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The Relationship between the Level of Pregnancy-Associated Plasma Protein A and Placenta Size and Thickness

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Abstract

Background: The low level of pregnancy-associated plasma protein A (PAPP-A) has a relationship with unfavorable outcomes in neonates. This study aimed to evaluate the association between the thickness and size of the placenta in singleton pregnant women.

Materials and Methods: In this prospective cohort study, 102 women were investigated in 18-23 weeks and PAPP-A level at the gestational age in 11-14 weeks with a singleton pregnancy who referred to Al-Zahra Hospital, Rasht, Iran, between 2017 and 2018. Serum PAPP-A of pregnant women was measured in the first trimester of pregnancy. Patients who had PAPP-A ≤ 0.5 Multiple of the Median (MOM) were dedicated to an exposed group and others to a non-exposed group. Placental thickness and size were assessed during the second trimester by ultrasound examination and described as abnormal high thickness if the thickness was > 4 cm or more than 50% of the placental length and abnormally small size when the maximum length was < 10 cm. Then, placental thickness and size were compared between the two groups.

Results: PAPP-A levels of > 0.5 and ≤ 0.5 were recorded in 60 and 34 patients, respectively. Women with low levels of PAPP-A in the first trimester had an increased incidence of abnormal placental thickness in 13 cases and small placental size in 7 cases, whereas this number was 12 and 7 cases, respectively, in the other group (P = 0.023). The sensitivity and specificity of PAPP-A < 0.55 were 72.3 and 56% for abnormal placental thickness, respectively; the sensitivity and specificity of PAPP-A < 0.55 were 69.3 and 57.1%, respectively, in the assessment of abnormal placenta size.

Conclusion

Based on the results, the size and thicknesses of the placenta were abnormal in women with a low level of PAPP-A (≤ 0.5).

Key Words: PAPP-A, Pregnancy, Placenta, Women.

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1- INTRODUCTION

Pregnancy-associated plasma protein-A (PAPP-A) is produced by the placenta and fetus. The amount of PAPP-A raises in the blood circulation of pregnant women. PAPP-A facilitates the activity of the insulin-like growth factor (IGF) family to advocate placental growth and function. Assessing PAPP-A late in the first trimester can determine the risk of fetal aneuploidy including trisomy 21, with a detection rate of over 90% for a 5% false-positive rate in pregnant women, in addition to maternal age, maternal serum Human Chorionic Gonadotropin (HCG), and fetal nuchal translucency (1-4). Furthermore, other studies emphasized that low plasma levels of PAPP-A were as a biochemical marker for pregnancy with an aneuploid fetus (5). Moreover, low levels were observed in situations such as intrauterine growth restriction (IUGR) (6), pre-eclampsia (7), placental abruption, premature birth, a fetus that is small for gestational age (SGA), and fetal death (8).

Two tests based on ultrasound including Uterine Artery (UtA) Doppler ultrasound and measurement of placental size and thickness have been advised as screening tools for placental insufficiency in the second trimester (18-23 weeks) among clinically high-risk women (9). According to the evidence, perinatal morbidity and neonatal outcome are worse in women with the thick placenta (10, 11). Placental measurement can be used as an independent predictor of birth weight (12). It is important to anticipate the consequences of pregnancy in order to take appropriate preventive measures. Measuring maternal serum PAPP-A in the first trimester can be a way for early detection of the adverse prenatal outcomes. However, considering the limitation of prior studies on this topic, this study aimed to investigate a possible association between PAPP-A levels and placental size and thickness in pregnant women to determine the high-risk pregnancies based on the abnormal placenta.

2- MATERIALS AND METHODS

2-1. Study design and population

This prospective cohort study was conducted in Al-Zahra Education and Research Hospital, a tertiary teaching hospital in Rasht, Guilan province, North of Iran, on 102 women with singleton pregnancies who were referred to the hospital between August 2017 and June 2018.

2-2. Methods

The required sample size was estimated by considering a 95% confidence interval (CI), a power of 80%, an expected clinical difference of at least 25%, and parameters of Mesdaghi-Nia E et al. study (9) through the following formula.

$$n = \frac{(z_{1-\frac{\alpha}{2}} + z_{1-\beta})^2 [p1(1-p1)+p2(1-p2)]}{d^2}$$

Systematic random sampling was used to choose study samples and 34 exposed and 68 non-exposed cases were included in the study. A single experienced radiologist who was blind to the patient group using a GE Voluson E6 device with a 2-5 MHZ convex probe (General Electric Company, USA) performed all second-trimester ultrasounds.

