



The evaluating of pregnancy-associated plasma protein-A with the likelihood of small for gestational age

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Objective

Recently, strong evidences were obtained on the association between low pregnancy-associated plasma protein-A (PAPP-A) levels in the first trimester and poor outcomes of pregnancy.

Methods

This cross-sectional study was conducted on all pregnant women who were referred to the Obstetrics and Gynecology Clinic at Imam Hossein Hospital in Tehran, Iran in 2014. Women were asked to attend clinical examinations and screening at 11–14 weeks of gestation.

Results

Based on the definition, 14.5% of neonates found to be small for gestational age (SGA). There was a strong association between PAPP-A levels and birth weight. The mean PAPP-A level in the mothers of neonates who were SGA was significantly lower than those without this poor outcome. Based on the receiver operating characteristic curve analysis, serum PAPP-A level was a main determinant in the prediction of SGA neonates.

Conclusion

The serum PAPP-A level at 11–13 weeks of gestation can effectively predict the increased risk for fetal growth retardation. In patients in this study, the best cutoff value for PAPP-A was 0.75 *MOM*, which signifies that lower levels of this marker can predict fetal growth restriction with high sensitivity and specificity.

Keywords: Pregnancy; Plasma protein-A; Gestational age

Introduction

Pregnancy-associated plasma protein-A (PAPP-A) is a zinc-bound metalloproteinase from the super family of metalloproteases [1]. PAPP-A is a large glycoprotein made up of the placenta, decidua, and fetuses; however, the main source of this protein in pregnancy is placental syncytiotrophoblast [2-7]. Various functions of PAPP-A have been described. Primarily, PAPP-A releases insulin-like growth factor (IGF) via the breakdown of IGF-binding protein-4 [8-12]. Thus, PAPP-A facilitates the function of IGF of accelerating and augmenting placental growth. Local IGF secretion plays an important role in increasing mitosis and cellular differentiation as well as in controlling trophoblastic invasion of the decidua [13].

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The role of IGFs in controlling fetal growth is important as they regulate the absorption of amino acids and glucose in the trophoblast. Currently, it is hypothesized that low PAPP-A levels in the maternal serum represent a decrease in the regional levels of the protein, which results in a reduction in active IGF levels. Thus, inadequate free IGF levels, which affect the development of the embryo, may lead to other complications of pregnancy, such as stillbirth, risk of small for gestational age (SGA) neonates, preeclampsia, and premature delivery [14,15]. In addition, other functions of PAPP-A include prevention of fetal targeting by the mother's immune system, uterine mineralization, and angiogenesis [16]. Pregnant women with PAPP-A levels less than 0.45 multiples of the median (MoM) have been significantly associated with increased risk of intrauterine growth restriction, SGA, premature labor, preeclampsia, and stillbirth [17]. In total, low PAPP-A levels in the first trimester of pregnancy have been strongly associated with poor outcomes [18]. In other words, low PAPP-A levels are indicative of poor primary placenta, leading to serious complications such as embryonic growth restriction, fetal death, preterm labor, and preeclampsia in the third trimester. Considering the heavy economic and social impact of chromosomal abnormalities and complications of pregnancy and childbirth for the community and given the fact that many of these complications are preventable, we attempted to examine the association between serum PAPP-A levels in the first trimester of pregnancy and the likelihood of SGA neonates.

Materials and methods

This cross-sectional study was conducted on all pregnant women who were referred to the Obstetrics and Gynecology Clinic at Imam Hossein Hospital in Tehran, Iran in 2014. At first, all participants gave written/verbal informed consent before commencement of the study, following which a complete biography of the mothers was obtained. Data on maternal age, gestational age, parity, and history of pregnancies with complications were also recorded. The participants were asked to attend clinical examinations and screening at 11–14 weeks of gestation during which ultrasonography performed and blood samples were taken to measure common biochemical indices and markers such as β -HCG. In addition to the usual tests, we measured PAPP-A levels in the blood

samples of these individuals. The cases with fetal crown-rump length ranging from 45 to 84 mm were asked to provide written informed consent if they wished to participate in the study. CRL values were converted to gestational age (GA) using Z score, and PAPP-A levels less than 5% in each GA were considered as low. Mothers were then followed up until delivery. During this period, all routine healthcare measures were performed for these mothers and any abnormalities were treated. In this study, the results were determined based on outcome of the delivery. In cases of presence of a disorder other than SGA fetuses/neonates during pregnancy or at the time of delivery, the mother was excluded from the study. Finally, the data were statistically analyzed. The institutional ethics committee of the Preventative Gynecology Research Center (PGRC) at Shahid Beheshti University of Medical Sciences approved the study protocol. For analyses, results were presented as mean \pm standard deviation (SD) for quantitative variables and as absolute frequencies and percentages for categorical variables. Normality of the data was analyzed using the Kolmogorov-Smirnoff test. Categorical variables were compared using chi-square test or Fisher's exact test when more than 20% of cells with expected count of less than 5 were observed. The quantitative variables were also compared with *t*-test or Mann-Whitney *U* test. The value of PAPP-A to predict SGA neonates was assessed using the receiver operating characteristic (ROC) curve analysis. Multi-variable logistic regression model was also used to determine the value of low PAPP-A levels in predicting SGA neonates using baseline characteristics. For statistical analyses, SPSS version 16.0 for Windows (SPSS Inc., Chicago, IL, USA) was used. *P*-values of 0.05 or less were considered significant.

