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Original Article

Maternal serum placental growth factor combined with second trimester aneuploidy screening to predict small-for-gestation neonates without preeclampsia

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ABSTRACT

Objective: To investigate the role of maternal serum placenta growth factor (PlGF) and quadruple test parameters in predicting the risk of small for gestational age (SGA) infants of mothers without preeclampsia.
Materials and methods: We prospectively enrolled 300 pregnant patients who underwent blood sampling at 15–18 weeks gestation and followed them until delivery. Cases with SGA neonate delivery (n = 100) were compared with matched AGA neonate controls (n = 200). The plasma PlGF and quadruple markers were measured by enzyme-linked immunosorbent assay. The results were analyzed with Mann–Whitney U tests, and regression analysis was used to develop a model for the prediction of SGA.
Results: Women who delivered SGA neonates had decreased levels of PlGF (median 0.71 MoM versus 0.7 MoM; $p < 0.01$), hCG (median 0.97 MoM versus 1.06 MoM; $p = 0.046$) and uE3 (median 0.92 MoM versus 1.04 MoM) compared to the AGA group. AFP, hCG and inhibin-A levels did not differ significantly. A PlGF concentration <0.37 MoM had a sensitivity of 28.0% (95% CI: 19.5–37.9) and a specificity of 89.5% (95% CI: 84.4–93.4) for the prediction of SGA neonates without PE.
Conclusion: SGA neonates in the absence of PE could potentially be identified at 15–18 weeks of pregnancy.

Introduction

Small-for-gestational age (SGA) fetuses have an increased risk of perinatal complications such as perinatal asphyxia, hypothermia, hypocalcemia, bronchopulmonary dysplasia, pulmonary hypertension and necrotizing enterocolitis [1]. These risks are reduced in SGA neonates diagnosed antenatally compared to those detected after birth [2]. In the early-detection group, early intensive care and proper decisions regarding delivery timing decreased adverse fetal outcomes by four-fold in SGA fetuses [2]. Thus, there is a need for markers to predict SGA early in pregnancy. In Korea, quadruple markers including inhibin-A, alpha-fetoprotein (AFP), human chorionic gonadotrophin (hCG), and unconjugated estriol (uE3) in early mid-trimester have been used for routine antenatal care. As many recent reports have suggested that quadruple markers may be associated with fetal growth disorders, we investigated these markers in our study [3].

Placental growth factor (PlGF) is a potent angiogenic factor that affects early placental vascular development. It is produced by trophoblasts [4] and increases throughout gestation until 26–30 weeks of pregnancy. The period of branching angiogenesis in normal pregnancy induces formation of capillaries and highly vascularized terminal villi, followed by “non-branching” angiogenesis in the third trimester [5]. As preeclampsia (PE) results from failure of angiogenesis of the spiral artery, the role of PlGF has mainly been focused on PE. Another study reported that elevated maternal receptor fms-like tyrosine kinase 1 (Flt-1)/PlGF ratio was

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seen in fetal growth restriction reaching values as high as those observed in preeclampsia or hemolysis, elevated liver enzymes and low platelets syndrome [6]. This reflects the relationship between PlGF and intrauterine growth disorders. We excluded patients with PE because SGA status may be a complication of PE.

The aim of this study was to evaluate early mid-trimester PlGF and quadruple markers in a low-risk population to predict SGA pregnancies in the absence of PE.

Materials and methods

Patients

This cohort study is drawn from prospective observational data on pregnant women who presented for early second-trimester screening and delivered at Seoul St. Mary's Hospital from September 2014 to August 2016. The patients were analyzed as a nested case–control study based on delivery outcomes. Maternal demographics, medical and obstetric history were recorded at the first visit. The gestational age was confirmed from the crown-rump length (CRL) during the early first trimester to avoid a misdiagnosis of SGA. The exclusion criteria included multiple gestation, maternal medical disease (e.g., maternal hypertensive disorder, gestational diabetes, etc.), preterm delivery and fetal anomaly. All of the patients underwent routine antenatal care. Once the estimated body weight of the fetus was below 10 percentile by ultra-sound, we evaluated maternal status and comorbidities, umbilical artery doppler velocimetry and Non Stress Test (NST) and Biophysical profile (BPP). If there was no reversed end-diastolic flow and non-reassuring fetal tracing, we repeated weekly follow up of umbilical artery doppler velocimetry and fetal testing (NST, BPP) and checked fetal growth by sonography every three to four weeks. If this was not the case, we considered optimal time of delivery. The study population was comprised of 100 cases who delivered SGA neonates after 37 weeks. The 200 controls were matched 2:1 for each case based on the date of quadruple marker sampling in order to control for the duration of storage. This study was approved by the Institutional Review Board-Human Research Committee of Seoul St. Mary's Hospital (no. XC15TIMI0004D). Written informed consent was obtained from each patient.

