotic therapy and evaluate treatment adherence.

The limitations of this study are its retrospective nature, small number of patients, and single-center study design. The patients with acute cystitis were also included in this study. Cystitis is a UTI confined to the bladder without signs and symptoms of systemic infection. Because of the discomfort caused by its symptoms, cystitis is often treated early. Although it does not cause a significant increase in pregnancy complications on its own, it causes a predisposition to bacterial colonization (1,34,35). We believe that the low sensitivity and specificity rates found in the present study can be explained by this situation, new cut-off values with higher sensitivity and specificity can be found with the inclusion of an ideal number of patients.

CONCLUSION

PLR and SII are useful in predicting composite maternal and neonatal outcomes in pregnancies with RUTI and can be used to guide patients' management. However, their effectiveness needs to be supported by prospective studies involving a larger number of patients.

Ethics Committee Approval: The study was approved by the Ethics Committee of Etlik Zübeyde Hanım Gynecology Training and Research Hospital (26.02.2021, 03/6).

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