Results

In total, 715 pregnant women were assessed. The mean age of participants was 27.88 ± 5.97 years (range, 17–38 years). Regarding gestational age at the time of screening, 34.5% were in the 11th week, 49.1% in the 12th week, and 16.4% in the 13th week of pregnancy. The mean body weight of the participants was 68.90 ± 12.55 kg (range, 47–105 kg). Average birth weight of neonates was $3,100.91 \pm 553.82$ g (range, 1,700–4,000 g). The mean PAPP-A level at the time of screening was 1.21 ± 0.66 (range, 0.28–3.37) (Table 1). Based on the definition of weight less than 10th percentile

based on gestational age, 14.5% of neonates were found to be SGA. There was no difference in the mean weight of mothers with and without SGA neonates (30.08 ± 8.63 years vs. 27.51 ± 5.43 years, $P=0.439$). No difference was also found in the mean weight of mothers with and without neonates who were SGA (73.81 ± 18.21 kg vs. 68.06 ± 11.39 kg, $P=0.413$). The overall prevalence of fetuses who were SGA at 11, 12, and 13 weeks of pregnancy was 26.3%, 3.7%, and 22.2%, respectively with no significant difference ($P=0.078$). There was a strong association between PAPP-A levels and birth weight ($r=0.442$, $P=0.001$) (Fig. 1). The mean PAPP-A level in mothers of neonates who were SGA was significantly lower than that in women with normal delivery

children (0.76 ± 0.61 vs. 1.29 ± 0.64 , $P=0.035$). Based on the ROC curve analysis (Fig. 2), the serum PAPP-A level was a main determinant in the prediction of SGA neonates (Area under the curve=0.811, $P=0.005$). The best cutoff value for PAPP-A to discriminate between SGA neonates and those with normal weight was 0.75 yielding a sensitivity of 80.9% and a specificity of 85.0%. According to the multivariable logistic regression model and with the presence of baseline variables including maternal age, weight, and gestational age, decreased PAPP-A levels could effectively predict the increased likelihood of SGA neonates (odds ratio, 12.347; 95% confidence interval, 0.012–165.917; $P=0.048$).

Table 1. Baseline characteristics of the study population

Characteristics	Values
Mean age (yr)	27.88±5.97
Gestational age at screening (wk)	
Eleventh week	34.5%
Twelfth week	49.1%
Thirteenth week	16.4%
Mean birth weight of neonates	3,100.91±553.82
The mean level of PAPP-A on screening time	1.21±0.66
The prevalence of SGA	14.5%

PAPP-A, pregnancy-associated plasma protein-A; SGA, small for gestational age.

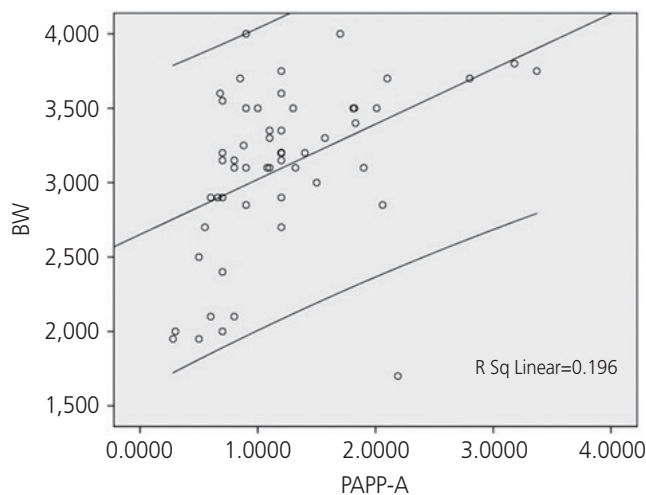


Fig. 1. The association between pregnancy-associated plasma protein-A (PAPP-A) level and birth weight (BW).