During an ultrasound examination, the placental thickness was measured through the thickest part of the placenta (13, 14) and placenta size was identified in its longitudinal plane by rotating the probe to find the longest axis (13). The abnormally high thickness of placenta (**Figure. 1**) was considered when the thickness was 4 cm or more, or more than 50% of the placental length (14). The placental size was considered to be abnormally small when the maximum length was < 10 cm (13). In the fundal or lateral position of the placenta, panorama or trace was used in

the setting for the measurement. PAPP-A was measured using an immunoassay system analyzer, which is used for a routine first-trimester prenatal screening program. PAPP-A values were converted to gestation-specific multiple of medians (MoM) using the Prisca software program. Levels of PAPP-A in all patients were measured by a single laboratory unit. A value ≤ 0.5 MOM was defined as a low level of PAPP-A (15). Based on PAPP-A levels, patients were divided into two groups: women with PAPA-A values of ≤ 0.5 and > 0.5 MOM were defined as exposed and unexposed groups, respectively.

Fig.1: Ultrasound assessment of placental thickness.

Maternal age, gravida, parity, gestational age, history of complicated pregnancies (such as preeclampsia, placental abruption, intrauterine fetal death (IUFD), and intrauterine growth retardation (IUGR) were recorded in a checklist. Gestational age was calculated from the first day of the last period and confirmed by ultrasonography at the first-trimester scan.

2-3. Measuring tools

Maternal age, gravida, parity, gestational age, history of complicated pregnancies (such as preeclampsia, placental abruption, intrauterine fetal death (IUFD), and intrauterine growth retardation (IUGR) were recorded in a checklist. Gestational age was calculated from the first day of the last period and confirmed by ultrasonography at the first-trimester scan.

2-4. Ethical consideration

Ethical approval for the study was obtained from the ethical committee and the Institutional Review Board of Guilan University of Medical Sciences, Rasht, Iran (registration code IR.GUMS.REC.1396.363).

2-5. Inclusion and exclusion criteria

Inclusion criteria were low-risk pregnant women (18-40 years of age) with less than 14-week gestational age at the first visit, the absence of known underlying diseases affecting pregnancy, performing the first screening test, including PAPP-A and willingness, to participate in the study. Exclusion criteria were the presence of fetal aneuploidy in the first-trimester screening test, twin or multiple pregnancies, fetal hydrops, and evidence of anomaly in an anomaly scan or maternal diabetes mellitus.

2-7. Data Analyses

Data were analyzed using SPSS software version 21.0. The qualitative variables were presented by frequency and percent, and quantitative variables were presented by the mean and standard deviation (SD). The normality of data was assessed with the Kolmogorov Simonov test. Placental thickness and size in the two groups were compared using the Mann-Whitney u test. Confounding variables were assessed by logistic regression analysis. Statistical significance was considered at $p < 0.05$. A cut-off as the predictor of abnormal placental size and thickness was determined using a Receiver Operating Characteristic (ROC) curve.

3- RESULTS

In the present study, 102 women with healthy pregnancies were evaluated in the study between the groups (a group with PAPP-A ≤ 0.5 MOM containing 34 cases and a group with PAPP-A > 0.5 MOM containing 68 cases). The baseline characteristics of the cohort are summarized in **Table**. **1**. The mean age of the patients was 28.2 (± 5.2) years. Mean age (P = 0.27), gestational age (P = 0.203), BMI (P = 0.984), weight (P = 0.466), history of hypertension (P = 0.093), and gravidity complicated pregnancies (P=0.82) were not significantly different between these groups.

Table-1: Baseline characteristics of the two study groups (exposed and non-exposed).

Parameter	Exposed group PAPP-A≤ 0.5	Non-exposed group PAPP-A >0.5	P-value*
Age (Year)	29.79	27.37	0.027
Gestational age (Week)	20.38	20.84	0.203
Gravidity (N)	1.56	.57	0.906
Weight (Kg)	75.06	76.34	0.466
BMI (Kg/m^2)	26.57	26.53	0.948

*Independent T-test, BMI: Body mass index, PAPP-A: Pregnancy-associated plasma protein-A.

