

# The role of PAPP-A and free B-HCG, which are among the first trimester tests, in predicting pregnancy complications

The first trimester screening tests

Fatih Şahin<sup>1</sup>, Fatma Yazıcı Yılmaz<sup>2</sup>

<sup>1</sup> Department of Obstetrics and Gynecology, Prof. Dr. Cemil Tascioglu City Hospital, Istanbul

<sup>2</sup> Department of Obstetrics and Gynecology, Private Clinic, Ankara, Turkey

## Abstract

**Aim:** In our study, we aimed to evaluate the predictive value of first-trimester maternal serum PAPP-A (Pregnancy Associated Plasma Protein-A) and B-HCG (human chorionic gonadotropin) levels in predicting pregnancy complications.

**Material and Methods:** The study included 489 singleton pregnancies undergoing first-trimester screening at the antenatal clinic, with perinatal records examined both before and after birth. Cases with PAPP-A <0.4 MoM and B-HCG <0.5 MoM values were investigated for associations with miscarriage, ectopic pregnancy, fetal death, preeclampsia, gestational diabetes mellitus (GDM), intrauterine growth restriction (IUGR), small for gestational age (SGA), large for gestational age (LGA), preterm labor, premature rupture of membrane (PROM), preterm premature membrane rupture (PPROM), cholestasis, and newborn requirements.

**Results:** In our study, patients with low PAPP-A values had a 2.6 times higher prevalence of preeclampsia, while in the B-HCG group, the prevalence was 2 times higher. Additionally, there was no significant association between the high-risk group and GDM, SGA, IUGR, and PROM.

**Discussion:** It has been observed that PAPP-A and HCG levels examined in the first trimester are associated with adverse pregnancy outcomes in the later weeks of pregnancy.

## Keywords

PAPP-A, B-HCG, Obstetric Ultrasound

DOI: 10.4328/ACAM.21877 Received: 2023-08-16 Accepted: 2023-09-18 Published Online: 2023-09-23 Printed: 2023-09-25 Ann Clin Anal Med 2023;14(Suppl 2):S176-179

Corresponding Author: Fatih Şahin, Department of Obstetrics and Gynecology, Prof. Dr. Cemil Tascioglu City Hospital, Istanbul, Turkey.

E-mail: fatih\_sahin67@hotmail.com P: +90 544 743 01 67 F: +90 212 230 35 35

Corresponding Author ORCID ID: <https://orcid.org/0000-0002-1621-5896>

This study was approved by the Ethics Committee of Şişli Etfal Training and Research Hospital (Date: 2014-09-02, No: 356)

## Introduction

Serum concentrations of free human chorionic gonadotropin (hCG) and pregnancy-associated plasma protein-A (PAPP-A) are used as indicators of chromosomal abnormalities in the context of first-trimester screening tests [1]. Placental insufficiency could result in a low PAPP-A outcome; PAPP-A and free hCG levels are produced in the placenta shortly after implantation, and low PAPP-A levels have been associated with conditions such as preeclampsia, stillbirth, preterm birth, and fetal growth restriction in investigations. However, debate continues regarding the findings of studies using free hCG [2].

Today, the combination of nuchal translucency (NT), pregnancy-associated plasma protein A (PAPP-A) and free  $\beta$ -human-derived chorionic gonadotropin ( $\beta$ -hCG) and serum levels is one of the most effective methods for screening in pregnancy [3]. However, maternal and pregnancy-related characteristics such as maternal age, ethnicity, smoking habits, weight, and conception procedures influence these tests. Multiples of the median (MoM) are calculated using each of these variables [4]. The screening method used in weeks 9-14 of pregnancy is not only employed for diagnosing chromosomal abnormalities, but also has the potential to predict adverse pregnancy outcomes based on the levels of these biomarkers [5].

In our study, we aimed to assess the predictive value of first-trimester maternal serum PAPP-A and B-HCG values in predicting pregnancy complications.

## Material and Methods

The study was conducted between January 1, 2014, and July 1, 2014, at Sisli Hamidiye Etfal Training and Research Hospital Antenatal Clinics. It included a total of 489 singleton pregnancies with ages ranging from 18 to 40 years, who presented for first-trimester prenatal screening tests. Perinatal records before and after birth of these patients were examined. The study commenced after obtaining approval from the hospital's ethics committee. Demographic information of all patients, results of the dual screening test, and serum free B-HCG and PAPP-A MoM values were scanned, recorded, and included in the study. Out of the 489 patients, those with normal first-trimester test results and those with values outside the normal range were compared in terms of the week of delivery, mode of delivery, newborn gender, birth weight, miscarriage, ectopic pregnancy, 1st minute APGAR, 5th minute APGAR, neonatal intensive care requirement, neonatal death, cholestasis, preeclampsia, gestational diabetes, placenta previa, placental abruption, fetal death, intrauterine fetal growth restriction, small for gestational age (SGA), large for gestational age (LGA), preterm labor, and preterm premature rupture of membrane. An analysis was undertaken to ascertain whether notable disparities existed in pregnancy complications between PAPP-A levels falling below or above the threshold of 0.4 MoM, as well as for free B-HCG levels below or above the threshold of 0.5 MoM. Maternal serum PAPP-A and B-HCG were measured using the IMMULITE 2000 system analyzers. The data were statistically evaluated using the SPSS 16.00 program. This study was approved by the Istanbul Sisli Etfal Hospital Clinical Research Ethics Committee on 02.09.2014 with approval No.356. In addition, written permission and informed consent were obtained from

the pregnant women. The study was conducted in accordance with the Principles of the Declaration of Helsinki

