Evaluation of the Relationship between Pregnancy-Associated Plasma Protein A (PAPP-A) and Pregnancy Outcomes

Minoo Movahedi, Somayeh Khanjani, Zahra Shahshahan, Maryam Hajihashemi, Farinaz Farahbod, Elaheh Shahsavandi

Department of Obstetrics and Gynecology, School of Medicine, Isfahan University of Medical Sciences, Isfahan, Iran

Abstract

Background: In the current study, we aimed to evaluate the association between pregnancy-related plasma protein-A (PAPP-A) levels measured in the first trimester and pregnancy outcomes.

Materials and Methods: This is a descriptive-analytical study that was performed in 2019--2021 on 1061 pregnant women in their first trimester. Demographic and basic information of all women were collected. These data included age, weight, parity, and date of delivery. Then the quantity of PAPP-A was recorded in three groups including less than 0.5 MOM, 0.5 to 2.5 MOM, and more than 2.5 MOM.

Results: Data of 1061 women were analyzed. 900 women (84.8%) had term delivery and 155 women (14.6%) had pre-term deliveries. PAPP-A levels were normal in 83.4% of women. BMI and number of pregnancies had significant relationships with PAPP-A ($p < 0.001$, $P = 0.03$ respectively). The mean BMI in mothers with PAPP-A higher than 2.5 was significantly more than mothers with normal or lower PAPP-A levels (26.2 ± 31, $P = 0.04$). The frequency of term labor in mothers with normal PAPP-A was higher than other mothers (86.3%, $P = 0.04$). The frequency of preeclampsia in recent pregnancies in mothers with normal PAPP-A was significantly lower than other mothers ($p < 0.001$) and the frequency of abortions in recent pregnancies in mothers with PAPP-A less than 0.5 was significantly higher than mothers with normal or elevated PAPP-A ($p < 0.001$).

Conclusion: Mothers with low PAPP-A levels are more likely to have poor pregnancy outcomes such as abortion, pre-term labor, and preeclampsia.

Keywords: Abortion, pre-eclampsia, pregnancy, PAPP-A protein, human

Address for correspondence: Dr. Elaheh Shahsavandi, Department of Obstetrics and Gynecology, School of Medicine, Isfahan University of Medical Science, Hezar Jarib St., Isfahan City, Isfahan Province, Iran.
E-mail: dr.shahsavandi@gmail.com

INTRODUCTION

Adverse pregnancy outcomes increased the cost of healthcare as well as the psychological impact on the family. Predictive methods allow obstetricians to improve pregnancy outcomes with increased obstetric surveillance and optimum management.[1] As modern medicine tries to classify high-risk populations using different screening programs, there is an effective program based on screening for aneuploidy and Down syndrome during pregnancy.[2] Non-invasive diagnosis is the basis of prenatal screening, which allows us to limit the use of invasive methods and also to determine the risk of chromosomal abnormalities in the fetus.[3] In the first trimester screening, a combination of serum markers, namely free beta HCG, and pregnancy-related plasma protein-A (PAPP-A) can be used in combination with ultrasound markers such as nasal bone presence and transparency thickness (NT), which studies showed that the detection rate of some screening method more than 90% with a false-positive rate of 5%. For the second trimester, serum levels of human choriogonadotropin (HCG),

Access this article online

Quick Response Code:

Website:
www.advbiores.net

DOI:
10.4103/abr.abr_344_21

alpha photoprotein (AFP), inhibin A, and estriol can be measured.[4,5]