According to **Table. 2**, the Chi-square test indicated the rate incidence of abnormal small placental size, which was higher in the non-exposed group (20.6%, PAPP-A≤ 0.5) than in the exposed group (10.3%, PAPP-A > 0.5); however, this 10% difference was not statistically significant (p = 0.154). The rate of abnormal placental thickness was 38.2% (13 cases)) in the exposed group (PAPP-A > 0.5) and 17.6% (12 cases) in the non-exposed group (PAPP-A≤0.5), with a notable statistical difference (p = 0.023).

Table-2: Comparison of normal and abnormal placental size and thickness based on PAPP-A level.

Variables	Sub-group		PAPP-A ≤ 0.5	PAPP-A > 0.5	P-value*
Placenta Size	Number (%)	Placenta size<10 cm	7	7	0.154
		Placenta size>10 cm	27	61	
Placenta Thickness	Number	Thickness ≥4 cm	13	12	0.023
		Thickness < 4 cm	21	56	

* Chi- Square test, PAPP-A: Pregnancy-associated plasma protein-A.

According to **Table.3**, the Mann-Whitney u test showed that the mean (±standard deviation) of placental size was 98.1 ± 17.6 mm (median =103 mm, confidence interval 95% =104.2-91.9 mm) in pregnant women with low levels of PAPP-A (≤ 0.5). In the group with normal PAPP-A (> 0.5), the placental size was 107.2 ± 13.1 (median=105, confidence interval 95% = 110.4-104.1), with a notable statistical difference (P = 0.003). On the other hand, the mean of placental thickness was more in the group of low-level PAPP-A than that with normal PAPP-A level (P< 0.001).

Table-3: Comparison of placental size and thickness level on PAPP-A level.

Variables	Mean (SD)		P-value*
	PAPP-A ≤ 0.5	PAPP-A > 0.5	
Placenta Size	98.10 (17.64)	107.29 (13.19)	0.003
Placenta thickness	43.10	29.26	< 0.001

*Mann Whitney U-test, SD: Standard deviation, PAPP-A: Pregnancy-associated plasma protein-A.

In evaluating the association of PAPP-A ≤0.5 MOM with abnormal placenta thickness and size and adjustment with age, gestational age, BMI, weight, history of hypertension, and gravidity based on logistic regression, no statistical difference was observed between PAPP-A level and abnormal placental size (P = 0.099). However, statistical relationships were observed again between PAPP-A ≤ 0.5 MOM and abnormal placental thickness (P= 0.036).

A cut-off as the predictor of abnormal placental size and thickness was determined using the ROC curve. The sensitivity and specificity of PAPP-A at values ≤ 0.55 were 72.3% and 56% for abnormal placenta thickness, respectively (**Figure. 2**). Besides, the sensitivity and specificity of PAPP-A at values ≤ 0.55 were 69.3% and 57.1%, respectively, in the assessment of abnormal placenta size (**Figure. 3**).

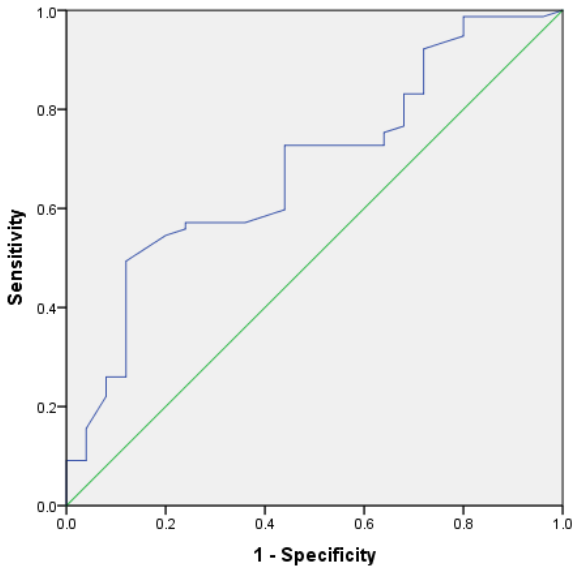

Fig.2: Roc curve: sensitivity and specificity of PAPP-A for abnormal placenta thickness.

