

Maternal Neutrophil-to-Lymphocyte Ratio Predicts Preterm Birth after Cerclage in Women with Cervical Insufficiency

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Received: March 20, 2019; **Published:** April 02, 2019

Abstract

Objective: To define factors associated with spontaneous preterm delivery at <34 weeks of gestation after cerclage in women with cervical insufficiency.

Materials and methods: We performed a retrospective study of women with known pregnancy outcomes who underwent emergency or urgent cerclage between March 2016 and April 2017. Pregnancy outcomes were analyzed using logistic regression analyses to identify risk factors predictive of spontaneous preterm delivery (<34 weeks of gestation).

Results: A total of 68 women receiving cerclage were included in this study, of which 19 (27.9%) experienced preterm birth (<34 weeks). Logistic regression analyses identified a high maternal neutrophil-to-lymphocyte ratio (NLR) in serum, preoperative shortening of the cervix, and early gestational age at cerclage as risk factors for spontaneous preterm delivery following cerclage.

Conclusion: High preoperative NLR was associated with increased risk for preterm delivery. NLR may serve as a noninvasive, cost-effective predictor of spontaneous preterm delivery after cerclage.

Keywords: Cervical insufficiency; cerclage; neutrophil-to-lymphocyte ratio; spontaneous preterm delivery

Introduction

Cervical insufficiency, characterized by painless cervical dilation in the absence of labor, is a potential etiological factor for spontaneous preterm delivery, responsible for approximately 10–25% of second-trimester pregnancy losses (Daskalakis et al.). Among the most common treatments for cervical insufficiency is cervical cerclage, a procedure in which a suture is applied around the

cervical opening to provide structural support to the cervix and maintain cervical length (Brix et al.). However, even with this treatment, women who undergo cerclage still exhibit a high risk for preterm birth, and may continue to experience cervical change during pregnancy, highlighting the need for better methods for assessing preterm birth risk in women with cervical insufficiency. Improved

Citation: Ji Eun Park, Ji Kwon Park, In Ae Cho, Hyun Chul Jo and Jong Chul Baek. (2019). Maternal Neutrophil-to-Lymphocyte Ratio Predicts Preterm Birth after Cerclage in Women with Cervical Insufficiency. *Journal of Gynaecology and Paediatric Care* 1(1).

diagnostic ability would enable more effective treatment and counseling for at-risk individuals, including administration of corticosteroids, hospital admission for high-risk pregnancies, or transfer to units with appropriate neonatal facilities.

Several studies have identified intraamniotic inflammation, a condition present in ~80% of patients with cervical insufficiency, as a risk factor for preterm delivery and adverse outcomes (S. E. Lee et al.; Jung, Park, Lee, Ryu and Oh). Analysis of amniotic fluid and biopsy of the placenta are effective methods for diagnosing intrauterine inflammation (Yoon et al.); however, fluid analysis must be accompanied by amniocentesis, which remains an invasive procedure and is itself a potential trigger of premature labor. Furthermore, most placental histologic examinations can only be performed after delivery, negating its use as a diagnostic test. Therefore, a rapid, noninvasive method for conceivable intrauterine inflammation and risk for preterm delivery is needed for women with cervical insufficiency.

Total leukocyte and neutrophil counts have historically been used as markers of infection. Applied more broadly, the neutrophil-lymphocyte ratio (NLR) has been used as an indicator of systemic inflammation and stress in various diseases, characterized by increases in neutrophil counts in combination with decreases in overall lymphocyte numbers. Several studies have reported elevated NLR levels as a predictor of poor clinical outcomes, and high NLR levels as a potential risk factor for placental inflammation (Walsh et al.; Jung, Park, Lee, Ryu, Joo, et al.; Kim et al.; Guthrie et al.). Together, these analyses indicate that the NLR may be helpful in predicting preterm birth in cervical insufficiency.

Here, we performed a retrospective analysis of clinical data from all women who had undergone urgent or emergent cerclage at our facility from March 2016 and April 2017. From these data we sought to identify a rapid, reliable, and noninvasive method for predicting preterm delivery in women with cervical insufficiency who underwent cerclage.

