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Value of Pregnancy-Associated Plasma Protein-A for Predicting Adverse Pregnancy Outcome

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Abstract
Background: It is suggested that pregnancy-associated plasma protein-A (PAPP-A) levels below the fifth percentile or less than 0.4 multiples of the median (MoMs) during the first trimester are closely associated with higher risk for neonatal abnormalities. We assessed the value of PAPP-A within the first trimester for predicting pregnancy outcome.
Methods: In a historical cohort study, we assessed 8460 consecutive pregnant women recruited for chromosomal abnormalities screening within the first trimester at Fertility Infertility and Perinatology Research Center, in Ahvaz Jundishapur University of Medical Sciences between April 2014 and April 2015. The women were categorized into two groups: pregnant women with PAPP-A levels below 0.4 multiples of MOM (n = 237) and those with higher levels of PAPP-A (n = 237).
Results: The median value of MOM PAPP-A was 0.82 ± 0.78, with 237 women having MOM PAPP-A lower than 0.4. Compared to women with MOM PAPP-A higher than 0.4, those with lower MOM PAPP-A had higher mean age, lower gestational age and lower birth weight. The prevalence of small for gestational age (SGA) was higher in women with MOM PAPP-A <0.4 compared to others. According to the ROC curve analysis, MOM PAPP-A <0.4 had a high value for predicting SGA. best cutoff value for MOM PAPP-A to predict SGA was shown to be 0.25, yielding a sensitivity of 84.7% and a specificity of 68.6%
Conclusion: Measuring the serum level of MOM PAPP-A during the first trimester is a valuable marker for predicting adverse outcomes of pregnancy such as SGA.
Keywords: Pregnancy, Pregnancy-associated plasma protein-A, Pregnancy outcome
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Introduction

For many years, serum biomarkers screening during the first trimester has been used for identifying fetal abnormalities and pregnancy outcome. The use of maternal serum markers can be effectively applied to rule out and predict the presence of any neonatal organ defects, chromosomal abnormalities, and other perinatal and postnatal risky conditions.[1-3] The main biomarkers to be considered for screening tests include beta human chorionic gonadotropin (βHCG), alphafetoprotein (AFP), inhibin-A, unconjugated estriol, and pregnancy-associated plasma protein-A (PAPP-A).[4-6] Since the introduction of PAPP-A by Lin et al in 1974, this marker has been identified as a valuable screening tool for assessment of pregnancy outcome.[7] PAPP-A is a macromolecular glycoprotein with a molecular weight of 800 kDa that is encoded by a gene located on chromosome 9q33.1.[8] The main source of producing PAPP-A is the placenta as a reproductive organ, as well as several non-reproductive

organs including colon, breast, kidney, and even bone marrow.[9] The function of PAPP-A is regulated by another molecule named proMBP as a proteinase inhibitor for PAPP-A. Thus, the PAPP-A/proMBP complex constitutes the main property related to PAPP-A functionality.[10] Several functions have been described for PAPP-A such as a zinc carrier, a barrier against phagocytic-proteolytic defense, and also as a predominating insulin-like growth factor binding protein-4 proteinase that can degrade this protein during pregnancy.[11,12]

It has been clearly demonstrated that PAPP-A has the highest serum level during pregnancy. Serum PAPP-A concentration increases exponentially with a doubling time of 34 days during the first trimester, and then the levels continue to rise throughout pregnancy until delivery.[13] It has been shown that the concentration rises up with a smaller gradient up to 36 weeks, after which the levels increase more steeply right up to term.[14] Maximum levels are attained at term. More interestingly, the oscillatory

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changes in serum PAPP-A level are specific in normal pregnancy and thus, any deviation in the level of this marker during pregnancy can reflect abnormality in this period.[15] For instance, considerably reduced PAPP-A levels have been shown in some abnormal neonatal conditions such as small for gestational age (SGA), intrauterine growth retardation (IUGR), stillbirth, neural defects, and preeclampsia. It has been reported that PAPP-A levels below the fifth percentile or less than 0.4 multiples of the median (MoMs) during the first trimester are closely associated with higher risk for neonatal abnormalities.[16] However, some studies could not demonstrate this predictive value for PAPP-A. The present study aims to assess the value of PAPP-A during the first trimester for predicting pregnancy outcome in a sample of Iranian pregnant women.

