Original Article

Journal of Iranian Medical Council, Volume 9, Issue no. 4
http://dx.doi.org/10.18502/jimc.v9i4.22461

Evaluating the Association of Pregnancy-Related Plasma Protein A with Pregnancy Outcome: A Single-Center Retrospective Study

Asieh Khodami[1], Sarang Younesi[2], Masoumeh Mirzamoradi[2]*, Parichehr Pooransari[2], Soraya Saleh Gargari[2], Zahra Naeiji[2], Nayereh Rahmati[2], Taraneh Arbabzadeh[2], Mohammad Mahdi Taheri Amin[3], Pourandokht Saadati[1], Soudabeh Jamali[4], Fatemeh Aasdi[3], Nikta Khalafi[3] and Mahmood Moosazadeh[5]

1. Department of Gynecology and Obstetrics, Shohada-e Tajrish Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran
2. Prenatal Screening Department, Nilou Laboratory, Tehran, Iran
3. Nilou Medical Laboratory, Tehran, Iran
4. Post Analytical Quality Control Department, Nilou Laboratory, Tehran, Iran
5. Gastrointestinal Cancer Research Center, Non-communicable Disease Institute, Mazandaran University of Medical Sciences, Sari, Iran

*** Corresponding author**

Masoumeh Mirzamoradi, MD
Department of Gynecology and Obstetrics, Shohada-e Tajrish Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran
Email:
dr.elhamvahabi@yahoo.com

Received: 19 Mar 2025
Accepted: 25 Aug 2025

Citation to this article
Khodami A, Younesi S, Mirzamoradi M, Pooransari P, Saleh Gargari S, Naeiji Z, et al. Evaluating the Association of Pregnancy-Related Plasma Protein A with Pregnancy Outcome: A Single-Center Retrospective Study. *J Iran Med Counc*. 2026;9(4):922-30.

Abstract

Background: Pregnancy-Associated Plasma Protein (PAPP-A) is a type of metalloproteinase that stimulates cell growth and plays a role in regulating the biological activity of Insulin-like Growth Factors (IGF). This enzyme plays an important role in the development of the fetus and placenta. Therefore, in this study, the relationship between the serum PAPP-A level and Maternal-fetal obstetrics abnormalities and aneuploidies disorders were examined.

Methods: Available data were used in this retrospective cohort study. The research population was made up of women with a history of pregnancy referring to Tajrish Martyrs' Hospital in 2018, which was approximately 15,000 people. All the prenatal aneuploidy screening tests of these patients were done in Nilou Medical Laboratory a referral Laboratory in Tehran, Iran. The data was collected using a checklist that was prepared in advance. Based on this, the demographic data of the patients was collected.

Results: The results show that most of the patients with chromosomal abnormalities had a PAPP-A level of <0.27 ($p<0.001$). It was found that the group of patients whose PAPP-A level was > or =3 had the highest structural anomaly ($p=0.021$). On the other hand, the highest maternal adverse outcomes [such as Premature Rupture of Membranes (PROM), pre-eclampsia, abortion, polyhydramnios, oligohydramnios, amniotic leakage, bleeding, and blood spotting] were in patients whose PAPP-A level was <0.27 ($p<0.001$). No significant difference in adverse fetal outcomes was observed in the above three groups ($p=0.61$).

Conclusion: In general, it can be said that the decrease in PAPP-A serum levels in pregnant mothers can be associated with maternal and fetal adverse outcomes. The occurrence of these complications can increase the risk of T18 and T21 in patients.

Keywords: Complication, Pregnancy, Plasma Protein A

Introduction

The adverse outcome of pregnancy can affect the quality of life of the baby and the mother in the short and long term, despite the mental and emotional damage (1). In addition, it can also cause the imposition of medical expenses, which in many cases, considering the amount of family income, becomes difficult for parents to manage it (2). The use of screening methods is expanding nowadays. Based on the progress of knowledge and also according to the physiological and clinical processes of the mother, different screening methods have been developed during the first to third trimesters of pregnancy (3). Based on the data, the use of screening methods today has resulted in preventing the birth of fetuses with genetic or developmental abnormalities. Also, the use of screening methods will detect abnormalities on time and ultimately reduce costs for families and the health system (4).

