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The Role of Inflammatory Markers in the Evaluation of Cerclage Success

Serklaj Başarısının Değerlendirilmesinde İnflamatuvar Belirteçlerin Rolü

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ABSTRACT

Aim: The aim of this study was to investigate the role of inflammatory markers in predicting cerclage success in patients who underwent a cerclage procedure.

Material and Method: Pregnant women who had undergone McDonald cerclage were included in the study. Sixty-one pregnant women participated in the study, of whom 32 (52.46 %) underwent elective cerclage and 29 (47.54 %) emergency cerclage. Laboratory analysis determined neutrophil-to-lymphocyte ratio (NLR), monocyte-to-lymphocyte ratio (MLR), plateletto-lymphocyte ratio (PLR), and systemic immune inflammation index (SII). Patients undergoing cerclage were compared into two groups, elective and emergency cerclage groups.

Results: The mean gestational week for cerclage insertion was 13.41 ± 0.83 weeks for elective cerclage and 17.45 ± 4.37 weeks for emergency cerclage. No significant difference was found between the groups in terms of age, gravid, week of delivery, mode of delivery and neonatal outcomes (p>.05). However, a significant difference was found in the values for history of abortion, cervical length, and period from cerclage placement to delivery (p<.05). No significant difference was found between the NLR, MLR, PLR, and SII values between the two groups in the study (p>.05), but a significant negative correlation was found between the SII value and the week of delivery (p<.05, r=-0.278).

Conclusion: The NLR, MLR, and PLR values were not found to be beneficial in predicting the success of the cerclage procedure in prolonging the duration of pregnancy. In contrast, the negative correlation between the SII value and the week of delivery proved to be inexpensive and easily determined prognostic marker that could be used to specify the success and prognosis of cervical cerclage.

Keywords: Cerclage, inflammatory marker, McDonald, neutrophil, systemic immune inflammatory index

ÖZ

Amaç: Serklaj prosedürü uygulanan hastalarda inflamatuar belirteçlerinin serklaj başarısını öngörmedeki rolünü araştırmaktır.

Gereç ve Yöntem: Çalışmaya McDonald yöntemi ile 32'sine (%52.46) elektif serklaj, 29'una (%47.54) acil serklaj uygulanan 61 gebeler dahil edildi. Laboratuvar analizinde hastaların nötrofil-lenfosit oranı (NLR), monosit-lenfosit oranı (MLR), trombosit-lenfosit oranı (PLR) ve sistemik immün inflamasyon indeksi (SII) belirlendi. Serklaj uygulanan hastalar elektif ve acil serklaj grupları olmak üzere iki gruba ayrıldı.

Bulgular: Ortalama serklaj uygulama haftası elektif serklaj için 13.41±0.83 hafta, acil serklaj için 17.45±4.37 hafta idi. Gruplar arasında yaş, gravide, doğum haftası, doğum şekli ve yenidoğan sonuçları açısından anlamlı fark bulunmadı (p>.05). Ancak düşük öyküsü, servikal uzunluk ve serklaj uygulamasından doğuma kadar geçen süre değerlerinde anlamlı fark bulundu (p<.05). Çalışmada iki grup arasında NLO, MLR, PLR ve SII değerleri arasında anlamlı fark bulunmadı (p>.05) ancak SII değeri ile doğum haftası arasında anlamlı negatif korelasyon bulundu (p<.05, r = -0.278).

Sonuç: NLO, MLR ve PLR değerleri, serklaj prosedürünün gebelik süresini uzatmadaki başarısını öngörmede faydalı bulunmadı. Buna karşılık, SII değeri ile doğum haftası arasındaki negatif korelasyonun, servikal serklaj başarısını ve prognozunu öngörmede kullanılabilecek ucuz ve kolay saptanan prognostik bir belirteç oldugu tespit edildi.

Anahtar Kelimeler: Serklaj, inflamatuar belirteç, McDonald, nötrofil, sistemik immün inflamatuar indeks

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INTRODUCTION

Cervical insufficiency is a disease whose etiology is not fully known. It causes miscarriage and preterm labor in the second trimester of pregnancy without symptoms such as uterine contraction and rupture of the membranes (1). Cervical cerclage is a surgical method commonly used in pregnant women who experience preterm delivery due to cervical insufficiency (2). Cervical insufficiency is seen in only 1% of the total obstetric population (3).