Several trials recently reported that low serum concentration of PAPP-A might be associated with poor neonatal and poor pregnancy outcomes.[6] PAPP-A was first discovered in 1974 in the serum of pregnant women. PAPP-A is a protease produced by syncytial trophoblast of the placenta and enters the maternal circulation immediately after implantation.[7,8] This protein is a metalloproteinase that cleaves insulin-like growth factor binding protein 4 (IGFBP4), acts as a growth-promoting enzyme by binding to cell surfaces and releasing bioactive insulin growth factor (IGF) adjacent to their receptors.[7] Therefore, due to the association between PAPP-A and levels of bioactive IGF, it can play an important role in placentation and fetal growth.[9] Gestational age increases the level of PAPP-A in maternal blood, with highest serum levels at term and decreases rapidly after delivery.[10] Also, Maternal PAPP-A concentrations are higher in primigravida pregnancies than multiple pregnancies. Nevertheless, PAPP-A is recognizable even in the plasma of both nonpregnant women and men with highly sensitive methods. Many factors such as weight, smoking status, maternal age, ethnicity, and the conception method can affect the serum concentration of PAPP-A.[11]

Low serum concentration of PAPP-A in maternal circulation is an important sign of early placental insufficiency in the first trimester of pregnancy. However, its complications on the fetus reach a detectable level in the second trimester.[12] Nevertheless, growth insufficiency determined in the second three months of pregnancy is also directly associated with poor neonatal and poor pregnancy outcomes.[13] When the level of PAPP-A in the maternal blood decreased, the availability of IGF is impaired. Hence, several studies have reported that the low level of PAPP-A might increase the risk of pregnancy complications associated with the placenta such as intrauterine growth restriction (IUGR), preterm delivery (PTD), small for gestational age (SGA), spontaneous abortion (SA), and preeclampsia (PE).[14,15] There are several investigations showing that the PAPP-A serum levels may have a weak inverse association with HbA1c levels.[16] Despite all the studies, none of them could determine the sensitivity of PAPP-A in determining low-risk or high-risk pregnancies in terms of adverse outcomes. The aim of this study was to investigate the association between PAPP-A levels measured in the first trimester and pregnancy outcomes. This indicates the novelty of our study.

MATERIALS AND METHODS

Study design

This is a descriptive-analytical study that was performed in 2019-2021 in educational medical centers affiliated to Isfahan University of Medical Science. The current study was conducted on all pregnant women in their first trimester referring to our medical centers. The study protocol was approved by the Research Committee of Isfahan University

of Medical Sciences and the Ethics committee has confirmed it (Ethics code: IR.MUI.MED.REC.1399.1003).

Inclusion and exclusion criteria

The inclusion criteria were pregnant women with age of 18-35 years, first visit during the first trimester of pregnancy, gestational age between 11 and 13 weeks + 6 days, spontaneous pregnancies, and signing the written informed consent to participate in this study. The exclusion criteria were previous history of cardiovascular diseases, diabetes and hypertension, chromosomal disorders of the fetus, multiple pregnancy and fetus anomalies, BMI more than 30 or less than 18 kg/m², smokers, usage of assisted pregnancy methods, patients with other ethnicities than Iranian, lack of regular follow-up, defect in the medical documents and mother's will to exit the study.

All women who met the inclusion criteria entered the study. Demographic and basic information of all women were collected. These data included age, weight, parity, and date of delivery.

Measurements

Then the quantity of PAPP-A was recorded in three groups including below 0.5 MOM (low levels), 0.5-2.5 MOM (normal levels), and more than 2.5 MOM (high levels). All patients were sampled in laboratory of Al-Zahra hospital, affiliated to Isfahan University of Medical Sciences. We should note that the PAPP-A levels were measured using IMO light method.

Data gathering

The women were followed to the end of the pregnancy by regular visits and also phone calls. The outcomes of the pregnancy and any complications were collected among women. These outcomes included: preeclampsia, eclampsia, age of delivery (preterm, term, and post-term), abortion and birth weight (macrosomic, normal, low birth weight (LBW) and very low birth weight (VLBW), stillbirth and third trimester disorders of pregnancy including Placental abruption, Placenta Previa, Placenta Accreta, vasa previa, and thick meconium.

