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Association of the Low Pregnancy-Associated Plasma Protein A and Pregnancy Complications in the First Trimester: A Prospective Cohort Study

Ameneh Abtahian[1], Hanieh Fakhredin[2], Soodabeh Darvish[3]

1- Department of Obstetrics and gynecology, Shahid Beheshti University of Medical Sciences, Tehran, Iran.
2- School of Medicine, Shahid Beheshti University of Medical Sciences, Tehran, Iran.
3- Assistant professor of Obstetrics and gynecology, Fellowship of Female pelvic medicine and reconstructive surgery, Taleghani Hospital, Department of Obstetrics and gynecology, Shahid Beheshti University of Medical Sciences, Tehran, Iran.

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Corresponding Author
Assistant professor of Obstetrics and gynecology,Fellowship of Female pelvic medicine and reconstructive surgery, Taleghani Hospital , Department of Obstetrics and gynecology,shahid Beheshti University of medical sciences , Tehran ,Iran Taleghani Hospital, Velenjak St,Shahid Chamran Highway , Tehran,Iran.
Tel:22439982
Fax:22439784

ABSTRACT

Background and Aims: This study aimed to assess the association between the low maternal serum of pregnancy-associated plasma protein-A (PAPP-A) during the first trimester and pregnancy outcomes.

Materials and Methods: We conducted a prospective cohort study of 118 pregnant women undergoing first-trimester screening between 2016 and 2017 at Taleghani and Imam Hussein hospital in Tehran, Iran. We recorded demographic data, and blood samples were taken to analyze the value of PAPP-A, based on which we divided the participants into two groups: PAPP-A >10th percentile as a control group, and PAPP-A ≤10th percentile as a study group. The pregnancies underwent follow-up observations for obstetric complications during pregnancy. Chi-square or Fisher exact test and Mann-Whitney U test were applied to analyze data by SPSS 26.

Results: In this study, 118 pregnant women were enrolled. Our results show a significant association between low PAPP-A (<10th percentile) and preterm labor, small for gestational age (SGA), hypertension, preeclampsia ($P < 0.05$), but no statistically significant difference was found between low PAPP-A and stillbirth. Demographic data, including age, gravida, parity, BMI, had no relationship with low PAPP-A, significantly ($P > 0.05$).

Conclusion: Low PAPP-A is associated with adverse outcomes; thus, measuring the PAPP-A within the first trimester is suggested for timely management.

INTRODUCTION

UppPregnancy complications are the consequence of risk factors; however, most of the adverse effects occur in women with no related risk factors [1]. Placenta as a barrier and nutritional transporter plays a major role in associated adverse outcomes of pregnancy, such as small for gestational age or preterm delivery in a fetus, developing hypertension or preeclampsia in pregnant women. Consequently, the impaired placental function owing to the failure of trophoblast invasion causes ischemia and fetus hypoxia, which predispose the pregnant women and their fetus to the following sequela. The syncytiotrophoblast secret PAPP-A, and the low level of PAPP-A would be detected in the placenta insufficiency. PAPP-A is a protease targeted insulin-like growth factor binding protein-4 (IGFBP-4), and a lower level of PAPP-A affects insulin-like growth factor (IGF) level. IGF stimulates the placenta and fetus development; thus, the lower level of IGF leads to restricted intrauterine growth and associated pregnancy complications such as preterm labor and preeclampsia [2-7].

The biomarkers reflect the fetus and maternal status in screening tests. ß-HCG, pregnancy-associated plasma protein-A(PAPP-A), progesterone, activin A, Inhibin A, artery pulsatility index, and the maternal serum of placental growth factor are the predictors [2, 8]. No single predictor is accurate to measure the risk of possible adverse effects [6], and recent studies suggest the combination screening study [9]. Assessment of the biomarkers and the maternal

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factors affecting them provide a diagnostical approach to manage the pregnancies.

PAPP-A, in part of the first-trimester screening test for Down's syndrome, provides an available predictor of maternal status [9]. Current studies support the association between the PAPP-A and increased risk of preeclampsia, SGA, preterm labor, and stillbirth [10, 11]. This study aims to investigate the association between low PAPP-A and pregnancy complications in low-risk women for SGA, stillbirth, preeclampsia, and preterm labor, and to figure out the relationship between the low PAPP-A and maternal factors in Iran.