When diagnosing cervical insufficiency, it is more informative to detect cervical shortness on transvaginal ultrasound (TVUSG) than on vaginal examination (1). Cervical shortness is defined as a cervical length below the 5th percentile or below 25 mm on TVUSG in the second trimester (4). Cervical cerclage can be performed vaginally (McDonald or Shirodkar cerclage) or abdominally. The McDonald and Shirodkar cerclage procedures are not superior to each other (5). Cerclage is performed as a prophylactic/elective (indicated by history) or emergency/rescue cerclage (cervical shortness on TVUSG or cervical dilation for vaginal examination).

Cerclage insertion can lead to complications such as chorioamnionitis, cervical laceration, hemorrhage, infection, and maternal sepsis (6). Cerclage suturing can lead to uterine activation in the presence of subclinical infection (7), and this inflammatory process can lead to preterm labor (8). The platelet-to-lymphocyte ratio (PLR) and neutrophil-to-lymphocyte ratio (NLR) reflect the severity of inflammation (9).

There are few studies in the literature on noninvasive inflammatory markers that predict how long cerclage can delay labor in patients with cervical insufficiency. The aim of this study was to evaluate the role of maternal inflammatory markers in predicting latency to delivery (clinical success of cerclage) in patients undergoing cerclage under prophylactic or emergency conditions.

MATERIAL AND METHOD

A total of 61 pregnant women who underwent McDonald cerclage at the Department of Obstetrics and Gynecology, Tokat Gaziosmanpaşa University between January 2018 and December 2021 were included in the study. In this retrospective cross-sectional study, patient information was obtained from hospital records. Prior to the study, approval was obtained from the ethics committee of our hospital (Date: 17.06.2021/ Project No: 21-KAEK-161).

Patients between 12 and 25 weeks of gestation who had a previous painless abortion and a second-trimester delivery, who had a cervical length of less than 25 mm

or a cervical dilatation of less than 5 cm, and intact membranes in their current pregnancy were included in the study. Week of gestation was confirmed using the first day of last menstrual period (LMP) or by ultrasound measurements in first-trimester patients whose LMP was unknown. In each patient, cervical dilation and length were determined by TVUSG (CL). TVUSG was performed by taking at least 3 measurements with mild suprapubic compression while the patients' bladders were empty. Patients were divided into two groups: prophylactic/ elective (indicated by history, n:32) and emergency/ rescue cerclage (indicated by ultrasound and vaginal examination, n:29). Patient demographics, age, gravidity, history of abortion, cervical length, time from cerclage placement to delivery, weeks of delivery, modes of delivery, and neonatal outcomes (birth weight, APGAR score) were recorded. Laboratory analyzes determined NLR, monocyte lymphocyte (MLR), PLR, and systemic immune inflammatory index (SII) values. Inflammatory parameters were compared between the elective and emergency cerclage groups. A regularly maintained device (Mindray BC-6800, China) was used for complete blood count.

Cerclage procedure: The patient was prepared under general anesthesia in lithotomy position under surgical conditions. Povidone iodine was applied to the cervix. The upper and lower lips of the cervix were then held in place with ring forceps. McDonald cerclage was performed by passing a 5-mm MERSILENE polyester suture from the nearest point to the internal os of the cervix. In patients with prolapsed membranes, the membrane was pushed into the uterine cavity using ring forceps with wet gauze, and a cerclage was placed after reduction. Each cerclage patient received progesterone (oral progesterone 200 mg S:2*1) and antibiotics (1st generation cephalosporin 2 g IV S:1*1 single dose). After the procedure, a single dose of a suppository containing 100 mg of a prostaglandin synthesis inhibitor and 1 ampule of hydroxyprogesterone caproate IM were administered. After the procedure, progesterone tablets were continued until 37 weeks' gestation or delivery. The cerclage suture was removed immediately in patients with active pain, chorioamnionitis, and rupture of the membranes; it was removed between 36 and 38 weeks of gestation in patients without the aforementioned complaints. If the method of delivery was cesarean section (CS), the suture was removed during surgery. In pregnant women with active vaginal bleeding, ruptured amniotic membrane, fetal anomaly, and dilatation greater than 4 cm, cerclage was not performed. Pregnant women who delivered between 24 and 34 weeks' gestation received 12 mg betamethasone in 2 doses 24 hours apart IM. Pregnant women who underwent abdominal cerclage, had a known multiple pregnancy, or underwent conization and whose data could not be determined were excluded from the study.

