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Original Article

Prediction of spontaneous preterm delivery in asymptomatic twin pregnancies using cervical length and granulocyte elastase

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ABSTRACT

Objective: The purpose of this study was to evaluate sonographic cervical length (CL) and granulocyte elastase (GE) in cervical secretion as predictors of preterm delivery in asymptomatic twin pregnancies.
Materials and methods: This study prospectively enrolled asymptomatic twin pregnancies with CL < 25 mm at 22–29 weeks of gestation. All women were hospitalized for preterm labor, and the cervical secretion was obtained for GE testing on admission. The results of CL measurement and GE testing were reviewed, and the relationship between each variables and preterm delivery prior to 34 weeks of gestation was assessed.
Results: Overall, we included 54 women with twin pregnancies, of which 12 (22.2%) had preterm deliveries prior to 34 weeks of gestation. A CL of <20 mm was significantly associated with preterm delivery with an odds ratio of 4.88 (95% confidence limit, 1.15–20.73). GE was not an independent predictive marker for preterm delivery. We also performed a subgroup analysis on the combination of CL and GE for predicting preterm delivery. Among the patients with GE(−), CL < 20 mm markedly increased the risk of preterm delivery with an odds ratio of 10.89 (95% confidence limit, 1.40–77.10). CL was not associated with preterm delivery among those with GE(+). Those with negative GE and shorter CL demonstrated the shortest duration of pregnancy after admission.
Conclusion: The combination of sonographic CL and GE of cervical secretion is useful to predict the risk of preterm delivery in asymptomatic twin pregnancies.

Introduction

The number and rate of twin births has increased over the past decades in developed countries [1]. Prematurity is the major cause of neonatal morbidity and mortality in twin births. The rates of preterm birth <37 weeks and <32 weeks for twin gestations were 10.8 and 7.7 times the rates for singleton gestations, respectively [2]. Prediction of spontaneous preterm delivery in twin pregnancies is of major importance. The identification of the patients at higher risk for preterm birth in twin pregnancies would allow more effective management to prevent adverse perinatal outcomes including antenatal administration of steroid. Moreover, the ability to predict preterm births would be useful to avoid unnecessary interventions and hospitalization in patients with lower risk.

It has been proposed that a short cervical length (CL) measured by transvaginal ultrasound is useful to predict spontaneous preterm delivery in singleton pregnancies [3,4]. More recently, there have been reports suggesting a predictive role in twin pregnancies [5].

Granulocyte elastase (GE) is a serine protease released from leukocytes, which is capable of degrading extracellular matrix proteins. This enzyme has been isolated in human cervical mucus and believed to play an important role in depolymerizing collagen in ripening cervix [6]. It has been reported that polymorphonuclear leukocyte and GE are abundant in the vagina of patients with preterm labor compared with those of normal pregnant women [7]. A more recent study demonstrated that the increased level of GE in cervical secretions was an independent predictive marker for preterm delivery prior to 34 weeks of gestation in singleton pregnancies [8]. To our knowledge, there have been no studies on GE in cervical secretion as a predictive marker for preterm delivery in twin pregnancies.

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The objective of this study was to evaluate CL, GE, and the combination of both as predictors of spontaneous preterm delivery prior to 34 weeks in preterm labor of asymptomatic twin pregnancies.

Materials and methods

We conducted a prospective observational study of women with twin pregnancies who received prenatal care and delivered at the Kyorin University hospital, the tertiary perinatal center in Tokyo, Japan, between January 2009 and July 2015. We prospectively included women with asymptomatic twin pregnancies whose CL was less than 25 mm between 22 weeks and 29 weeks of gestation with intact fetal membrane as the study participants. All participants provided written informed consent for participation in the study, which was approved by the institutional review board. For risk assessment of preterm delivery, we routinely performed CL measurement by transvaginal ultrasound on all outpatients with twin pregnancies every 2 weeks from 20 weeks' gestation. We used the cutoff of 25 mm for indication of hospitalization, which is below the 10th percentile at 24 weeks of gestation in a population delivering at term [4]. Sonographic scan of the uterine cervix was performed with a 7.5-MHz transvaginal probe (SONOVISTA-C3000; Siemens Medical Systems, Tokyo, Japan) with the patient in the lithotomy position and having an empty bladder. The optimal image was defined according to the criteria reported by Iams et al [4]. CL was measured from the internal to the external cervical os. Each scan was performed by a trained obstetrician. A short CL was defined as a CL of less than 20 mm, as the cutoff of 20 mm has been validated in other studies [9,10].

