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CLINICAL ARTICLE

Predicting outcomes of emergency cerclage in women with cervical insufficiency using inflammatory markers in maternal blood and amniotic fluid

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ABSTRACT

Objective: To identify inflammatory markers in maternal blood and amniotic fluid that can predict outcomes of emergency cerclage in women with cervical insufficiency. *Methods:* This retrospective cohort study included patients at 18–24 weeks of pregnancy who underwent amniocentesis before receiving emergency cerclage for cervical insufficiency between August 2004 and August 2013 at a university teaching hospital in South Korea. Total and differential white blood cell counts were measured during amniocentesis. Amniotic fluid was cultured and analyzed for the presence of interleukin (IL)-6 and IL-8. The primary outcome measure was spontaneous preterm delivery (SPTD) at less than 32 weeks of pregnancy following cerclage placement. *Results:* Of 37 patients, 18 (49%) experienced SPTD at less than 32 weeks of pregnancy. These patients were found to have significantly more advanced cervical dilatation at presentation, as well as higher mean neutrophil–lymphocyte ratios (NLRs) and higher IL-6 and IL-8 levels in amniotic fluid in comparison with those who did not experience SPTD at less than 32 weeks of pregnancy. In a multivariable analysis, a high NLR and high amniotic fluid IL-8 levels showed a significant correlation with the occurrence of SPTD at less than 32 weeks of pregnancy ($P = 0.032$). *Conclusion:* Pre-operative NLR and amniotic fluid IL-8 levels may be important markers for predicting emergency cerclage outcomes in women with cervical insufficiency.

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1. Introduction

Although acute cervical insufficiency is relatively rare, accounting for less than 0.5% of all pregnancies, in the absence of intervention it has a number of devastating outcomes associated with extreme preterm birth [1,2]. Emergency cerclage placement is often the only hope for prolonging pregnancy for patients with this condition, resulting in fetal salvage rates of 46–100% [3–5]. However, despite the importance of this procedure, information on predictors of success in women undergoing emergent cerclage, especially using non-invasive methods, remains limited.

Intrauterine infection and/or inflammation are associated with a poor prognosis following emergency cerclage [6–9], and their prenatal diagnosis is particularly important because they may increase the risk of long-term handicap in preterm infants who survive [10]. Therefore, numerous studies have focused on discovering biomarkers for this condition, finding that the levels of interleukin (IL)-1, IL-6, and IL-8 in the amniotic fluid can be used to predict the success of emergency cerclage in patients [6–8]. However, these studies have been limited by very small numbers of patients [8] and have not included important variables such as amniotic-fluid culture results and white blood cell (WBC) counts [7]. Moreover, these studies have not examined the use of maternal blood inflammatory markers as less invasive predictors [6]. Maternal systemic inflammatory biomarkers in peripheral blood, such as WBC counts and C-reactive protein (CRP), have been reported to reflect infection/inflammation resulting from subclinical chorioamnionitis in women with preterm labor or preterm premature rupture of membranes [11,12]. Importantly, recent studies have demonstrated that the blood neutrophil–lymphocyte ratio (NLR), which reflects systemic inflammation, is an independent diagnostic and prognostic factor of subclinical inflammatory diseases, including preterm labor and gestational diabetes [13,14]. However, little information is available on whether these systemic inflammatory biomarkers are related to adverse outcomes in patients undergoing emergency cerclage for cervical insufficiency. The present study aimed to identify inflammatory markers in maternal blood and amniotic fluid, and to assess their effectiveness in predicting outcomes of emergency cerclage for cervical insufficiency.

2. Materials and methods

This retrospective cohort study included consecutive patients who underwent emergency cerclage following a diagnosis of cervical

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insufficiency at Seoul National University Bundang Hospital (Seongnamsi, South Korea) between August 1, 2004 and August 31, 2013. The inclusion criteria were singleton gestation; presence of a live fetus at between 18 + 1 weeks and 24 + 6 weeks of gestation; transabdominal amniocentesis conducted prior to cerclage to evaluate the microbiologic and inflammatory status of the amniotic cavity, and/or to reduce tension in the amniotic cavity; maternal blood drawn at the time of amniocentesis to determine the WBC count and CRP level; and intact amniotic membranes. The exclusion criteria were major congenital anomalies, prophylactic cerclage early in the pregnancy, clinical chorioamnionitis, preterm labor, preterm premature rupture of membranes, vaginal bleeding, and multiple gestations. Patients with healthy singleton pregnancies who underwent genetic amniocentesis between 16 + 3 and 18 + 6 weeks of pregnancy at the same hospital during the same period, and who delivered at term, were included as a control cohort for the amniotic-fluid cytokine study. The primary outcome measure was spontaneous preterm delivery (SPTD) at less than 32 completed weeks of pregnancy. An additional analysis of SPTD at less than 37 weeks of pregnancy was performed. Written informed consent for the collection and use of amniotic-fluid samples was obtained from all study subjects. The local ethics committee at Seoul National University Bundang Hospital approved the study (project number B-1311/228-010).

Cervical insufficiency was defined as painless cervical dilatation of at least 1 cm with exposed fetal membranes without contractions of the uterus; this was determined by visual evaluation during a sterile speculum examination. Emergency cerclage was offered to patients with cervical insufficiency and was performed using the McDonald technique under spinal anesthesia. For patients with advanced cervical dilatation and bulging membranes, amnioreduction was performed to decrease intra-amniotic-fluid pressure and, if necessary, an inflated number-16 Foley catheter was used to push the amniotic membranes back into the uterine cavity during suture placement. All patients received prophylactic antibiotics. After the cerclage procedure, all patients were continuously monitored using a tocodynamometer for at least 2 hours. Tocolytics were used at the discretion of the attending obstetrician if regular uterine contractions developed. Prenatal corticosteroids were administered to patientswith cervical insufficiency at 24–34 weeks of pregnancy to enhance fetal lung maturity . Prenatal corticosteroids and antibiotics were administered following amniocentesis.