MATERIALS and METHODS

We conducted a prospective cohort observational study of 118 pregnancies in the first trimester referred to Taleghani and Imam Hussein hospital between 2016 and 2017 for prenatal care. Informed consent was obtained from the participants, and The Research Committee of Shahid Beheshti University issued Codes of ethics for the study (IR.SBMU.MSP.REC.1397.42). All singleton pregnancies undergoing first-trimester screening tests were included, and the exclusion criteria were twin pregnancies, history of congenital abnormal parturition, and inaccessibility to the participants or incomplete follow-up. Demographic data, including age, gravida, parity, and BMI prospectively, were recorded at the time of blood sampling. Samples of 5 ml venous blood were transferred to the laboratory certified by the Ministry of Treatment and Medical Education of Iran. The concentration of PAPP-A was adjusted for gestational age, maternal weight, ethnicity, smoking, number of fetuses, and method of conception, which was expressed in multiples of the median (MoM). The recruited pregnancies were divided into two groups: a) low PAPP-A defined as <10th percentile as a study group and b) normal PAPP-A defined as ≥10th percentile (equivalent to 0.53 MoM) as a control group. The outcomes were the rate of SGA, preterm delivery, stillbirth, hypertension, and preeclampsia that were assessed in both groups. According to International guidelines, preeclampsia referred to hypertension (≥140/90 mmHg twice 6-hour apart) and proteinuria (≥300mg/day on 24-hour urine output or ≥+1 in dipstick on a midstream urine sample at least twice 24-hour apart), SGA referred to bodyweight <10th percentile for gestational age and preterm delivery considered as gestational age < 37 weeks. WHO defines stillbirth, a fetus is born dead ≥ 28 weeks' gestation. We used IBM SPSS statistics 26 for statistical analysis. Chi-square and Fisher exact test for categorical variables and Mann-Whitney U test for continuous non-distributed variables were applied to compare pregnancy complications. P-value ≤0.05 was considered statistically significant.

RESULTS

In this study, 118 women in the first trimester were enrolled. In 59 of the participants, low PAPP-A MoM was detected. Demographic data are demonstrated in table 1.

The mean BMI of pregnancies were 29.8±26.24. In the study group, 38 cases of the study group and 38 women of the control group had BMI>25. The age of participants ranged from 21 to 34, with 27.51±3.78 as the average; 22 women of the study group and 23 women of the control group were ≥30 years. BMI, gravida, parity, and age were statistically similar in both groups; however, BMI, age, gravity, and parity were higher in the low PAPP-A group.

Seven out of eight cases with SGA were in the study group and showed a statistically significant (P-value < 0.05). The correlation between SGA and demographic data was surveyed, but the results indicated an insignificant prevalence. Low PAPP-A group constituted a higher prevalence of preterm delivery, 6.77% of 8.47% cases, and showed a significant difference compared to the control group (P-value < 0.05). Table 2 outlines more prevalence of pregnancy hypertension (15.25% versus 3.38%) and preeclampsia (11.86% versus 1.69%) in the low PAPP-A MoM group. Significant differences in pregnancy hypertension (P = 0.02) and preeclampsia (P = 0.02) were observed between the two groups. All stillbirths with the low frequencies of 2 cases were in the low PAPP-A MoM group, but no significant differences were detected between the two groups (P = 0.15). No association was found between stillbirth and age or BMI of pregnant women.

DISCUSSION

The study considers the low PAPP-A (<10th percentile) as a predictor of preterm labor, SGA, preeclampsia, and pregnancy hypertension based on the results, but none of the demographic factors such as BMI, age, parity, and gravida had a significant relation with the PAPP-A.