Pregnancies with uterine anomalies, major fetal anomalies, intrauterine fetal death, twin–twin transfusion syndrome, cervical cerclage placement, or medically indicated delivery including preeclampsia prior to 34 weeks were excluded. We also excluded the symptomatic women with gross cervical bleeding, cervical change (effacement of at least 50% or dilatation of at least 2 cm), or painful and regular uterine contractions. The gestational age was based on the last menstrual period, a reliable menstrual history, and an ultrasound examination in the first trimester.

All women were hospitalized and underwent cervical secretion sampling for GE detection on admission. Prior to digital examinations, cervical secretion was taken with a sterile swab for GE assessment. The swab stick was rolled gently across the endocervix. The concentration of GE was measured using Inotech Elastase kit (Sanwakagaku Kenkyusho, Nagoya, Japan) based on latex immunoassay. The cutoff value was 1.6 μg/mL for GE, according to the manufacturer's instruction. According to the manufacturer's data, the minimal detectable dose was 0.1 μg/mL, and the intra- and interassay coefficients of variation were 3.4% and 6.5%, respectively.

All hospitalized women received the therapy for preterm labor including bed rest, intravenous administration of tocolytic agents (beta stimulator and/or magnesium sulfate), and vaginal administration of urinary trypsin inhibitor and metronidazole irrespective of the results of CL or GE until delivery or 34 weeks of gestation.

The relationship between each variables and preterm delivery prior to 34 weeks of gestation was assessed by Mann–Whitney *U* test or Fisher's exact test. Spontaneous labor and spontaneous preterm birth after the premature rupture of membranes were included as preterm delivery in the current study. An adjusted odds ratio was calculated by multivariate logistic regression, in which we controlled for maternal age, parity, chorionicity of the twins, and gestational age at testing.

Kaplan–Meier survival analysis was applied to evaluate the duration of pregnancy after admission according to each variables. The log rank test was used to compare differences in the duration of pregnancy after admission between the groups. Data were examined using a statistics program (SPSS Statistics ver19; IBM, Tokyo, Japan). A p value < 0.05 was taken to indicate a significant test result.

Results

A total of 54 women with twin pregnancies were included during the study period. All were hospitalized at 22–29 weeks of gestation because the CL was below 25 mm. The demographic characteristics of participants are shown in Table 1. Among the 54 women, 12 (22.2%) had preterm deliveries prior to 34 weeks of gestation. There were no significant differences between those who delivered prior to and after 34 weeks with respect to maternal age, parity, chorionicity of the twins, or gestational age on admission.

The median (range) of CL on admission was 20 (6.2–24.0) mm, and 25 patients (46.3%) had a CL below 20 mm. Patients with a CL < 20 mm were significantly more likely to deliver at <34 weeks of gestation ($p = 0.04$), with an adjusted odds ratio of 4.88 [95% confidence interval (CI), 1.15–20.73] (Table 2).

Twenty-three patients (42.6%) showed a positive GE result on admission. As shown in Table 2, GE alone was not a significant predictive marker of spontaneous preterm delivery prior to 34 weeks ($p = 0.53$).

We then examined the combination of GE and CL testing as a risk factor for preterm delivery. Among the patients with positive GE, there was no significant difference in the rate of preterm delivery with respect to CL ($p = 0.62$, Table 3). In contrast, the patients with negative GE and CL < 20 mm had significantly higher rate of preterm delivery prior to 34 weeks, compared with those who had negative GE and CL ≥ 20 mm ($p = 0.04$), with an adjusted odds ratio of 10.89 (95% CI, 1.40–77.10) (Table 3).

The duration of pregnancy after admission according to each variables is shown in terms of survival curves in Figure 1. The

Table 1
Demographic data of twin pregnancies.

	Twin pregnancies included in the study
N	54
Maternal age (y)	35 (21–43)
Nulliparous women	39 (72.2)
Monochorionic twin	28 (51.8)
Gestational weeks on admission (wk)	27 (22–29)
Gestational weeks at delivery (wk)	35 (28–36)

Data are presented as median (range) or number (%).

Table 2
Risk of spontaneous preterm delivery in twin pregnancies based on cervical length and granulocyte elastase alone.

	N	Rate of preterm birth <34 wk (%)
Cervical length (CL)		
<20 mm	25	36.0
≥20 mm	29	10.3
p value		0.04
OR (95% CI)		4.88 (1.15–20.73)
PPV (%)		17.3
NPV (%)		74.2
Granulocyte elastase (GE)		
GE(+)	23	17.3
GE(−)	31	25.8
p value		0.53
OR (95% CI)		0.61 (0.17–2.22)
PPV (%)		36.0
NPV (%)		89.7

CI = confidence interval; NPV = negative predictive value; OR = odds ratio; PPV = positive predictive value.