Statistical analysis

The obtained data were entered into the Statistical Package for Social Sciences (SPSS) version 24. We used one way ANOVA, Tukey post hoc, Chi square, Likelihood Chi square, and Pearson correlation tests to compare data. *P* Value <0.05 was considered as significance threshold.

RESULTS

In the present study, data of 1061 women were analyzed. Primary analysis of demographic data showed that the mean age of the women was 29.8 ± 3.8 years with the range of 18 to 35 years. The mean body mass index (BMI) of women was 24.3 ± 3.04 and the mean gravidity of women was 1.8 ± 0.8.

The outcomes of the present pregnancy were as following: 900 women (84.8%) had term delivery, 155 women (14.6%) had pre-term deliveries and 6 women (0.6%) had unknown results.

As indicated in Table 1, the PAPP-A levels were normal in 83.4% of women and 93.8% of pediatrics had normal weight.

Table 2 also indicates the frequencies of various current delivery complications and as shown, tick meconium was the most prevalent complication (7.3%).

One way ANOVA test showed that maternal age was not significantly associated with PAPP-A ($p = 0.18$) but BMI and number of pregnancies had significant difference based on PAPP-A ($p < 0.001$ for BMI and $P = 0.03$ for number of pregnancies).

Tukey post hoc test showed that the mean BMI in mothers with normal PAPP-A levels was significantly lower than mothers with PAPP-A levels less than 0.5 MOM ($p = 0.003$) or greater than 2.5 MOM ($p < 0.001$). Meanwhile, the mean BMI in mothers with PAPP-A higher than 2.5 MOM was significantly more than mothers with normal or lower PAPP-A levels ($p = 0.04$).

The mean number of pregnancies in mothers with PAPP-A less than 0.5 MOM was significantly higher than mothers with normal PAPP-A ($p = 0.03$) and mothers with PAPP-A greater than 2.5 MOM ($p = 0.04$). But no significant difference was observed between mothers with normal PAPP-A and mothers with PAPP-A greater than 2.5 MOM ($p = 0.96$). These data are summarized in Table 3.

Chi-square test showed that the frequency of term labor in mothers with normal PAPP-A was higher than other mothers ($p = 0.04$). Likelihood Chi-square test showed that the birth weight ($p = 0.07$) had no significant relationship with maternal PAPP-A [Table 4].

Likelihood Chi-square test showed that the frequency of preeclampsia in recent pregnancies in mothers with normal PAPP-A was significantly lower than other mothers ($p < 0.001$) and the frequency of abortions in recent pregnancies in mothers with PAPP-A less than 0.5 MOM was significantly higher than mothers with normal or elevated PAPP-A ($p < 0.001$). The frequency of other complications in recent pregnancy was not significantly associated with maternal PAPP-A ($p > 0.05$) [Table 5].

DISCUSSION

In this study, we showed that 83.4% of all study population had normal values for PAPP-A levels. We showed that the frequency of term labor in mothers with normal PAPP-A was higher than other mothers and the frequency of preeclampsia in recent pregnancies in mothers with normal PAPP-A was significantly lower than other mothers and the frequency of abortions in recent pregnancies in mothers with PAPP-A less than 0.5 was significantly higher than mothers with normal or elevated PAPP-A.

These data show that PAPP-A levels could be used as a useful marker contributing to pregnancy outcomes. Previous studies have also claimed the possible uses of PAPP-A levels in

Table 1: Frequency distribution of PAPP-A in mothers and birth weight of infants

Variable	Number/mean	Percent/SD
Age	29.8	3.8
BMI	24.3	3.04
PAPP-A		
Below 0.5	118	11.1
0.5-2.5 (normal)	885	83.4
More than 2.5	58	5.5
Birth weight		
VLBW	6	0.6
LBW	49	4.6
Normal	995	93.8
Macrosomia	4	0.4
Unknown	7	0.7