Statistical Analysis

Statistical analyzes were performed with SPSS version 20.0 (SPSS, Inc. Chicago). The Kolmogorov-Smirnov test was used to evaluate the distribution model of the variables. Categorical variables were expressed as percentages and compared with the chi-square test. The correlation between categorical variables and parametric variables was analyzed with Student's t test. For analysis of multiple categorical variables, a one-way ANOVA test was used. Data were planned to be presented as mean \pm standard deviation (SD). For correlation of parametric data, Pearson's correlation analysis was performed. P < 0.05 was considered statistically significant.

RESULTS

The elective cerclage group consisted of 32 pregnant women and the emergency cerclage group consisted of 29 pregnant women. In 5 (8.2%) patients, it was the first pregnancy. The remaining 56 (91.8%) patients had undergone a painless abortion and second trimester delivery. Twenty (32.8%) patients had a history of painless abortion before 20 weeks and 36 (59%) had a history of a painless delivery after 20 weeks. Of the patients, 5 had a history of cerclage. The CLs of 18 (62%) patients who underwent emergency cerclage were less than 25 mm on TVUSG examination, whereas the cervical dilatation of 8 (27.5%) patients ranged from 1 to 4 cm on vaginal examination. The mean age of the patients included in the study was 29.70±5.26 years, while the mean gestational week at the time of cerclage placement was 15.33±2.51 weeks. While the APGAR score was 8 and above in 25 of the infants in the elective cerclage group, the APGAR score was 8 and above in 14 of the infants in the emergency cerclage group. No statistically significant value was found when APGAR scores and inflammatory markers were compared. Demographic characteristics of the groups are compared in Table 1.

The mean preoperative and postoperative white blood cell (WBC) values of the elective cerclage patients were 12.17 \pm 1.07 and 10.85 \pm 3.34, respectively, whereas the mean WBC values of the emergency cerclage patients were 11.78 \pm 1.09 and 9.92 \pm 3.51, respectively. The inflammatory markers of the two groups are compared in **Table 2**.

In the emergency cerclage group, two patients experienced cervical rupture during labor. The bleeding was controlled by suturing the laceration under anesthesia with a size 0 absorbable suture. Chorioamnionitis did not occur in any of the patients. No statistically significant results were obtained when comparing inflammatory markers in the group with APGAR scores below and above 8. In correlation analyzes, positive correlations were found between APGAR score and the number of parities, type of delivery (abortion, CS, NVB), week of birth, and birth weight. There were also positive correlations between the number of parities and week of delivery, birth weight, and between cervical length, gravid number and abortion number. A statistically significant negative correlation was observed between SII and week of delivery (r= -0.278). There was no correlation between cerclage history and week and other parameters. The correlation analyzes are shown in **Table 3**.

Table 1 C

groups							
	Prophylactic/ Elective cerclage (n=32)	Emergency/ Rescue cerclage (n=29)	P value				
Age (years)	29.25±6.10	30.21±4.35	0.48				
Gravity	3.97±1.15	3.34±1.71	0.09				
Parity	1.38±.79	1.38±1.17	0.98				
Miscarriage history	1.69±0.20	0.97±.25	0.029*				
Cervical length (mm)	31.16±3.36	15.52±5.78	< 0.001*				
Cerclage week of pregnancy (wk)	13.41±0.83	17.45±4.37	<0.001*				
Time cerclage placement to birth (wk)	22.06± 4.74	14.59±8.50	<0.001*				
week of birth (wk)	35.41±4.91	32.10±6.70	0.031*				
Newborn weight (gr)	2727±890	2246±966	0.052				
APGAR	8.44±2.03	7.17±3.25	0.071				
Delivery modes			-				
CS	26	14					
NVB	5	12					
Miscarriage	1	3					
week of birth (wk) Newborn weight (gr) APGAR Delivery modes CS NVB Miscarriage	35.41±4.91 2727±890 8.44±2.03 26 5 1	32.10±6.70 2246±966 7.17±3.25 14 12 3	0.031* 0.052 0.071 -				

Data are mean (standard deviation); Wk:week; gr:grams; mm:milimetres; CS:caesareau section; NVB: normal vaginal birth, *:P<0.05

