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Original Article

Early midtrimester serum insulin-like factors and cervical length to predict preterm delivery

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ABSTRACT

Objective: To investigate which ultrasound findings or serum biomarkers, including insulin-like growth factor 1 (IGF-1) and insulin-like growth factor binding protein 1 and 3 (IGFBP-1 and IGFBP-3, respectively), in the first and early second trimesters are the best predictors for preterm delivery.
Materials and Methods: This was a case–control study conducted between March 2011 and March 2013 with women presenting for routine antenatal care at 11–18 weeks. We collected serum samples from pregnant women and stored them at −80°C. All patients underwent cervical length (CL) measurement at 18–21 weeks. We retrieved frozen samples for analysis from women with subsequent preterm and term delivery. Prediction models were developed using multivariate stepwise logistic regression. Receiver-operating characteristics curves were used to determine the most useful cutoff point.
Results: Of the 72 women recruited, 24 women underwent spontaneous preterm delivery, and 48 women with term delivery were randomly selected as the control group, in a 1:2 ratio. The maternal serum concentration of IGFBP-3 and CL were significantly associated with preterm birth.
Conclusion: Among the various known ultrasound findings and serum biomarkers in the early midtrimester, only CL and IGFBP-3 are independent predictors for preterm delivery in asymptomatic women.

Introduction

Preterm delivery (birth before 37 weeks of gestation) causes substantial perinatal mortality and long-term morbidity in neonates [1]. Because the rate of preterm delivery continues to rise [1], the early detection of preterm delivery remains one of the major focuses of antenatal care even in developed countries. In addition, prenatal identification of pregnancies at increased risk of preterm birth is beneficial in that it provides an opportunity for increased prenatal monitoring [2] and preventive treatments such as progesterone [3–5] and cervical cerclage [6,7].

Sonographic cervical length (CL) measurement is known to be the most useful tool available to assess the risk of spontaneous preterm birth in asymptomatic women in midpregnancy [8]. Several other screening measures and biomarkers have been proposed. Serum aneuploidy markers, especially alpha-fetoprotein (AFP), have been proposed as predictors for preterm delivery [9–12]; moreover, cholesterol levels are known to be associated with preterm delivery [9]. Several biomarkers including interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α)—that have been previously measured in the serum, amniotic fluid, and vaginal fluid—are known to be associated with preterm birth in symptomatic women [13–15]. Most of the biomarkers are inflammatory markers, which are extracted from the amniotic fluid or vaginal discharge of symptomatic pregnant women. Few studies have measured serum biomarker levels in asymptomatic women in the early midtrimester.

Insulin-like growth factors (IGFs) play a role in the control of fetal and placental growth [16]. In the circulation, IGFs are bound to insulin-like growth factor binding protein-3 (IGFBP-3), which prolongs the IGF half-life and delays its clearance [17]. Previous studies have noted that phosphorylated IGFBP-1 in vaginal discharge was associated with preterm birth [18]. However, limited data are available on the relationship between IGFs and IGFBPs during the early midtrimester and preterm delivery.

The aim of this study was to investigate which ultrasound findings or serum biomarkers, including IGF-1, IGFBP-1, and

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IGFBP-3, in the first and early second trimesters are the best predictors for preterm delivery.

Methods

This was a case–control study conducted between March 2011 and March 2013 with women presenting for routine antenatal care at 11–18 weeks, who consented to serum sampling for study purposes at the Seoul St. Mary Hospital in Seoul, Korea. All patients signed an informed consent form approved by the Ethics Committee at the Clinical Research Coordinating Center, Catholic Medical Center. The study participants were only women with singleton pregnancies. Women with the following characteristics were excluded from this study: maternal diabetes, preeclampsia, preterm delivery without spontaneous labor, macrosomia and fetal growth restriction, known aneuploidy, major congenital malformation, and pregnancies lost to follow-up. Of the study participants, women with spontaneous preterm delivery from 24^{+0} to 36^{+6} weeks were classified as the case group. The control group comprised women randomly selected from among the study participants, matched according to maternal age and gestational age at serum extraction, in a 1:2 ratio.

Obstetric history data were retrieved from electronic medical records. Clinical and ultrasound variables included age, weight, height, parity, a history of previous preterm delivery, body mass index (BMI), neonatal birth weight, and CL measured at 18–21 gestational weeks. CL measurement was performed according to the protocol established by Iams et al [19] and the shortest measurement was used for each patient. A lipid panel, including total cholesterol and high-density lipoprotein cholesterol, was obtained at the first visit. Serum measurements measured as part of routine screening for aneuploidy included estriol, AFP, inhibin A, and human chorionic gonadotropin in the second trimester. These analytes were expressed as adjusted multiple of medians (MoMs).