Materials and Methods

This retrospective cohort study included pregnant women admitted to Gyeongsang National University Changwon Hospital, Changwon, Gyeongsangnam-do, Korea, with a diagnosis of cervical insufficiency and who underwent emergency or urgent cerclage between March 2016 and April 2017. The cohort consisted of pregnant women

between 15 + 0 and 26 + 6 weeks of gestation, with available outcome data. Inclusion criteria for urgent or emergency cerclage at our facility include visible membranes by speculum examination, prior spontaneous preterm birth with transvaginal cervical length < 25 mm, or follow-up ultrasonography revealing a decrease in cervical length (<20 mm) prior to 27 weeks gestation despite the use of progesterone. Exclusion criteria included women who had fetuses with major malformations, active preterm labor, preterm premature rupture of membranes, vaginal bleeding, clinical chorioamnionitis consisting of pyrexia (persistent body temperature > 38°C), uterine tenderness, increased white blood cell count > 15,000/mm³, C-reactive protein levels > 2.0 mg/dL, and/or persistent fetal tachycardia (>180 bpm).

Clinical characteristics were retrieved from a review of medical records. All patients were treated with a modified Shirodkar-type purse string cerclage using 5 mm Mersilene tape. Maternal blood collection and vaginal swab were performed at the time of admission, prior to administration of antibiotics, corticosteroids, or tocolytics. The NLR was defined as the absolute neutrophil count divided by the absolute lymphocyte count. In addition, positive vaginal culture was defined as overgrowth of aerobic and anaerobic bacteria such as *Ureaplasma urealyticum* or *Mycoplasma hominis* at the time of admission.

All women received prophylactic intravenous antibiotics (ampicillin or cefazolin) at the time of cerclage, which was continued for 3 days post-operation. In addition, patients received 1 g azithromycin orally and were treated with tocolytics with intravenous magnesium sulfate or atosiban on an individual basis. Prenatal corticosteroids were administered for fetal lung maturation in cases of onset of labor (persistent painful uterine contractions) or rupture of membranes, which were considered an indication for preterm removal of the cerclages; otherwise, the cerclages were electively removed at 36 gestational weeks. Clinical covariates collected for all 68 women included maternal age, body mass index (BMI), parity, multiple pregnancy, gestational age at cerclage, cervical length at cerclage, positive or negative vaginal culture at cerclage, NLR in maternal blood drawn immediately prior to cerclage, cerclage-delivery period, and gestational age at delivery. Comparisons for each variable were performed based on gestational age at delivery, with patients divided into two groups: <34 weeks and ≥34 weeks.

Categorical variables were compared using χ^2 or Fisher's exact tests, and are presented as total numbers and percentages. Continuous variables were analyzed using the Mann-Whitney U test and are presented as medians (range). Risk factors associated with spontaneous preterm birth at <34 gestational weeks were identified by univariate logistic regression analyses. Multivariate logistic regression was performed using the backward stepwise technique to determine which combination of factors generated the best predictive model for outcome. Variables with a P value < 0.05 in univariate analyses were entered into stepwise modeling, and a P value < 0.05 was required for final inclusion in the model. Receiver operating characteristic (ROC) curves for the prediction of spontaneous preterm birth at <34 weeks were generated for NLR and for clinical variables, and used to identify the best cut-off values for each variable. All statistical analyses were conducted with SPSS for Windows version 21.0 and R package (3.4.1).

Results and Discussion

Results

Sixty-eight patients were included in this study. The mean gestational age at delivery was 33.7 ± 6.9 weeks, with a mean prolongation of pregnancy after cerclage placement of 12.5 ± 6.9 weeks. Among the 68 women, 19 (27.9%) delivered before 34 gestational weeks, with the remaining 49 (72.1%) delivering at or after 34 gestational weeks. An overview of the clinical and obstetrical characteristics of the study population are presented in Table 1. Gestational age at cerclage was typically earlier, and preoperative cervical length was shorter in among those delivering before 34 weeks, compared to those in the ≥ 34 -week group. Maternal serum NLR was higher in the <34-week group, but otherwise no significant differences in maternal age, BMI, parity, presence of multiple pregnancy, or positive vaginal culture were evident between groups.

	Delivery at <34w (n = 19)	Delivery at ≥ 34 w (n = 49)	P-value
Maternal age (years)	34.0 (25–39)	34.0 (22–44)	0.967
Body mass index	22.9 (20.1–32.0)	23.3 (19.5–39.2)	0.58
Multiparity	37% (7/19)	47% (23/49)	0.625
Multiple pregnancy	16% (3/19)	18% (9/49)	0.555
Gestational age at cerclage (weeks)	20.4 (15.3–26.9)	21.4 (12.4–26.9)	0.037*

Preoperative cervical length (Guthrie et al.)	0.00 (0–2.5)	1.25 (0–2.4)	<0.001*
Positive vaginal culture	53% (10/19)	57% (28/49)	0.473
Maternal serum NLR	5.3 (2.3–9.3)	4.0 (1.5–7.2)	<0.001*
Cerclage-delivery period (weeks)	2.0 (0.3–14.0)	16.6 (9.8–25.7)	<0.001*

Values are given as the median (range) or n (%); NLR, neutrophil to lymphocyte ratio; *statistical significance.