Table-2. Comparison of inflammatory markers between groups							
	Prophylactic/ Elective cerclage (n=32)	Emergency/ Rescue cerclage (n=29)	P value				
Preop WBC (10 ³ /mL)	12.17±1.07	11.78±1,09	.16				
Preop Hb (gr/dL)	9.61±2.15	10.10±2,84	.45				
Neutrophils (10 ³ /mL)	6941±1990	7494±2618	.35				
Lymphocytes (10 ³ /mL)	1998±498	1792±505	.11				
Monocyte (10 ³ /mL)	540±180	565±200	.61				
PLT (10 ³ /mL)	251.6±71.3	241.6±42.7	.51				
MPV	9.96±1.24	9.74±1.17	.48				
PDW	13.70±2.99	13.69±3.01	.99				
NLO	3.66±1.51	4.31±2.04	.16				
MLO	0.28±0.11	0.35±0.17	.10				
PLO	131.6±45.6	137.2±45.3	.63				
Sİİ	918±407	1012±512	.44				
Postop WBC (10 ³ /mL)	10.85±3.34	9.92±3.51	.29				

Data are mean (standard deviation); preop: preoperative; postop: postoperative WBC:White blood cells; Hb: Hemoglobin; PLT:platelet; MPV:Mean platelet volume; PDW: platelet distribution width; NLO: Neutrophil/lymphocyte ratio;MLO: Monocyte / Lymphocytes ratio ;PLO: Platelet Lymphocytes ratio; SII: systemic immune inflammatory index

Table-3. Correlation table of parametric data										
	Parity	Gravity	Miscarriage	APGAR	Cerclage history	Cerclage week	Delivery modes	Delivery week (wk)	Newborn weight (gr)	SII
Gravity	.536**									
Miscarriage	142	.731**								
APGAR	.314*	.227	.021							
Cerclage history	.098	.112	.082	.142						
Cerclage week	136	066	.046	083	121					
Delivery modes	.126*	.077	220	.333**	129	.262				
Delivery week (wk)	.477**	.375**	.060	.598**	.074	212	.252*			
Newborn weight (gr)	.348*	.344*	.111	.477**	.059	278	.011	.926**		
SII	110	060	.068	240	190	.154	024	278*	130	
Cervical length (mm)	009	.373*	.457**	.257	.122	441**	237	.269	.265	.112
Data are mean (standard deviation); *. Correlation is significant at the 0.05 level (2-tailed); **. Correlation is significant at the 0.01 level (2-tailed). wk:week; SII: systemic immune inflammatory index argrams: mmmilimetres										

DISCUSSION

Preterm labor is the most common obstetric cause of neonatal death, and cervical insufficiency is one of the causes. There are several treatment options to prevent preterm labor and miscarriage, such as pessaries, progesterone, tocolytic therapy, cervical cerclage, and bed rest. Apart from cerclage, there are no invasive treatments for cervical insufficiency (10). In a study of 108 pregnant women, Harpham et al. reported that insertion of a cerclage before 14 weeks resulted in worse pregnancy outcomes in pregnant women who had previously suffered a mid-trimester miscarriage than in women who had not suffered a miscarriage (10). In Stupin et al.'s study of 161 pregnant women, the average birth weight of emergency cerclage patients was 1340 g, which had a positive effect on perinatal outcomes (11). In our study, prophylactic and emergency cerclage procedures were found to prolong pregnancy and have a positive impact on neonatal outcomes in both patients with and without previous midtrimester miscarriage. Cerclage outcomes may differ in prophylactic and emergency situations. For example, a meta-analysis compared prophylactic cerclage patients with emergency cerclage patients, with patients in the emergency cerclage group delivering their babies earlier and having lower newborn weights (12).