VLBW: Very low birth weight, LBW: Low birth weight

Table 2: Frequency of different pregnancy complications in pregnant women aged 18-35 years in Isfahan-Iran

Pregnancy complications	Number	Percentage
Preeclampsia	28	2.6
Eclampsia	0	0
Stillbirth	3	0.3
Placental abruption	11	1
Placenta previa	4	0.4
Vasa previa	0	0
Placenta accrete	3	0.3
Abortion	7	0.7
Thick meconium	77	7.3

Table 3: Mean age, body mass index and number of pregnancies by PAPP-A

Variable	Below 0.5 MOM		0.5-2.5 MOM		More than 2.5 MOM		P
	Mean	SD	Mean	SD	Mean	SD	
Age	29.4	3.9	29.9	3.8	29.1	3.6	0.18
BMI	25.04	3.6	24.1	2.9	26.2	3.1	<0.001
Number of pregnancies	2	1.01	1.7	0.8	1.8	0.9	0.03

BMI: Body mass index

predicting the outcomes of pregnancy. Morris and colleagues performed a study on 32 studies including 175240 women in 2017. They evaluated the relationships between PAPP-A levels and pregnancy outcomes in these studies and showed that the first trimester low maternal serum PAPP-A is associated with adverse pregnancy outcomes. They explained that women with abnormal PAPP-A levels might have pre-term labor and also abortion. But also mentioned that the predictive values for these issues are low and further studies should be performed in this regard.[17] Another study was performed by Hughes and colleagues in 2019 that assessed the relationships between first trimester PAPP-A levels and placentally-related adverse pregnancy outcomes. This study included 4057 women and indicated that women with low PAPP-A levels are more

Table 4: Frequency distribution of type of current delivery and birth weight of infants by maternal PAPP-A level

Variable	Below 0.5 MOM		0.5-2.5 MOM		More than 2.5 MOM		P
	n	%	*n*	%	*n*	%	
Type of delivery							
Preterm	21	18.6	121	13.7	13	22.8	0.04
Term	92	81.4	764	86.3	44	77.2	
Birth weight							
VLBW	0	0	4	0.5	2	3.5	0.07
LBW	9	8	35	4	5	8.8	
Normal	102	91.1	843	95.3	50	87.7	
Macrosomia	1	0.9	3	0.3	0	0	

VLBW: Very low birth weight, LBW: Low birth weight

Table 5: Frequency distribution of complications in recent pregnancy by maternal PAPP-A

Complications in recent pregnancy	Below 0.5 MOM		0.5-2.5 MOM		More than 2.5 MOM		P
	n	%	*n*	%	*n*	%	
Preeclampsia	9	7.6	14	1.6	5	8.6	<0.001
Stillbirth	0	0	2	0.2	1	1.7	0.26
Placental abruption	1	0.8	10	1.1	0	0	0.52
Placenta previa	1	0.8	3	0.3	0	0	0.61
Placenta accrete	1	0.8	2	0.2	0	0	0.52
Abortion	6	5.1	0	0	1	1.7	<0.001
Thick meconium	8	6.8	63	7.1	6	10.3	0.67

vulnerable to fetal growth restriction, severe preeclampsia and stillbirth.[18]

In another study, data of 961 women were analyzed and it was declared that low PAPP-A was associated with adverse pregnancy outcomes such as aneuploidies, spontaneous abortion, preterm delivery, pre-eclampsia, small for gestational age neonates and stillbirths.[19] The findings of our study were also in line with these data showing the associations between low PAPP-A levels and pregnancy complications including pre-term delivery, preeclampsia and abortions.

As Cohen and colleagues showed, a combination of first and second trimester serum biomarkers [PAPP-A, free βhCG, and maternal serum alpha-fetoprotein (msAFP)] that are currently used in screening of Down syndrome may also be used to predict additional adverse pregnancy outcomes such as pre-term delivery and abortion. It was also recommended that further studies should be carried out in this regard.[20] Patil and others also claimed that PAPP-A levels in the first trimester of pregnancy is an important predictor of future obstetric outcomes but also showed that this marker has low predictive values and should be determined in associations with other pregnancy markers.[21] We discussed the results of studies with larger study populations. These studies have higher validity compared to studies on restricted populations.