Materials and Methods

In a historical cohort study, we assessed 8460 consecutive pregnant women recruited for chromosomal abnormalities screening within the first trimester (gestational age of 11 to 13 weeks) between April 2014 to April 2015 (ethical board approval number: IRAJUMS.REC.1396.3). The exclusion criteria were unavailability of patients' information, the impossibility for contact with the patient or lack of her cooperation with collecting the required information, or multiple pregnancies. According to the routine nationwide program, all Iranian women are screened at the end of the first trimester of pregnancy for trisomy 21 and also for assessing the level of serum biomarkers including βHCG, AFP, and PAPP-A. Due to the high cost of laboratory kit available for assessing MOM PAPP-A and based on biostatistics consultation, we had to randomly select a number of patients in both groups with MOM PAPP-A <0.4 and another group with higher values. In this regard and based on the value of PAPP-A recorded in hospital files, the women were categorized into two groups: pregnant women with PAPP-A levels below 0.4 multiples of MOM (n = 237) and those with higher levels of PAPP-A (n = 237). The baseline characteristics of women including mother age, age at pregnancy, birth weight, and pregnancy-related complications such as preeclampsia, SGA, IUFD, stillbirth, premature birth, or trisomy 21 were all extracted from recorded files. All biomarkers were measured in a single laboratory using the same techniques and protocols. The serum level of PAPP-A was measured using the enzyme-linked Immunosorbent Assay (ELISA) techniques (Quantikine, R&D Systems, Minneapolis, MN, USA). The study endpoint was to assess the role of serum PAPP-A level in predicting adverse outcome of pregnancy.

Results were presented as mean ± standard deviation (SD) for parametric quantitative variables or median (1st, 3rd quartiles) for nonparametric quantitative variables and were summarized by absolute frequencies and percentages for categorical variables. Normality of data was analyzed using the Kolmogorov-Smirnov test. Categorical variables were compared using chi-square test or Fisher exact test when more than 20% of cells with expected count of less than 5 were observed. Quantitative variables were also compared with t test or Mann-Whitney U test. The predictive value of PAPP-A and the best cutoff point of this marker for predicting adverse pregnancy outcome was determined by assessing the area under the ROC curve. The statistical software SPSS version 16.0 for windows (SPSS Inc., Chicago, IL) was used for all analyses. *P* values of 0.05 or less were considered statistically significant.

Results

In total, 474 pregnant women were assessed with a mean age of 29.83 ± 4.95 years, ranging 18 to 44 years, mean weight gain of 13.58 ± 4.39 kg, and mean gestational age of 38.12 ± 1.75 weeks. The overall prevalence of SGA (<10 the centile) was 7.6% and that of LGA was 0.9%. Also, 7.4 % of neonates suffered from preterm birth. Preeclampsia was reported in 4.6% of women and abortion in 3.2%. No case of stillbirth or trisomy was detected in the study population. The median value (quartiles 1st, 3rd) of MOM PAPP-A was estimated to be 0.82 ± 0.78 (0.006, 6.98) with 237 women (2.99%) having MOM PAPP-A lower than 0.4. As shown in Table 1, compared to women with MOM PAPP-A higher than 0.4, those with lower MOM PAPP-A had similar mean age, lower gestational age at pregnancy, similar mean maternal weight gain, and lower birth weight. The overall prevalence of SGA was higher in women with MOM PAPP-A < 0.4 compared to other women (10.7% versus 4.7%, *P* < 0.001). Similarly, the prevalence of abortion was significantly higher in the former group (5.1% versus 3%, *P* < 0.03). The women with MOM PAPP-A < 0.4 were similar in terms of prevalence of preeclampsia compared to other pregnant women (6.2% versus 3%, *P* = 0.114). There were 22 (9.8%) cases of preterm birth in the group with MOM PAPP-A < 0.4 and 12 (5.1%) in the other group, indicating no significant difference between the two groups. In total,

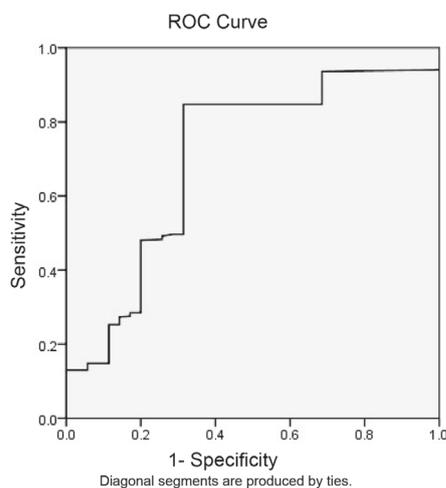**Table 1.** Comparing Maternal and Neonatal Characteristics According to the Value of MOM PAPP-A