Today, many markers are used to screen fetuses in the first to third trimester of pregnancy. The evaluation of these markers is based on non-invasive methods and includes total β-HCG, unconjugated estriol, Alpha Feto Protein (AFP), and Dimeric Inhibin A (DIA) in Second Trimester Screening (STS) and Pregnancy-Associated Plasma Protein (PAPP-A) and free β-HCG in First Trimester Screening (FTS) (5,6).

PAPP-A is a type of metalloproteinase that stimulates cell growth and plays a role in regulating the biological activity of Insulin-like Growth Factors (IGF). This enzyme plays an important role in the development of the fetus and placenta. 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 effects on the fetus reach a detectable level in the second trimester (7). Growth failure determined in the second trimester of pregnancy is also directly related to adverse neonatal and pregnancy outcomes (8). Several studies have reported that low levels of PAPP-A may increase the risk of placenta-related pregnancy complications such as Intrauterine Growth Restriction (IUGR), Preterm Labor (PTD), and spontaneous abortion (9). In pregnant women who are at risk of chromosomal disorders, the serum PAPP-A level is low (10). Therefore, in this study, the relationship between the serum PAPP-A level and genetic abnormalities in newborns was examined.

Materials and Methods

Design study

Available data were used in this retrospective cohort study. The research population was made up of women with a history of pregnancy referring to Tajrish Martyrs' Hospital in 2018, which was approximately 15,000 people. All the prenatal aneuploidy screening tests of these patients were done in Nilou Medical Laboratory a referral Laboratory in Tehran, Iran.

Patient selection criteria

Included criteria were being Iranian, singleton, age between 18-40 years old, gestational age 11-14 weeks based on ultrasound in the first trimester of pregnancy, no history of gestational diabetes, no history of type 1 and 2 diabetes, no obvious diabetes, no history of a baby weighing 4 *kg* or more, no history of pre-eclampsia, eclampsia, high blood pressure, no history of stillbirth, no history of an abnormal baby or fetus and repeated abortion, no smoking and drug use, and no use of assisted reproduction methods. It was in the current pregnancy. Exclusion criteria included violations in records or unwillingness of patients to continue cooperation.

Data collection

The data was collected using a checklist that was prepared in advance. Based on this, the demographic data of the patients was collected. Data collection was done in two parts. The researcher collected information related to the research by referring to the hospital archive and studying the patients' files. If a file did not have the desired information or was incomplete, it was excluded from the study. In the next part, the researcher had a phone call with each sample and collected some data from the patients through interviews.

Statistical analysis

The collected data was analyzed by SPSS v.22 software. The Kolmogirov-Smirnov test was used for the normality of the data. Descriptive statistics (mean, standard deviation, frequency, and percentage) were used to report demographic variables. To check the quantitative variables from the t-test, to check the

qualitative variables from the chi-square test, to check the ranked variables from the Mann-Whitney test (for non-parametric data), and to check the probability of pregnancy complications in the normal and abnormal PAPP-A group, the relative risk was calculated. ROC analysis was used to assess the association between PAPP-A MoM with total adverse outcomes and chromosomal abnormalities. A p-value of less than 0.05 was considered significant.

Results

Evaluation of PAPP-A cut-off in patients

In this study, PAPP-A cutoff was divided into three categories: <0.27, 0.27-2.99, and >=3. Based on the results, it was shown that the average PAPP-A in the three categories was 1.01±1.73, 1.64±0.73, and 1.59±0.34, respectively. The results showed that these differences were statistically significant (p=0.003). Additionally, the PAPP-A MoM level compares the final risk of Down syndrome across three groups: low risk (risk less than 1:1500) to the extent of 7162 (47.7%), intermediate risk (risk between 1:251 and 1:1500) to the extent of 2660 (17.7%), and high risk (risk greater than or equal to 1:250) to the extent of 5188 (34.6%).

Results of descriptive information of patients

The following table shows the demographic and descriptive information of the patients. In terms of gender, the sex of the fetuses was female in 51% of cases. In terms of chromosomal abnormalities 18 and 21, most of the patients were in the low-risk category. Also, in terms of maternal and fetal outcomes and chromosomal abnormalities, the percentage of each is shown in table 1.