Outcome measures

Maternal demographic characteristics, biochemical results, quadruple markers, and ultrasonographic measurements were recorded in a computer database. Data on pregnancy outcomes were collected from hospital obstetric records. The admission records including nursing data were examined to determine whether the patient developed PE or another medical illness. SGA was defined as a neonatal birth weight below the 10th percentile of a reference range, the newborn centile data of the Royal Prince Alfred hospital newborn care. We selected cases with SGA newborns without PE who delivered after 37 weeks of gestation.

Sample analysis

At the routine quadruple marker sampling during 15–18 weeks of gestation, maternal blood samples (5 cc) were collected under sterile conditions in serum-separating tubes and serum was separated for markers (AFP, hCG, uE3, and inhibin-A) quantification, and in citrate tubes for PlGF quantification. AFP, hCG, and uE3 were analyzed with chemiluminescence assay and inhibin-A was analyzed with radioimmunoassay. Plasmasamples were analyzed for PlGF using the Triage® PlGF Test and the Triage® Meter (Alere, San Diego, California) within 3 h after sampling This is a fluorescent immunoassay that uses two different mouse antibodies against PlGF. First, 250 μL sample of plasma are dropped into the PlGF test cartridge. The cartridge is then inserted into the Triage Meter and the results are displayed in 10–15 min. It is reported that the test has measurable range of 12–3000 pg/mL and the limit of detection of 8 pg/mL. Results were expressed in pg/mL, and the researchers were blinded to clinical diagnosis during analysis.

Statistical analysis

For each patient in the SGA and non-SGA groups, the measured AFP, hCG, u-E3, inhibin-A and plasma PlGF were converted to multiples of the expected normal median (MoM). Comparisons between the SGA and non-SGA groups were conducted with the $\chi 2$ or Fisher's exact test for categorical variables and the Mann–Whitney U test for continuous variables. A receiver operating characteristic curve (ROC) was analyzed to predict SGA neonates in the absence of PE using hCG, u-E3, and PlGF alone as well as the combination of those three markers. Statistical software SPSS 16.0 (SPSS Inc., Chicago, Ill., USA) was used for data analysis.

Results

Clinical characterization

The maternal characteristics of each group are summarized in Table 1. We analyzed 200 patients in the AGA group and 100 patients in the SGA group. There were no significant differences between the two groups in maternal age and gestational age at sampling and delivery. The mean birth weight was 3249 ± 365.5 g in the AGA group and 2624 ± 211.6 g in the SGA group ($p < 0.01$). The percentile of birth weight in each group was significantly different, weighing 40.48 ± 23.67 in the AGA group and 4.64 ± 2.44 in the SGA group ($p < 0.01$).

Table 2 and Fig. 1 show the MoM values of PlGF and the quadruple markers in the AGA and SGA groups without PE. Women who delivered SGA neonates had decreased levels of PlGF (median 0.71 MoM versus 0.7 MoM; $p < 0.01$), hCG (median 0.97 MoM versus 1.06 MoM; $p = 0.046$) and uE3 (median 0.92 MoM versus 1.04 MoM) compared to the AGA group. On the other hand, AFP and Inhibin-A did not show any differences between the SGA and AGA groups.

The area under the ROC curve for the prediction of SGA neonates was analyzed for uE3, hCG, PlGF and the combination of all three markers. The AUC of the combined markers was higher than that of the other three markers, at 0.670 (95% CI: 0.614–0.723, $p = 0.032$). A PlGF concentration <0.37MoM had a sensitivity of 28.0% (95% CI: 19.5–37.9) and a specificity of 89.5% (95% CI: 84.4–93.4) for the prediction of SGA neonates without PE.

Table 1
Baseline characteristics and pregnancy outcome data of patients.

Variable	AGA (n = 200)	SGA (n = 100)	*p* value
Maternal age (years)	33.39 ± 3.27	33.62 ± 3.65	0.573
Gestational age at delivery (weeks)	38.7 ± 1.1	38.72 ± 1.1	0.853
Birth weight (gram)	3249 ± 365.5	2624 ± 211.6	<0.01
Birth weight (percentile)	40.48 ± 23.67	4.64 ± 2.44	<0.01
Gestational age at sampling (weeks)	16.0 ± 0.97	15.9 ± 0.74	0.226
Cesarean deliveries	57 (28.5%)	32 (32%)	0.532
Fetal distress	4 (2%)	4 (4%)	0.325
Prolonged delivery	13 (6.5%)	4 (4%)	0.377
NICU admission	26 (13%)	16 (16%)	0.480

Values are expressed as mean (±standard deviation) for continuous variables and n(%) for categorical values.