Biomarker measurements

At enrollment, serum samples were obtained from all participants at 11 and 18 weeks of gestation. Blood specimen collection and preparation of EDTA plasma were performed using standard operative procedures, with samples centrifuged and stored at −80°C until analysis. Laboratory personnel were blinded to the pregnancy outcome status. Prior to biomarker analysis, the sample was thawed and centrifuged. The resultant supernatant was collected and analyzed. Concentrations of the following markers were measured: IGF-1, IGFBP-1, IGFBP-3, C-reactive protein (CRP), procalcitonin, neutrophil gelatinase-associated lipocalin (NGAL), placental growth factor (PLGF), IL-2, IL-6, IL-10, IL-12, IL-17, interferon gamma-γ (IFN-γ), and TNF-α. An enzyme-linked immunosorbent assay (Abcam, Cambridge, UK) was used for IGF-1, IGFBP-3, IGFBP-1, procalcitonin, NGAL, and PLGF analysis. An immunoturbidimetric assay (Beckman Coulter, Inc, Brea, CA, USA) was used for CRP analysis. A multiplex bead-based immunoassay (MILLIPLEX Map Human Cytokine/Chemokine Magnetic Bead Panel; Millipore Corp., Billerica, MA, USA) run on a Luminex 200 instrument (Luminex Corp, TX, USA) was used to quantify IL-2, IL-6, IL-10, IL-12, IL-17, IFN-γ, and TNF-α.

Statistical analysis

All statistical analyses were performed using SPSS software (version 16.0; SPSS Inc., Chicago, IL, USA). The clinical characteristics of the patients in the case and control groups were compared using either the Chi-square or Fisher exact test for categorical variables, and the Mann–Whitney *U* test for continuous variables. The significance level was limited to *p* values of less than 0.05.

Multivariate logistic regression with backward elimination was performed to compute odds ratios (ORs) as well as 95% confidence intervals (CIs) to estimate the association between preterm birth and each biomarker. Areas under the receiver-operating characteristic (ROC) curve (AUCs) were calculated and compared.

Results

During the study period, 463 women agreed to participate. A total of 134 women were excluded due to maternal diabetes ($n = 10$), preeclampsia ($n = 12$), multiple gestation ($n = 23$), preterm delivery without spontaneous labor ($n = 31$), macrosomia ($n = 2$), fetal growth restriction ($n = 25$), known aneuploidy ($n = 3$), major congenital malformation ($n = 5$), and loss of follow-up ($n = 23$), which left 329 women for analysis. Among these, 24 women who underwent spontaneous preterm delivery were classified as the case group. The control group ($n = 48$) comprised women with term delivery who were randomly selected from among the study participants, matched according to maternal age and gestational age at serum extraction, in a 1:2 ratio. The gestational age (median) at sampling and delivery were 12^{+4} (range 10^{+4}–18^{+1}) and 38^{+4} (range 25^{+2}–41^{+2}) weeks. The maternal characteristics at recruitment and the pregnancy outcomes are summarized in Table 1. The median gestational age at delivery in the preterm group was 35 weeks. Women in the control group did not differ from those in the preterm group with regard to maternal age, height, weight, BMI, nulliparity, and prior spontaneous preterm birth.

The median concentrations of all biomarkers in the maternal serum, and the CL in the two groups are shown in Table 2. Women in the preterm group had significantly higher levels of IGF-1 (0.3 ng/mL vs. 0 ng/mL; $p = 0.043$), IGFBP-3 (226 ng/mL vs. 177 ng/mL; $p < 0.001$), AFP (1.217 MoM vs. 0.875 MoM; $p = 0.009$), and CL (3.22 cm vs. 3.9 cm; $p = 0.001$). In the preterm group, there was no significant difference in the concentrations of other biomarkers.

The multivariate analysis of the biomarker data is shown in Table 3. Multivariate logistic regression with backward elimination confirmed that, even when other risk factors were accounted for, an elevated serum IGFBP-3 level (OR 1.010; 95% CI 1.001–1.019) and CL (OR 0.296; 95% CI 0.115–0.765) were independent predictors of spontaneous preterm delivery.

The ROC curves illustrating the predictive accuracy of serum IGFBP-3 are shown in Figure 1A. The AUC with 95% CIs in predicting spontaneous preterm delivery was 0.790 (95% CI 0.663–0.886; $p < 0.001$). The cutoff value of 194.9 predicted preterm delivery

Table 1
Clinical characteristics of patients enrolled in the study.

	Cases ($n = 24$)	Controls ($n = 48$)	*p*
Age (y)	32 (29–34)	33 (31–36)	0.245
Height (cm)	160 (157–166)	162 (157–165)	0.650
Weight (kg)	54 (50–58)	56 (50–66)	0.099
Body mass index (kg/m^2)	21 (20–22)	22 (19–25)	0.062
Gestational age at delivery (wk)	35 (34–36)	39 (38–40)	<0.001
Birth weight (kg)	2.43 (2.24–2.78)	3.19 (3.03–3.40)	<0.001
Nulliparity	14 (58.3)	23 (47.9)	0.460
Prior spontaneous preterm birth	3 (12.5)	3 (6.3)	0.393

Values are expressed as numbers (%) and median (interquartile rage).