Discussion

Two methods of clinical examination and arterial Doppler are not very sensitive and precise for predicting fetal growth restriction (FGR) and may lead to over-estimation of cases that are SGA. In this regard, the use of biochemical markers (such as cystatin C, macrophage migration inhibitory factor,

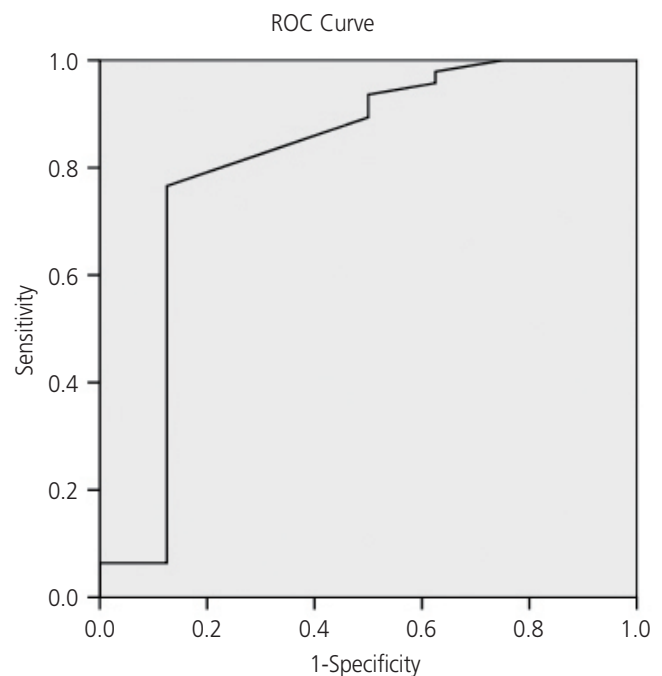


Fig. 2. The receiver operating characteristic (ROC) curve analysis to determine the value of pregnancy-associated plasma protein-A (PAPP-A) to predict small for gestational age (SGA).

plasminogen activator inhibitor 2, and PAPP-A), maternal medical history (history of smoking, parity, body mass index, and increased systolic blood pressure), and some dynamic vascular parameters such as uterine artery pulsatility during the first or second trimester have been considered as predictors of FGR. Accordingly, in recent years, experts have considered the assessment of serum free β -HCG and PAPP-A levels in the prediction of FGR. Some studies have reported that increased β -HCG levels and decreased PAPP-A levels are critical in predicting FGR. However, a few important points are still questionable. First, the power and diagnostic capability of these biomarkers have not been tangibly considered in the prediction of FGR. Second, the best cut-off point for these biomarkers in predicting FGR in different communities may vary and should, therefore, be considered in future studies. The present study aimed to determine the capability and value of PAPP-A in predicting FGR in a sample of Iranian population. First, our study showed that the assessment of serum PAPP-A levels was effective to predict FGR with high sensitivity and specificity. Second, based on the results of the ROC curve analysis, the best cutoff point for PAPP-A was 0.75; thus, lower levels of this marker strongly correlated with high risk of FGR. However, the obtained cutoff value in our study was notably higher than that previously reported in some studies (0.75 vs. 0.30). As reported by Agarwal et al. [19] in 2017, with a cutoff value of 0.45, the specificity and positive predictive value of PAPP-A for FGR were 92.6% and 56.2%, respectively. However, in another study by Sung et al. [20] in 2017, the best cut-off value of PAPP-A for predicting a SGA infant was 1.06 MoM, which was significantly higher than that reported in the present study. This discrepancy might be caused by several factors such as the difference in the tools used for measurement of PAPP-A, the effect of genomic factors, and different gestational ages. In general, there is consensus among all studies with regard to the capability of PAPP-A in the prediction of FGR. In a study by Hansen et al. [21], low PAPP-A levels were associated with the risk of SGA neonates. In a study by D'Antonio et al. [22], serum PAPP-A levels were significantly lower in women with SGA children than in those with normal delivery children. Another study by Loncar et al. [23] reported similar findings. In a survey by Kirkegaard et al. [24], PAPP-A levels less than 0.4 with a growth index less than 10 percentile were accompanied with an increased risk of SGA neonates up to 5.8-fold. Salvig et al. [25] reported that the growth rate of infants from the first to

second trimester significantly correlated with PAPP-A levels. In a study by Fox and Chasen [26], PAPP-A levels below the fifth percentile was associated with an increased rate of FGR in the third trimester, preterm birth, neonatal intensive care unit admission, intrauterine or neonatal death, smaller median birth weight, and earlier median gestational age at delivery. They also showed that PAPP-A values below the 10th percentile and the 25th percentile were associated with poor outcomes. Finally, Carbone et al. [27] indicated that PAPP-A below the 5th percentile had the highest sensitivity with a specificity of 82.1% for screening of SGA neonates.

In conclusion, the measurement of serum PAPP-A levels at 11–13 weeks of gestation can effectively predict the increased risk of SGA neonates. In patients in the present study, the best cutoff value for PAPP-A was 0.75, which signifies that lower levels of this marker can predict SGA with high sensitivity and specificity.

Conflict of interest

No potential conflict of interest relevant to this article was reported.

Ethical approval

The study was approved by the Institutional Review Board of Shahid Beheshti University of Medical Sciences and performed in accordance with the principles of the Declaration of Helsinki.

Patient consent

The patients provided written informed consent for the publication and the use of their images.

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