Table 1: Clinical Characteristics.

Associations between independent variables and preterm birth were assessed using univariate logistic regression analyses. Gestational age at cerclage, preoperative cervical length, and maternal NLR were all significantly associated with risk for preterm birth after cerclage (Table 2).

	OR	Univariate or 95% CI	P-value
Maternal age	0.99	0.88–1.13	0.916
Body mass index	1.04	0.92–1.18	0.568
Multiparity	0.77	0.15–3.75	0.722
Multiple pregnancy	1.2	0.29–5.01	0.803
Gestational age at cerclage	0.68	0.46–1.00	0.048*
Preoperative cervical length	0.14	0.05–0.41	<0.001*
Positive vaginal culture	1.2	0.41–3.48	0.737
Maternal serum NLR	3	1.64–5.46	<0.001*

OR, odds ratio; CI, confidence interval; NLR, neutrophil to lymphocyte ratio; *statistical significance.

Table 2: Univariate analyses for prediction of delivery before 34 weeks.

In an attempt to better predict which women with cervical insufficiency would deliver spontaneously at <34 weeks, independent variables were entered into a backward selection logistic regression to identify predictors associated with spontaneous preterm delivery. Of the eight variables tested, only preoperative cervical length and maternal NLR were retained in the best prediction model (Table 3).

	Adjusted or	Adjusted or 95% CI	P-value
Gestational age at cerclage	0.8	0.62–1.04	0.097
Preoperative cervical length	0.15	0.04–0.58	0.006*
Maternal serum NLR	2.64	1.38–5.07	0.003*

OR, odds ratio; CI, confidence interval; NLR, neutrophil to lymphocyte ratio *statistical significance.

Table 3: Multiple logistic regression analyses of potential risk factors for delivery before 34 weeks.

Using ROC curve analysis, we compared the diagnostic indices and predictive values of NLR, preoperative cervical length, and gestational age at cerclage for predicting spontaneous preterm delivery before 34 gestational weeks. NLR had the highest AUC value of 0.843 (95% CI, 0.718–0.968), with a cutoff value of 4.8 identified as the optimal threshold. The overall sensitivity of this marker was 73.7%, with a specificity of 89.8% for predicting the occurrence of spontaneous preterm birth after urgent or emergency cerclage ($P < 0.001$). The areas under the curves for preoperative cervical length and gestational age at cerclage were 0.829 (95% CI, 0.711–0.947) and 0.664 (95% CI, 0.514–0.813), respectively ($P < 0.001$ and $P = 0.037$; Figure. 1).

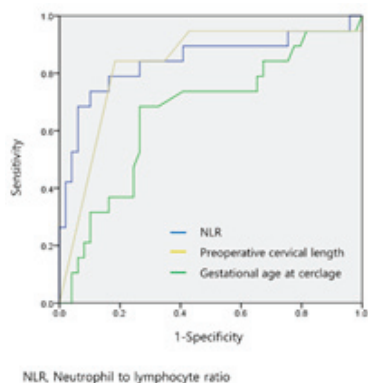


Figure 1: Receiver operating characteristic (ROC) curve for predicting spontaneous preterm delivery before 34 gestational weeks.

Discussion

This study generated three major findings associated with use of cerclage in women with cervical insufficiency. First, the NLR provided a better overall diagnostic performance than any other clinical factor tested for predicting spontaneous preterm delivery before 34 weeks of gestation in women with cervical insufficiency. Second, earlier gestational age at time of cerclage was significantly associated with the likelihood of spontaneous preterm delivery before 34 weeks of gestation. Third, shorter cervical length immediately before cerclage was linked to a higher probability of spontaneous preterm delivery before 34 weeks of gestation.