Table 1. Description of the characteristics of the studied population according to different variables

Variables		No.	%
Sex	Female	3458	51
	Male	3323	49
Family marriage	Yes	1620	19.3
	No	6766	80.7
NB present	Yes	5551	99.7
	No	19	0.3
Levels of PAPP-A MoM	<0.27	1349	9
	0.27-2.99	12984	86.5
	>=3	672	4.5
T18 Risk group*	LR	12983	90.4
	IR	621	4.3
	HR	760	5.3
T21 Risk group*	LR	7162	47.7
	IR	2660	17.7
	HR	5188	34.6
Chromosomal abnormalities	No	14536	96.84
	Yes	474	3.16
Structural anomaly	No	14309	98.44
	Yes	227	1.56
Maternal adverse outcomes	No	13689	94.2
	Yes	847	5.8
Fetal adverse outcomes	No	13903	95.6
	Yes	633	4.4
Total adverse outcomes	No	12605	86.7
	Yes	1931	13.3

*HR: High Risk, IR: Intermediate Risk, LR: Low Risk.

Evaluation of chromosomal abnormalities and outcomes based on maternal serum PAPP-A levels

The results show that most of the patients with chromosomal abnormalities had a PAPP-A level of <0.27 (p<0.001). It was found that the group of patients whose PAPP-A level was > or =3 had the highest structural anomaly (p=0.021). On the other hand, the highest maternal adverse outcomes [such as Premature Rupture of Membranes (PROM), pre-eclampsia, abortion, polyhydramnios, oligohydramnios, amniotic leakage, bleeding, and blood spotting] were in patients whose PAPP-A level was <0.27 (p<0.001). No significant difference in adverse fetal outcomes was observed in the above three groups (p=0.61). Overall, the incidence of chromosomal disorders, structural abnormalities, and adverse pregnancy outcomes in both the mother and fetus was higher in the group with PAPP-A levels below 0.27 compared to other groups (p=0.031). In addition, in terms of T21 and T18 risk groups, a significant relationship was observed with the mother's serum PAPP-A level (p<0.001) (Table 2).

Table 2. Evaluation of chromosomal abnormalities and outcomes based on maternal serum PAPP-A MoM levels

Variables		Total	PAPP-A MoM						p-value
			<0.27		0.27-2.99		>=3		
			No.	%	No.	%	No.	%	
Chromosomal abnormalities	No	14536	2006	92.3	12370	97.6	160	98.8	<0.001
	Yes	474	167	7.7	305	2.4	2	1.2	
Structural Anomaly	No	14309	3234	98.9	10989	98.3	86	95.6	0.021
	Yes	227	36	1.1	187	1.7	4	4.4	
Maternal adverse outcomes	No	13689	1437	91.6	12156	94.5	96	91.5	0.042
	Yes	847	132	8.4	704	5.5	9	8.5	
Fetal adverse outcomes	No	13903	4018	97.9	9760	94.7	125	95.4	0.086
	Yes	633	85	2.1	542	5.3	6	4.6	
Total adverse outcomes	No	12603	1638	81.6	10839	87.5	126	92	0.031
	Yes	1927	369	18.4	1547	12.5	11	8.0	
T18 Risk group*	LR	13008	474	3.6	11891	91.5	641	4.9	<0.001
	IR	735	214	29.1	521	70.9	0	0	
	HR	760	344	45.2	416	54.8	0	0	
T21 Risk group*	LR	6655	795	10.4	6215	81.1	657	8.5	<0.001
	IR	2660	292	11.0	2332	87.8	31	1.2	
	HR	5188	318	6.1	4840	93.3	30	0.6	

* HR: High Risk, IR: Intermediate Risk, LR: Low Risk.

Evaluation of chromosomal abnormalities based on T18 and T21 risk group

The results of data analysis showed that chromosomal abnormalities, structural abnormalities, and fetal and maternal adverse obstetrics outcomes were more in the high-risk group for both T18 and T21 ($p<0.001$) and intermediate-risk group for both T18 and T21 ($p<0.001$) (Tables 3 and 4).

Evaluation of chromosomal abnormalities and outcomes based on fetal sex

The results indicate no significant relationship between fetal gender and chromosomal abnormalities, structural anomalies, maternal adverse outcomes, or total adverse outcomes ($p>0.05$). However, the rate of adverse fetal outcomes is significantly higher in female fetuses compared to male fetuses ($p=0.035$). The risk of screening for trisomy 18 is higher in male fetuses than in female fetuses within the high-risk and intermediate-risk groups ($p<0.001$). This increased risk for male fetuses is also observed in the screening for trisomy 21, but only within the high-risk group (Table 5) ($p<0.001$).