Before cerclage placement, transabdominal amniocentesis was performed to obtain amniotic fluid using an aseptic technique with ultrasound guidance. The amniotic fluid was cultured for aerobic bacteria, anaerobic bacteria, and genital mycoplasma, and was analyzed to make a WBC count according to a previously described method [15]. The remaining amniotic fluid was centrifuged at 1500 *g* at 4 °C for 10 minutes; the supernatant was aliquoted and immediately stored at −70 °C until assayed. IL-6 and IL-8 in the stored amniotic fluid were measured using an enzyme-linked immunosorbent assay human DuoSet Kit (R&D System, Minneapolis, MN, USA). All samples were measured in duplicate. The calculated intra- and inter-assay coefficients of variation were each lower than 10%.

Maternal blood was collected immediately after amniocentesis for determining the WBC counts and CRP levels. The maternal blood total and differential WBC counts were determined using an automated hemocytometer (XE-2100; Sysmex, Tokyo, Japan). The CRP level was measured with a latex-enhanced turbidimetric immunoassay (Denka Seiken, Tokyo, Japan) and an automated analyzer (Toshiba 200FR; Toshiba, Tokyo, Japan). The NLR was defined as the absolute neutrophil count divided by the absolute lymphocyte count. Clinical and histologic chorioamnionitis was diagnosed according to previously described definitions [12,16].

Statistical analyses were performed using SPSS for Windows version 20.0 (IBM, Armonk, NY, USA). The Shapiro–Wilk test was conducted to test the normal distribution of the data. A univariate analysis was performed using the Student t-test, Mann–Whitney U-test, Fisher exact test, or χ^2 test, as appropriate. Variables showing a significant correlation or a tendency towards an association with SPTD at less than 32 weeks of pregnancy in the univariate analysis ($P < 0.1$) were then further analyzed using a logistic regression model to select independent predictors of this outcome. In the logistic regression model, continuous indicators were transformed into dichotomous variables for the purposes of prediction or decision, and receiver-operating characteristic (ROC) curves were used to identify the best cut-off values for dichotomization. A ROC-curve analysis was used to display the relationship between the sensitivity (true-positive rate) and false-positive rates, and to select the best cut-off values for the NLR, amniotic fluid IL-6, and amniotic fluid IL-8 levels in predicting SPTD at less than 32 weeks of pregnancy. The cerclage-to-delivery interval was assessed with a Kaplan–Meier analysis and was compared between the groups using a log-rank test. Cox proportional hazards modeling was used to examine the relationship between the cerclage-to-delivery interval and the results of the analyses of the potential biomarkers after adjusting for other prognostic variables. Participants who underwent delivery preterm for either maternal or fetal indications were included in this analysis, with a censoring time equal to the cerclage-to-delivery interval. The correlation analysis was performed using the Spearman rank correlation test. $P < 0.05$ was considered statistically significant.

3. Results

Of the 42 patients who fulfilled the inclusion criteria, failed cerclage during rescue cerclage placement occurred in four patients, and one had no amniotic fluid available for IL measurement, leaving 37 participants suitable for evaluation. Of the patients included in the present study, the time of cerclage ranged from 18 + 3 weeks to 24 + 6 weeks of pregnancy. Positive amniotic-fluid cultures were obtained from 4 (11%) individuals. The microorganisms isolated from the amniotic-fluid samples included *Ureaplasma urealyticum* (from four patients) and *Mycoplasma hominis* (present in three patients). Polymicrobial invasion was present in three of the four cases. SPTDs at less than 32 weeks of pregnancy and less than 37 weeks of pregnancy occurred in 18 (49%) and 26 (70%) patients, respectively. The control cohort enrolled 18 patients.

Table 1 shows the baseline demographic and clinical characteristics of the study and control cohorts. Amniotic fluid IL-6 and IL-8 levels were significantly higher in the cerclage group than in the control group ($P < 0.001$). The control group was older and had a significantly lower length of pregnancy at the time of amniocentesis ($P < 0.001$).

The demographic and clinical characteristics of the study population when stratified according to SPTD following cerclage placement at both less than 32 weeks of pregnancy and less than 37 weeks of pregnancy are shown in Table 2. Patients who experienced SPTD at less than 32 weeks of pregnancy had significantly more advanced cervical dilatation ($P = 0.012$) at presentation, a higher mean NLR ($P = 0.017$), and higher amniotic fluid IL-6 ($P = 0.036$) and IL-8 ($P = 0.020$) levels than those who did not deliver spontaneously at less than 32 weeks of pregnancy. However, no significant associations were found between SPTD at less than 32 weeks of pregnancy and maternal age, parity, duration

Table 1
Clinical characteristics of the study and control cohorts.[a]

Variable	Cerclage cohort (n = 37)	Control cohort (n = 18)	*P* value
Maternal age, y	31.8 ± 3.2	35.2 ± 3.9	<0.001
Duration of pregnancy at amniocentesis, wk	21.4 ± 1.4	17.3 ± 0.7	<0.001
Duration of pregnancy at delivery, wk	30.8 ± 7.0	38.6 ± 1.3	<0.001
Amniotic fluid IL-6 level, ng/mL	11.33 ± 19.67	0.27 ± 0.29	<0.001
Amniotic fluid IL-8 level, ng/mL	4.40 ± 4.62	0.38 ± 0.35	<0.001
Cervical length assessed by ultrasound, mm		38.6 ± 7.6	

Abbreviation: IL, interleukin.
[a] Values are given as mean ± SD unless indicated otherwise.

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