PAPP-A: Pregnancy-associated plasma protein-A

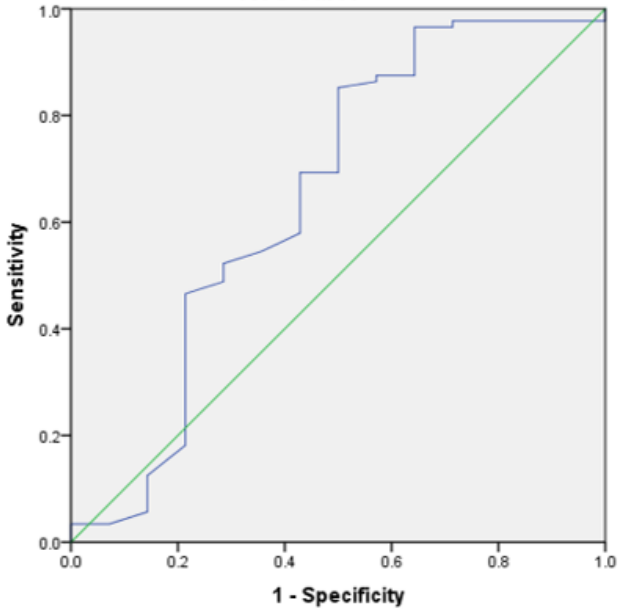

Fig.3: Roc curve: Sensitivity and specificity of PAPP-A for abnormal placenta size.

4- DISCUSSION

This study aimed to investigate the possible association between PAPP-A levels and placental size and thickness in pregnant women. Our study demonstrated that women with PAPP-A ≤ 0.5 MOM had more placental thickness and a smaller size than PAPP-A > 0.5 MOM. On the other hand, 89.7% and 82.4% of pregnant women who had PAPP-A > 0.5 (normal level) did not have a smaller placental size and thickness. The sensitivity and specificity of PAPP-A at values ≤0.55 were 72.3% and 56% for abnormal placenta thickness and 69.3% and 57.1%, respectively, in the assessment of abnormal placenta size. These findings suggested that a level of PAPP-A > 0.5 MOM could be associated with a normal

pregnancy with low complications. The secretion of PAPP-A in the first trimester of pregnancy was correlated with the placental thickness in the second trimester (18-23 weeks). PAPP-A is primarily produced from the placental syncytiotrophoblasts helping the normal implantation and placental development (16-18). In some studies, a relationship has been shown between placental thickness and size adverse consequences in pregnancy (19, 20). The combined use of PAPP-A levels and placental size in the second trimester has been suggested to be helpful in identifying women at high risk for pregnancy complications (21, 22). The following are two studies that evaluated placental thickness and size with low PAPP_A levels. Mesdaghi-nia et al. evaluated 187 pregnant women in a cohort study with two groups. Patients who had PAPP-A ≤ 0.8 MOM were dedicated to the exposed group and those with PAPP-A > 0.8 were identified as an unexposed group.

The study revealed that 87 and 93 patients had PAPP-A levels > 0.8 and ≤0.8, respectively. Women with low levels of PAPP-A in the first trimester had an increased incidence (34.4%) of placental thickness, whereas the other group had about 15% (p = 0.002) (9). Proctor et al. examined 90 normal singleton pregnancies with first-trimester PAPP-A ≤ 0.30 MOM. Maternal serum α-fetoprotein (AFP) at 15-18 weeks of gestation and second-trimester placental size and uterine artery (UtA) Doppler indices were assessed as the predictors of pregnancy outcome. The results of this study indicated that small placental size and low PAPP-A were at high risk of IUGR, extreme preterm delivery, and stillbirth (15).

Our study is unique because both the thickness and size of the placenta were investigated concurrently unlike the abovementioned studies. In summary, PAPP-A ≤ 0.5 MOM was associated with abnormally high placental thickness and small size (maximum measured length < 10 cm). It is necessary to pay special attention to placental thickness and size when a low level of PAPP-A is reported for the diagnosis of complicated pregnancy, which is associated with abnormal placental function.

4-1. Study Limitations

The major limitations of our study were the relatively small patient population and the presence of sparse data in some composed contingency tables.

5- CONCLUSION

Results of this study showed that the thicknesses of the placenta were high (> 4 cm or > 50 percentage of placental length) in women with low levels of PAPP-A (≤ 0.5), and the size of the placenta was smaller (maximum length measurement < 10 cm). Our data also displayed that the sensitivity and specificity of PAPP-A values < 0.55 for abnormal placental thickness were 72.3% and 56%, respectively. These figures were reported 69.3% and 57.1%, respectively, for abnormal placenta size.

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7- CONFLICT OF INTEREST: None.

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