Evaluation of chromosomal abnormalities and outcomes based on ROC curve and area under the curve (AUC)

Establishing a specific cut-off point based solely on PAPP-A MoM levels for adverse pregnancy outcomes, such as structural abnormalities, adverse fetal outcomes, or adverse maternal outcomes, presents significant challenges when using the ROC curve. While the ROC curve is effective in identifying a cut-off point for chromosomal abnormalities, such as Down syndrome, it falls short of defining a single threshold for other pregnancy complications. This limitation highlights the complexity of predicting non-chromosomal adverse outcomes solely based on PAPP-A MoM levels. In the present analysis, the optimal cut-off point for identifying chromosomal

Table 3. Evaluation of chromosomal abnormalities and outcomes based on T18

Variables		Total	Levels of T18						p-value
			LR		IR		HR		
			No.	%	No.	%	No.	%	
Chromosomal abnormalities	No	14029	12800	98.4	693	95.2	536	70.8	<0.001
	Yes	474	210	1.6	42	5.7	222	29.2	
Structural anomaly	No	14276	12868	98.9	709	96.5	699	91.3	0.005
	Yes	227	140	1.1	26	3.5	61	8.7	
Maternal adverse outcomes	No	13656	12334	94.8	681	92.1	641	84.3	<0.001
	Yes	847	674	5.2	54	7.9	119	15.7	
Fetal adverse outcomes	No	13870	12757	97.3	650	88.4	463	60.9	<0.001
	Yes	633	251	1.9	85	11.6	297	39.1	
Total adverse outcomes	No	12572	11604	89.2	561	76.3	407	53.6	<0.001
	Yes	1931	1404	10.8	174	23.7	353	46.4	

* HR: High Risk, IR: Intermediate Risk, LR: Low Risk.

Table 4. Evaluation of chromosomal abnormalities and outcomes based on T21

Variables		Total	Levels of T21						p-value
			LR		IR		HR		
			n	%	n	%	n	%	
Chromosomal abnormalities	No	14536	6555	98.5	2413	97.2	4883	94.1	<0.001
	Yes	474	100	1.5	69	2.8	305	5.9	
Structural anomaly	No	14309	6601	99.1	2643	99.3	5041	97.2	<0.001
	Yes	227	41	0.6	39	1.5	147	2.8	
Maternal adverse outcomes	No	13689	6406	96.1	2539	95.9	4711	90.8	<0.001
	Yes	847	249	3.9	121	4.5	477	9.2	
Fetal adverse outcomes	No	13903	6391	92.5	2534	95.1	4945	95.3	<0.001
	Yes	633	264	3.9	126	4.9	243	4.7	
Total adverse outcomes	No	12603	6106	91.8	2368	90.0	4108	79.2	<0.001
	Yes	1931	547	8.2	304	11.4	1080	20.8	

* HR: High Risk, IR: Intermediate Risk, LR: Low Risk.

abnormalities was determined to be 0.625, whereas for total adverse outcomes, the cut-off was established at 0.585. The Area Under the Curve (AUC) for chromosomal abnormalities was 77%, with a 95% confidence interval ranging from 74 to 79%. In contrast, the AUC for total adverse outcomes was 64%, with a 95% confidence interval ranging from 63 to 66% (p<0.001). Based on the AUC, it was 76.8% for chromosomal abnormalities, indicating that the determined cut-off has good accuracy. For total

Table 5. Evaluation of chromosomal abnormalities and outcomes based on fetal sex

Variables		Total	Gender				p-value
			Female		Male		
			No.	%	No.	%	
Chromosomal abnormalities	No	6513	3523	96.2	2990	95.9	0.551
	Yes	268	139	3.8	129	4.1	
Structural anomaly	No	6636	3643	98.2	2992	97.5	0.066
	Yes	145	67	1.8	78	2.5	
Maternal adverse outcomes	No	6230	3389	92.4	2841	91.3	0.344
	Yes	551	279	7.6	272	8.7	
Fetal adverse outcomes	No	6382	3172	93.3	3210	95.0	0.035
	Yes	399	228	6.7	171	5.0	
Total adverse outcomes	No	5560	3078	82.9	78	11.7	0.419
	Yes	1221	634	17.1	587	88.3	
T18 Risk group*	LR	5944	3078	91.9	2866	88.6	<0.001
	IR	327	138	4.1	189	5.8	
	HR	315	135	4	180	5.6	
T21 Risk group*	LR	4624	2316	67	2308	69.5	<0.001
	IR	1558	859	24.8	699	21	
	HR	599	283	8.2	316	9.5	

* HR: High Risk, IR: Intermediate Risk, LR: Low Risk.

adverse outcomes, the figure was 64.4%, suggesting that the cut-off provides moderate accuracy (Figures 1 and 2).