Table 1. Demographic data

Variable	Number	Value
The mean BMI †		26.24±2.06
Mean Age ‡		27.51±3.78
The prevalence of Gravid §	(1-2)	72 (61.01%)
	(3-4)	46 (38.99%)
The prevalence of Parity §	(0-1)	78 (66.1%)
	(2-3)	40 (33.9%)

† **(kg/m²±SD);** ‡ **(year±SD);** § **n(%)**

Table2. Association of PAPP-A with demographic and maternal factors

Variable	PAPP-A		P-value
	Normal (N=59)	Low (N=59)	
BMI †	26.21±2.06	26.28±2.09	0.88
Age ‡	27.56±3.84	27.47±3.76	0.89
Gravid ¶	2.42±0.72	2.389±0.71	0.79
Parity ¶	1.35±0.71	1.30±0.72	0.70
PTL §	2(3.38%)	8(13.55%)	0.04*
SGA §	1(1.69%)	7(11.86%)	0.02*
stillbirth§	0(0%)	2(3.38%)	0.15
HTN §	2(3.38%)	9(15.25%)	0.02*
Preeclampsia §	1(1.69%)	7(11.86%)	0.02*

Abbreviation: PTL: preterm labor; SGA: small for gestational age; HTN: hypertension; * p-value<0.05; † (kg/m²±SD); ‡ (year±SD); ¶ (mean±SD); § n(%)

In our study, no correlation was found between low PAPP-A and stillbirth which confirm the results of other studies [12]. A large scale prospective surveys on 33395 women by L.Dugoff et al. (FASTER trial) reported that the PAPP-A≤5th percentile has a significant association with spontaneous fetal loss at ≤24 weeks of gestation and intrauterine fetal death >24 weeks of gestation [13].

PAPP-A is considered as a predictor for gestational hypertension in common with other studies [14] and E.Antwi et al. suggested adding PAPP-A and PIGF to the clinical algorithm [15]. In our study, we observed a significant relation between preeclampsia (PE), pregnancy hypertension, and low PAPP-A in the agreement of other studies [16], but not in several studies [17] possibly for a low incidence of PE. Since the high BMI as confounding factor can contribute to developing preeclampsia, we excluded women's BMI ≥30 in our study. Luewan et al. enrolled 3663 women; 357 cases with low PAPP-A (<10th percentile) and 3306 women with normal PAPP-A, which found an increased risk of preeclampsia in association with the low PAPP-A [18]. Poon et al. reported a bigger fall of PAPP-A level in developing early preeclampsia [19]. M.Honarjoo et al. stated that the low PAPP-A (<4 MoM) shows a 2.05-fold increase in developing preeclampsia based on the evaluation of 4605 pregnant Iranian women [20].

Low PAPP-A association with SGA is well established [16]. M.Hoseini et al. evaluated 715 pregnant women in Imam Hussein hospital and concluded that the best cutoff PAPP-A value to predict SGA in the Iranian population is 0.75 MoM with high sensitivity and specificity [21]. In another study by Cowen and Spencer, it was found that the severity of SGA has a linear relation with a decrease in PAPP-A [22], and the sensitivity of the PAPP-A test increases with rising the severity of SGA [23].

Our results show the association between preterm labor and low PAPP-A, which is consistent with previous studies [24]. FASER trial indicated that similar to SGA, increasing the sensitivity is accompanied by increasing the severity of preterm labor; however, the studies considered the PAPP-A as a poor biomarker for determination of SGA and the preterm labor [13, 23]. Consistent with the findings; a meta-analysis of 32 studies assessed 175240 pregnant women, which reported 67.4% sensitivity and 67.5% specificity for PAPP-A ≤0.745 MoM [25].

Although some studies have suggested adding the other screening tests such as biophysical markers would be more predictable, the screening test should be evaluated depending on the clinical resources. For example, Poon et al. improved the diagnosis of preeclampsia by the uterine artery pulsatility index as the most promising screening test [19, 26] that accessibility testing is questionable.

The strength of this study is the prospective investigation of pregnant women attending prenatal screening tests to detect a chromosomal abnormality and to examine fetal growth. Second, reducing the impact of confounding factors such as BMI by applying the women's BMI <30. The limitation of this study is that the small population involved in the study.

CONCLUSION

The findings demonstrate that pregnancies with PAPP-A <10th percentile have an increased risk of adverse outcomes; however, the current studies considered it a poor predictor. Thus, PAPP-A combination with the other related predictors would improve the sensitivity and specificity of the screening. Second-trimester biomarkers to closely follow up the high-risk pregnancies for complications should be determined to prevent adverse complications.

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