Some studies have shown that elective cerclage prolongs pregnancy and leads to better neonatal outcomes (12-14). In the present study, the procedure in the prophylactic cerclage group was performed at an earlier gestational week, the latency to delivery was longer, and better neonatal outcomes (8< Apgar score) were obtained. Our study is consistent with the literature. In emergency cerclage patients, cerclage success decreases when cervical dilatation > is 1.5 cm and the amniotic membrane is prolapsed (13). In the study by Terkildsen et al., emergency cerclage was performed in two groups with and without prolapsed membranes, and the procedure was more successful in patients without prolapsed membranes (15). Patients undergoing emergency cerclage are more likely to experience complications such as ruptured membranes and chorioamnionitis (16). Therefore, when performing a cerclage, the patient should be informed that pregnancy may be prolonged and positive neonatal outcomes may be achieved, but negative feto-maternal complications may also occur (17). Chorioamnionitis did not occur in the present study, and cervical laceration was observed in two patients during labor. Administration of antibiotics and tocolysis is a common method to alleviate the complications of cervical cerclage and increase its success (18). There are studies showing that amnioreduction is performed before the procedure to decrease the perioperative complications (rupture of membranes) of cerclage and increase its success (19). In our opinion, this seems contradictory because it could increase the risk of intrauterine infection and decrease the success of cerclage. Further prospective studies on this topic are needed.

NLR and PLR have been studied as prognostic factors in obstetrics and gynecology. Neutrophil granulocytes and lymphocytes are markers that can be easily obtained from a complete blood count (9). NLR has been studied as a prognostic factor in oncologic disease, ovarian torsion, preeclampsia, and acute-chronic inflammatory processes (20-23). Because labor is an inflammatory process, NLR may predict preterm labor. In patients with cervical cerclage, an increased rate of NLR has been associated with preterm labor before 28 weeks (2). PLR is also known to be associated with ovarian, breast, and colorectal cancer (24,25). In our study, we concluded that NLR, MLR, and PLR values have no prognostic significance in predicting the success of prophylactic and emergency cerclage procedures. There are studies in the literature that suggest that NLR can predict spontaneous and late preterm labor, and there are studies that accept 4.7 (2) and 6.2 (26) as cut-off values, although no specific NLR values are available for predicting the above labor. In a clinical study, Song et al. showed that NLR is a valuable factor for predicting pregnancy outcome after cerclage (1). In our study, no significant results were obtained between the prophylactic and emergency cerclage groups when both cut-off values were considered.

The value of mean platelet volume (MPV), one of the complete blood parameters, indicates platelet activity and function. In one study, it was reported that low MPV values indicate the severity of inflammation in various inflammatory diseases. MPV were found to decrease in highly inflammatory diseases such as acute/chronic obstructive pulmonary disease, active rheumatoid arthritis, and familial Mediterranean fever (27). In contrast, İncebiyik et al. reported low MPV in pelvic inflammatory diseases (28). To predict this, we thought that MPV could be checked in addition to NLR and PLR because labor is an inflammatory process. In the present study, MPV was not statistically significant in the emergency cerclage group, but it was lower than in the elective cerclage group. More extensive studies are needed to determine the cut-off value of this parameter. SII is a parameter that reflects the systemic inflammatory response based on the combination of platelet count and neutrophil-to-lymphocyte ratio and can be easily determined from the complete blood count. SII was used by Hu et al. to determine hepatocellular carcinoma and by Hong et al. to determine inflammatory and immune status in patients with squamous cell carcinoma (29). It was found that the SII was more significant than NLR and PLR in assessing poor prognosis. This may be because the SII is based on the number of lymphocytes, neutrophils, and platelets and reflects the balance of host inflammatory and immune status more comprehensively than other scores. Therefore, we thought it might precede other parameters in predicting preterm labor. In our study, the SII was not statistically significant in the emergency cerclage group, but it was higher than that in the elective cerclage group. When the correlation between the SII and the week of labor was analyzed, a statistically significant negative correlation was found. This result suggests that the SII may be useful to indicate poor prognosis. More extensive studies with control groups are needed to determine the cut-off value of this parameter. To our knowledge, this study is the first to use the SII value to determine pregnancy prognosis in cerclage patients. The limitation of the study is that it is a retrospective study at a single center with a limited number of patients.

CONCLUSION

Prophylactic and emergency cerclage procedures can be performed in patients with cervical insufficiency considering their clinical status. Timely placement of a cerclage in appropriate patients results in better neonatal outcomes. The SII can be used as a simple and inexpensive prognostic marker to determine the success and prognosis of cervical cerclage. However, prospective studies with larger groups of patients are needed for the SII to be incorporated into practical application.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was approved by Tokat Gaziosmanpaşa University Clinical Research Ethics Committee (Date: 17.06.2021, Project No: 21-KAEK-161).

Informed Consent: Because the study was retrospective, written informed consent wasnot obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

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

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