Discussion

In the present study, the results showed that the decrease in PAPP-A level was associated with

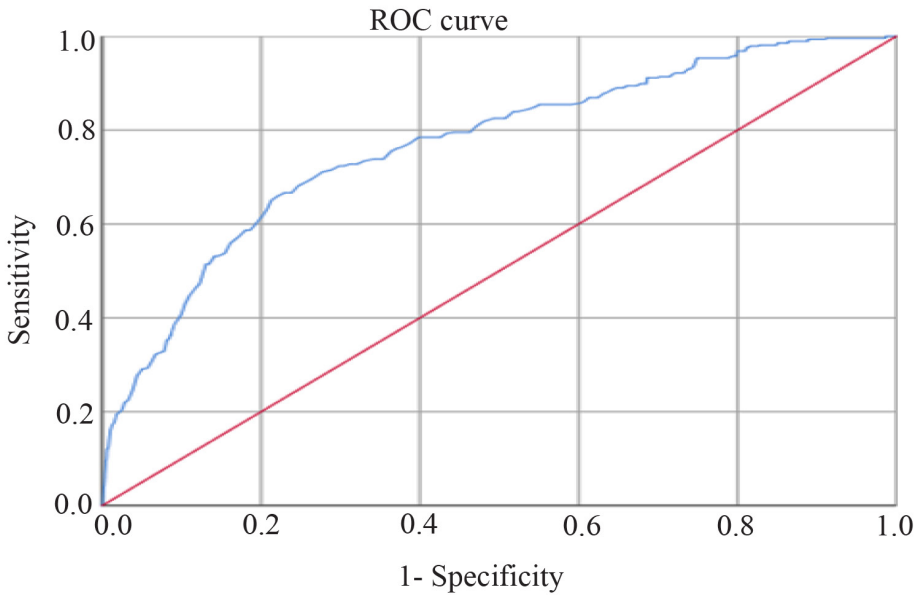

Figure 1. ROC curve of PAPP-A MoM and chromosomal abnormalities.

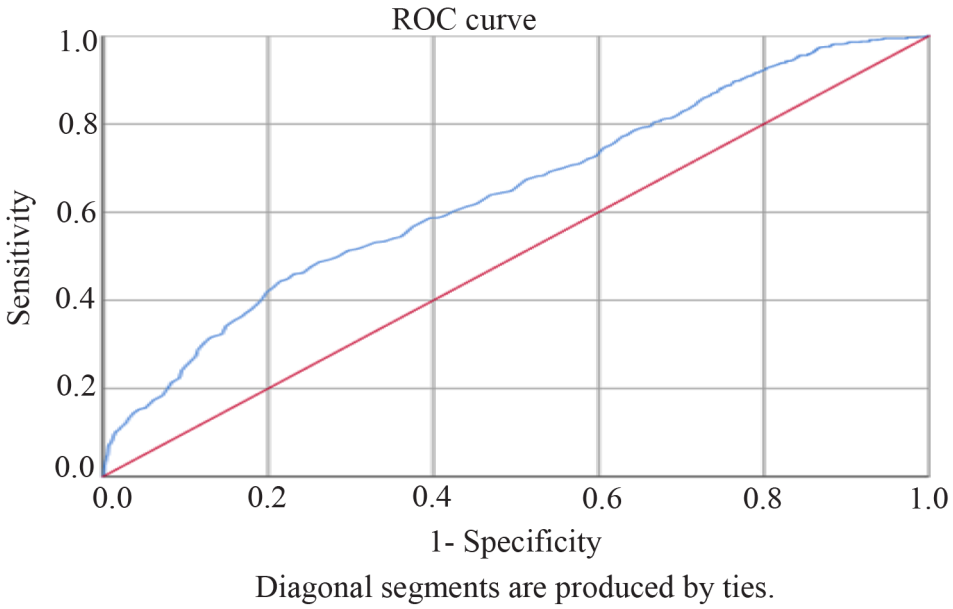

Figure 2. ROC curve of PAPP-A MoM and total adverse outcomes.

an increase in pregnancy outcomes as well as chromosomal abnormalities. In addition, the risk of T18 and T21 in born fetuses also increases.