	Group with MOM PAPP-A < 0.4	Group with MOM PAPP-A ≥ 0.4	*P* Value
Age, year	29.99 ± 5.05	29.68 ± 4.85	0.494
Gestational age, week	37.95 ± 1.95	38.28 ± 1.51	0.041
Weight gain, kg	13.23 ± 4.05	13.92 ± 4.67	0.313
Birth weight, g	3057.49 ± 595.71	3242.65 ± 490.76	0.001
SGA, %	24(10.7)	11 (4.7)	0.024
Preterm birth, %	22(9.8)	12(5.1)	0.078
Preeclampsia, %	14(6.2)	7 (3)	0.119
Abortion	12(5.1)	3(1.3)	0.034

Abbreviations: PAPP-A, pregnancy-associated plasma protein-A; SGA, small for gestational Age; MOM, multiple of the median.
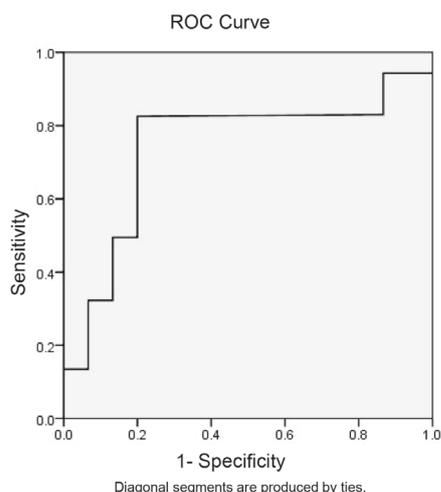
MOM PAPP-A < 0.4 was associated with a 2.2-fold risk for SGA. According to the ROC curve analysis (Figure 1), MOM PAPP-A < 0.4 had a high value for predicting SGA (AUC = 0.705, 95% CI: 0.622–835). In this regard, the best cutoff value for MOM PAPP-A to predict SGA was shown to be 0.25, yielding a sensitivity of 84.7% and a specificity of 68.6%. Similarly, the area under the ROC curve for predicting abortion by assessing MOM PAPP-A was 0.741, indicating a partially acceptable role for this biomarker in predicting abortion (Figure 2). The best cutoff value for MOM PAPP-A to predict abortion was 0.25, yielding a sensitivity of 82.6% and a specificity of 80%.

Discussion

In line with previous literature on the value of MOM PAPP-A in predicting adverse outcome of pregnancy, our study attempted to examine this goal in a large sample of pregnant Iranian women. Similar to previous studies, considering a cutoff value of 0.4 for this biomarker measured at the end of the first trimester, MOM PAPP-A could effectively predict SGA and abortion as the two major adverse outcomes of pregnancy. However, it was less valuable for predicting preeclampsia and preterm birth in those women. Another important point was that in our population, the cutoff point of 0.3 for MOM PAPP-A might yield better accuracy for predicting the outcome of pregnancy.

Reviewing the literature reveals similar findings on the high predictive value of MOM PAPP-A < 0.4 for pregnancy outcome. In a systematic review on 22 published papers, Morris et al[17] indicated that MOM PAPP-A < 0.4 had a moderate correlation with some pregnancy outcomes including preeclampsia (with 2-fold risk), premature birth (with 2-fold risk), and total adverse outcome of pregnancy (with 3.3-fold risk). In a study by Kaijomaa et al,[18] MOM PAPP-A < 0.3 was associated with increased risk for aneuploidy and abortion; however, it was not associated with preeclampsia, stillbirth, and need for cesarean section. In another study by Balcı et al,[19] a considerably higher cutoff value was achieved for MOM PAPP-A (0.72) for predicting pregnancy outcome with high sensitivity (82.4%), but low specificity (29.8%). Lo et al.[20] showed that MOM PAPP-A could predict pregnancy outcome with an AUC of 0.626; however, they introduced a cutoff value of 0.23 for this marker that yielded a low sensitivity for predicting outcome. Finally, Gundu[21] showed a significant association between MOM PAPP-A < 0.4 and preterm labor which is similar to our result.

In conclusion, measuring the serum level of MOM PAPP-A during the first trimester can be a valuable marker for predicting adverse outcomes of pregnancy such as SGA and abortion. The best cutoff value for this marker to predict the outcome is 0.3 in pregnant Iranian women.

Few studies have assessed the value of PAPP-A in prediction of outcome, and assessment of this value is the main strength of the present study. Also, determination of the optimal cutoff point for this marker can be very helpful in predicting the outcome of concern. Nevertheless, recruiting a small number of patients and not comparing the predictive value of this marker to other biomarkers can be considered as the main limitations of this study.

Figure 1. ROC Curve Analysis to Determine the Value of PAPP-A to Predict Small for Gestational Age (SGA).

Figure 2. ROC Curve Analysis to Determine the Value of PAPP-A to Predict Abortion.

Authors' Contribution
RMJ supervised the study implementation; SM, MB, and EM collected the study information; SS wrote the draft and MS analyzed the data.

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