Based on these studies, the use of PAPP-A levels in predicting pregnancy outcomes could be a valuable tool but should not be used alone. The findings of our study support the use of PAPP-A levels and its correlations with some adverse pregnancy outcomes. As other studies have shown, the frequencies of pre-term labor, stillbirth, preeclampsia and abortion could be higher in mothers with low PAPP-A levels. It has also been declared that abnormal maternal BMI (lower or higher than normal range) could be associated with abnormal PAPP-A levels, but these relationships require further investigations and there are still much to discover due to low predictive values of this maker.[1,22,23] The limitations of the current study included not evaluating other pregnancy markers and the roles of other variables such as hormonal balance and medications. But we believe that our findings could have beneficial roles in further studies.

CONCLUSION

Mothers with low PAPP-A levels are more likely to have poor pregnancy outcomes such as abortion, pre-term labor and preeclampsia. Based on our findings, the mothers with normal PAPP-A levels had more normal pregnancy outcomes. Previous studies have also indicated the importance of PAPP-A levels as a screening tool but also showed that this marker should be used along with other markers. We believe that further studies might be required in this regard.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Bilagi A, Burke DL, Riley RD, Mills I, Kilby MD, Katie Morris R. Association of maternal serum PAPP-A levels, nuchal translucency and crown–rump length in first trimester with adverse pregnancy outcomes: Retrospective cohort study. Prenat Diagn 2017;37:705-11.
2. Kalousova M, Muravska A, Zima T. Pregnancy-associated plasma protein A (PAPP-A) and preeclampsia. Adv Clin Chem 2014;63:169-209.
3. Ziolkowska K, Tobola-Wrobel K, Dydowicz P, Zurawski S, Pietryga M, Wysocka E. The significance of maternal blood pregnancy-associated plasma protein A (PAPP-A) and free beta-subunit of human chorionic gonadotropin (β-hCG) levels for the risk assessment of fetal trisomy 18 during the first prenatal testing between 11 and 13+6 weeks of pregnancy. Ginekol Pol 2020;91:748-54.
4. Alldred SK, Takwoingi Y, Guo B, Pennant M, Deeks JJ, Neilson JP, *et al.* First trimester ultrasound tests alone or in combination with

first trimester serum tests for Down's syndrome screening. Cochrane Database Syst Rev 2017;CD012600.

5. Rafiee Zadeh A, Ghadimi K, Mohammadi B, Hatamian H, Naghibi SN, Danaeiniya A. Effects of estrogen and progesterone on different immune cells related to multiple sclerosis. Caspian J Neurol Sci 2018;4:83-90.

6. Balcı S. Predictive values of maternal serum PAPP-A level, uterine artery Doppler velocimetry, and fetal biometric measurements for poor pregnancy and poor neonatal outcomes in pregnant women. J Turk Ger Gynecol Assoc 2016;17:143-9.

7. Zadeh AR, Eghbal AF, Mirghazanfari SM, Ghasemzadeh MR, Nassireslami E, Donyavi V. Nigella sativa extract in the treatment of depression and serum Brain-Derived Neurotrophic Factor (BDNF) levels. J Res Med Sci 2022;27:28.

8. Sifakis S, Androutsopoulos VP, Pontikaki A, Velegrakis A, Papaioannou GI, Koukoura O, *et al*. Placental expression of PAPPA, PAPPA-2 and PLAC-1 in pregnacies is associated with FGR. Mol Med Rep 2018;17:6435-40.