Movahedi *et al* showed that the frequency of term labor was higher in pregnant mothers who had normal PAPP-A levels. This was despite the fact that the decrease in PAPP-A level can be associated with pregnancy complications including preeclampsia and preterm labor and many other cases (11). In line with the present study, Scott *et al* showed that the decrease in PAPP-A serum level can be associated with the increase of genetic abnormalities and Down syndrome in patients. They also stated that the reduction of PAPP-A level may be accompanied by normal karyotype, however, the risk of genetic abnormalities in patients should be considered (12). In another study, it was shown that only 53% of patients whose PAPP-A levels were decreased had trisomy 21. Therefore, they concluded that reducing the level of PAPP-A in Alzheimer's disease cannot increase the risk of trisomy 21 in all patients (13). In several other studies, it was found that the decrease in maternal PAPP-A level can be associated with an increase in the incidence of pregnancy outcomes and genetic disorders in newborns (14-16).

In general, it can be said that the reduction of maternal PAPP-A level can be associated with pregnancy outcomes in patients, however, in many conditions, it can be associated with normal karyotype. Therefore, to accurately diagnose high-risk patients exposed to genetic abnormalities, it is better to evaluate PAPP-A levels during pregnancy along with other biomarkers. The present study showed that the incidence of adverse fetal outcomes is significantly higher in female fetuses compared to male fetuses. The risk of screening for trisomy 18 is higher in male fetuses than in female fetuses within the high-risk and intermediate-risk groups. This increased risk for male fetuses is also observed in the screening for trisomy 21, but only within the high-risk group.

In contrast to the present study, Neuman *et al* also showed that the incidence of pre-eclampsia in pregnant mothers with reduced PAPP-A levels whose babies were male was higher compared to females (17). In line with the present study, Cowans *et al* also showed that the incidence of trisomy 21 was higher in male infants who were accompanied by a decrease in maternal PAPP-A levels (18). In previous studies, it was also shown that the risk of T18 and T21 was higher in male fetus compared to female (19). The present study showed that the risk of T18 and T21 increases in babies with pregnancy outcomes and genetic abnormalities.

Specifically, based on evidence, it has been determined that chromosomal abnormalities can be one of the risk factors for genetic diseases (20). A decrease in

PAPP-A levels in many patients can lead to a series of pregnancy consequences. These consequences, even though they can disrupt the development of the fetus, in some cases may lead to genetic and structural abnormalities. These abnormalities increase the risk of T18 and T21 in patients (21).

Finally, according to the present study, the optimal cut-off point for identifying chromosomal abnormalities was determined to be 0.625, whereas for total adverse outcomes, the cut-off was established at 0.585. Based on the AUC, it was 76.8% for chromosomal abnormalities, indicating that the determined cut-off has good accuracy. For the total adverse outcomes, the figure was 64.4%, suggesting that the cut-off provides moderate accuracy. In line with the present study, Kantomaa *et al* showed PAPP-A ≤0.40 MoM should be considered as a primary screening cut-off for adverse pregnancy outcomes as approximately 23% will develop either Small for Gestational Age (SGA), Hypertensive Disorder of Pregnancy (HDP) or Preterm Birth (PTB) (22).

Conclusion

In general, it can be said that the decrease in PAPP-A serum level in pregnant mothers can be associated with maternal and fetal adverse outcome. The occurrence of these complications can increase the risk of T18 and T21 in patients. Therefore, monitoring PAPP-A serum level during pregnancy can help in identifying high risk patients.

Ethical approval

This article does not contain any studies with human participants or animals performed by any of the authors. All the procedures performed in the studies involving human participants were in accordance with ethical standards of Local Ethics Committee of Shahid Beheshti University of Medical Sciences (IR.IUMS.REC.1401.607), as well as 1964 Helsinki Declaration.

Conflict of Interest

The authors declare that they have no conflict of interest.

References

1. Theme-Filha MM, Baldisserotto ML, Fraga ACSA, Ayers S, da Gama SGN, Leal MdC. Factors associated with unintended pregnancy in Brazil: cross-sectional results from the Birth in Brazil National Survey, 2011/2012. Reprod Health 2016;13:235-43.