Intra-amniotic inflammation has been reported in up to 80% of patients with cervical insufficiency, with positive associations with both premature rupture of membranes and preterm birth (S. E. Lee et al.; Romero et al.). Recent studies have shown that elevated concentrations of proinflammatory cytokines and chemokines, such as interleukin (IL)-6, metalloproteinases (MMP)-1, MMP-8, and tumor necrosis factor- α (TNF- α), in the amniotic fluid of women with cervical insufficiency are associated with a greater risk for spontaneous preterm birth before 34 weeks of gestation (Son et al.; S. E. Lee et al.; S. M. Lee et al.). Moreover, several proteins found in the cervical vaginal fluid, including vitamin D binding protein (VDBP), tissue inhibitor of metalloproteinases (TIMP)-1, and Dickkopf-related protein 3 (DKK3), may be predictive of spontaneous premature labor (SPTD) in patients with cervical dysfunction (Yoo et al.). However, while effective, these methods require the use of risky, expensive, and invasive procedures, often requiring specialized equipment. Implementation of these procedures in patients already at risk for preterm delivery presents a significant burden, significantly limiting their use in clinical settings. Therefore, the development of a noninvasive, cost-effective, and easily implemented method for diagnosing intra-amniotic inflammation would be a significant advancement in the diagnosis and treatment of these patients.

Hemocytometers are widely available in most hospitals and are routinely used in many clinical diagnostic tests. A systemic inflammatory response involves changes in the relative levels of circulating leukocytes, characterized by neutrophilia in combination with moderate lymphocytopenia. This type of simple measurement, in the form of an NLR, has been suggested as a simple parameter for assessing the extent of systemic inflammation, and is a useful prognostic indicator in various diseases (Gürol et al.; Tomita et al.; Gibson et al.). Importantly, NLR has recently been used as a prognostic biomarker for identifying women at risk for spontaneous preterm

delivery (Kim et al.). Our data strongly support these previous findings, demonstrating that a high preoperative NLR is a risk factor for preterm birth in high-risk patients who undergo cerclage.

Based on a selected logistic regression model and in ROC curve analyses, preoperative NLR (>4.8) was the strongest predictor of preterm birth, over and above that of other clinical factors. Given the relatively noninvasive nature of the test, NLR testing in pregnant women with cervical insufficiency may represent an effective option for reducing the need for amniocentesis and other invasive tests. Moreover, NLR is easily measured using existing facilities without additional equipment or reagents, highlighting the ease and accessibility of this test.

Studies looking at the effects of gestational age at cerclage relative to pregnancy outcomes have shown significant variability in their outcomes. In one study, cerclage placement before 22 weeks was associated with better outcomes compared to later procedures (Ventolini et al.), while other studies reported the opposite result, with earlier gestation at cerclage associated with increased risk for failure (Abo-Yaqoub, Mohammed and Saleh; Terkildsen et al.). In our study, pregnancy outcomes associated with spontaneous preterm birth were generally poor in cases where early cerclage was needed, compared to much lower probability of spontaneous preterm birth in those treated with more advanced gestational age. This suggests that early cervical changes may be due to the cervix itself being less competent from the start. Moreover, recent studies have also reported benefits of surgery after 24 weeks of gestational age in relation to decreases in neonatal morbidity due to preterm birth (Ragab and Mesbah). Based on these results, we recommend that if surgery is technically feasible, it may be desirable to perform cerclage in the late second trimester in the hope of reducing the risk for neonatal morbidity.

We found a close relationship between shorter cervical length prior to cerclage and spontaneous preterm birth after cerclage, in line with a previous study (Odibo et al.). In addition to cervical length, the accuracy of preterm birth predictions may be improved by studying the cervical funneling and quantification of cervical elastography (Fuchs et al.; Molina et al.).

The present study had several limitations. The major limitation was the heterogeneous nature of our patient cohort, including those requiring both urgent and emergency cerclage. In addition, this study

was limited by its retrospective nature, combined with the relatively small sample size from a single center. Additional prospective studies conducted on larger patient cohorts are necessary to confirm these findings.

Conclusion

Our data suggest that preoperative maternal NLR may serve as a noninvasive, cost-effective predictor of pregnancy outcomes after cerclage. Additional prospective studies are necessary to better establish the link between maternal NLR and pregnancy outcomes, allowing better therapeutic interventions and patient counseling to yield better outcomes in this population.

Disclosure

All authors have and declare that: (i) no support, financial or otherwise, has been received from any organization that may have an interest in the submitted work; and (ii) there are no other relationships or activities that could appear to have influenced the submitted work.

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Citation: Ji Eun Park, Ji Kwon Park, In Ae Cho, Hyun Chul Jo and Jong Chul Baek. (2019). Maternal Neutrophil-to-Lymphocyte Ratio Predicts Preterm Birth after Cerclage in Women with Cervical Insufficiency. *Journal of Gynaecology and Paediatric Care* 1(1).

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