9. Mikkelsen JH, Resch ZT, Kalra B, Savjani G, Kumar A, Conover CA, *et al*. Indirect targeting of IGF receptor signaling *in vivo* by substrate-selective inhibition of PAPP-A proteolytic activity. Oncotarget 2014;5:1014-25.

10. Fruscalzo A, Cividino A, Rossetti E, Maurigh A, Londero AP, Driul L. First trimester PAPP-A serum levels and long-term metabolic outcome of mothers and their offspring. Sci Rep 2020;10:1-9.

11. Hasegawa J, Wada S, Kasamatsu A, Nakamura M, Hamanoue H, Iwata E, *et al*. Distribution of PAPP-A and total hCG between 11 and 13 weeks of gestation in Japanese pregnant women. J Matern Fetal Neonatal Med 2020;33:2017-22.

12. Livrinova V, Petrov I, Samardziski I, Jovanovska V, Boshku AA, Todorovska I, *et al*. Clinical importance of low level of PAPP-A in first trimester of pregnancy-an obstetrical dilemma in chromosomally normal fetus. Open Access Maced J Med Sci 2019;7:1475-9.

13. Di Lorenzo G, Ceccarello M, Cecotti V, Ronfani L, Monasta L, Brumatti LV, *et al*. First trimester maternal serum PIGF, free β-hCG, PAPP-A, PP-13, uterine artery Doppler and maternal history for the prediction of preeclampsia. Placenta 2012;33:495-501.

14. Kaijomaa M, Ulander VM, Hämäläinen E, Alfthan H, Markkanen H, Heinonen S, *et al*. The risk of adverse pregnancy outcome among pregnancies with extremely low maternal PAPP-A. Prenat Diagn 2016;36:1115-20.

15. Gupta S, Goyal M, Verma D, Sharma A, Bharadwaj N, Kabra M, *et al*. Adverse pregnancy outcome in patients with low pregnancy-associated plasma protein-A: The Indian E xperience. J Obstet Gynaecol Res 2015;41:1003-8.

16. Kapustin RV, Kascheeva TK, Alekseenkova EN, Shelaeva EV. Are the first-trimester levels of PAPP-A and fb-hCG predictors for obstetrical complications in diabetic pregnancy? J Matern Fetal Neonatal Med. 2022;35:1113-1119.

17. Morris RK, Bilagi A, Devani P, Kilby MD. Association of serum PAPP-A levels in first trimester with small for gestational age and adverse pregnancy outcomes: Systematic review and meta-analysis. Prenat Diagn 2017;37:253-65.

18. Hughes AE, Sovio U, Gaccioli F, Cook E, Charnock-Jones DS, Smith GC. The association between first trimester AFP to PAPP-A ratio and placentally-related adverse pregnancy outcome. Placenta 2019;81:25-31.

19. Kaijomaa M, Rahkonen L, Ulander VM, Hämäläinen E, Alfthan H, Markkanen H, *et al*. Low maternal pregnancy-associated plasma protein A during the first trimester of pregnancy and pregnancy outcomes. Int J Gynecol Obstet 2017;136:76-82.

20. Cohen JL, Smilen KE, Bianco AT, Moshier EL, Ferrara LA, Stone JL. Predictive value of combined serum biomarkers for adverse pregnancy outcomes. Eur J Obstet Gynecol Reprod Biol 2014;181:89-94.

21. Patil M, Panchanadikar T, Wagh G. Variation of papp-a level in the first trimester of pregnancy and its clinical outcome. J Obstet Gynecol India 2014;64:116-9.

22. Odibo A, Patel K, Spitalnik A, Odibo L, Huettner P. Placental pathology, first-trimester biomarkers and adverse pregnancy outcomes. J Perinatol 2014;34:186-91.

23. Quattrocchi T, Baviera G, Pochiero T, Basile F, Rizzo L, Santamaria A, *et al*. Maternal serum PAPP-A as an early marker of obstetric complications? Fetal Diagn Ther 2015;37:33-6.