2. Van Ditzhuijzen JM. Abortion and mental health: A longitudinal study of common mental disorders among women who terminated an unwanted pregnancy (Doctoral dissertation, Utrecht University).

3. Yeşilçinar İ, Güvenç G. Counselling and education for prenatal screening and diagnostic tests for pregnant women: Randomized controlled trial. Int J Nurs Pract 2021;27(5):e13000.

4. Kenny LC, Thomas G, Poston L, Myers JE, Simpson NA, McCarthy FP, et al. Prediction of preeclampsia risk in first time pregnant women: Metabolite biomarkers for a clinical test. PLoS One 2020;15(12):e0244369.

5. Rafiee Zadeh A, Ghadimi K, Mohammadi B, Hatamian H, Naghibi S, Danaeiniya A. Effects of Estrogen and Progesterone on Different Immune Cells Related to Multiple Sclerosis. Caspian J Neurol Sci 2018;4(2):83-90.

6. Dereke J, Nilsson C, Strevens H, Landin-Olsson M, Hillman M. Pregnancy-associated plasma protein-A2 levels are increased in early-pregnancy gestational diabetes: a novel biomarker for early risk estimation. Diabet Med 2020;37(1):131-7.

7. 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(9):1475.

8. 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(6):495-501.

9. 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(6):1113-9.

10. Palomaki GE, Wright DE, Summers AM, Neveux LM, Meier C, O'donnell A, et al. Repeated measurement of pregnancy-associated plasma protein-A (PAPP-A) in Down syndrome screening: A validation study. Prenat Diagn 2006;26(8):730-9.

11. Movahedi M, Khanjani S, Shahshahan Z, Hajihashemi M, Farahbod F, Shahsavandi E. Evaluation of the Relationship between Pregnancy-Associated Plasma Protein A (PAPP-A) and Pregnancy Outcomes. Advanced Biomedical Research 2023;12(1):91.

12. Scott F, Coates A, McLennan A. Pregnancy outcome in the setting of extremely low first-trimester PAPP-A levels. Aust N Z J Obstet Gynaecol 2009;49(3):258-62.

13. Ziolkowska K, Dydowicz P, Sobkowski M, Tobola-Wrobel K, Wysocka E, Pietryga M. The clinical usefulness of biochemical (free β-hCg, PaPP-a) and ultrasound (nuchal translucency) parameters in prenatal screening of trisomy 21 in the first trimester of pregnancy. Ginekol Pol 2019;90(3):161-6.

14. 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(3):253-65.

15. 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.

16. 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 Gynaecol Obstet 2017;136(1):76-82.

17. Neuman RI, Alblas van der Meer MM, Nieboer D, Saleh L, Verdonk K, Kalra B, et al. PAPP-A2 and Inhibin A as Novel Predictors for Pregnancy Complications in Women With Suspected or Confirmed Preeclampsia. J Am Heart Assoc 2020;9(19):e018219.

18. Cowans NJ, Stamatopoulou A, Maiz N, Spencer K, Nicolaides KH. The impact of fetal gender on first trimester nuchal translucency and maternal serum free β-hCG and PAPP-A MoM in normal and trisomy 21 pregnancies. Prenatal Diagnosis: Published in Affiliation With the International Society for Prenat Diagn 2009;29(6):578-81.

19. Tynan JA, Kim SK, Mazloom AR, Zhao C, McLennan G, Tim R, et al. Application of risk score analysis to low-coverage whole genome sequencing data for the noninvasive detection of trisomy 21, trisomy 18, and trisomy 13. Prenatal Diagnosis 2016;36(1):56-62.

20. Porreco RP, Garite TJ, Maurel K, Marusiak B, Ehrich M, van den Boom D, et al. Noninvasive prenatal screening for fetal trisomies 21, 18, 13 and the common sex chromosome aneuploidies from maternal blood using massively parallel genomic sequencing of DNA. Am J Obstet Gynecol 2014;211(4):365 e1-e12.

21. Tartaglia NR, Howell S, Sutherland A, Wilson R, Wilson L. A review of trisomy X (47, XXX). Orphanet J Rare Dis 2010;5:1-9.

22. Kantomaa T, Vääräsmäki M, Gissler M, Sairanen M, Nevalainen J. First trimester low maternal serum pregnancy-associated plasma protein-A (PAPP-A) as a screening method for adverse pregnancy outcomes. J Perinat Med 2022 Sep 23;51(4):500-509.