## Statistical Analysis

The data obtained for our study were analyzed using the IBM SPSS software (version 20.0) within a computational environment. The socio-demographic features of the research group were presented through cross-tabulations and descriptive statistical presentations, involving percentages and numerical representations. Mean values and standard deviations were provided for continuous variables. The conformity of data to a normal distribution was assessed using the Kolmogorov-Smirnov test. The chi-square analysis was employed to contrast categorical variables. A t-test was executed to assess normally distributed data between the two cohorts, while for non-normally distributed data, the Mann-Whitney U test was implemented; in instances with more than two groups, the Kruskal-Wallis test was utilized. To explore interconnected variables, correlation analysis was conducted. A logistic regression analysis was employed to estimate the need for Neonatal Intensive Care Unit (NICU) based on pertinent factors. Prediction of NICU necessity associated with PAPP-A value was accomplished using ROC analysis. The threshold for statistical significance was established at a p-value of less than 0.05.

## Ethical Approval

Ethics Committee approval for the study was obtained.

## Results

The demographic characteristics and obstetric histories of the patients included in our study are summarized in Table 1.

Table 2 examines the relationship between PAPP-A and perinatal complications. There were 123 newborns with an APGAR score below 7 at the 5th minute. Among them, 22 newborns had PAPP-A values below 0.4 MoM, constituting 31% of the population. There were 101 newborns with APGAR scores below 7 at the 5th minute and PAPP-A values above 0.4

**Table 1.** Demographic and clinical characteristics of the patients.

	n=489	%
Maternal age (years)	28.0±5.5	
Paternal age (years)	31.5±6	
Gravida	2.1±1.2	
Parity	1.7±0.8	
BMI (kg/m <sup>3</sup> )	40.5±7.6	
Tobacco Use		
Yes	12	2
No	477	98
Newborn Gender		
Female	271	55
Male	218	45
Mode of delivery		
NSVD	288	59
C/S	201	41
C/S indications		
Old C/S	69	15
Fetal Distress	61	13
Breech presentation	16	3
Non-progressing labor	27	6
Macrosomia	7	2
Preeclampsia-HELLP	21	4

**Table 2.** Relationship of first trimester PAPP-A with perinatal complications.

	N	n(%)	p value	OR
Apgar at 5 min <7		123		
PAPP-A <0.4	72	22 (31)	0.395	1.117
PAPP-A ≥0.4	417	101 (24)		
Newborn weight				
PAPP-A <0.4	72	2926 ± 538.7	0.012	
PAPP-A ≥0.4	417	3095.1 ± 519.8		
Neonatal ICU		117		
PAPP-A <0.4	72	24 (33.3)	0.043*	1.7
PAPP-A ≥0.4	417	93 (22.3)		
Preeclampsia		69		
PAPP-A <0.4	72	19 (26.4)	0.001*	2.631*
PAPP-A ≥0.4	417	50 (12)		
GDM		68		
PAPP-A <0.4	72	11 (15.3)	0.716	1.139
PAPP-A ≥0.4	417	57 (13.7)		
Preterm Delivery		61		
PAPP-A <0.4	72	19 (26.4)	0.0001*	3.201*
PAPP-A ≥0.4	417	42 (10.1)		
PROM		23		
PAPP-A <0.4	72	4 (5.6)	0.761	1.232
PAPP-A ≥0.4	417	19 (4.6)		
SGA		38		
PAPP-A <0.4	72	9 (12.5)	0.105	1.911
PAPP-A ≥0.4	417	29 (7)		

Gestational diabetes mellitus (GDM), intrauterine growth restriction (IUGR), small for gestational age (SGA), preterm labor, premature rupture of membrane (PROM), Appearance, Pulse, Grimace, Activity, and Respiration (APGAR)

MoM, representing 24% of the entire population. There was no significant relationship between PAPP-A values and the 5th minute APGAR score. The number of newborns requiring intensive care was 117. Among them, 24 newborns had PAPP-A values below 0.4 MoM, making up 33.3% of the population. There were 93 newborns with PAPP-A values above 0.4 MoM requiring intensive care, representing 22.3% of the population. There was a significant relationship between PAPP-A and the need for newborn intensive care. The need for newborn intensive care was higher at 33% in the high-risk group (p: 0.045).

There was a significant relationship between PAPP-A values and preeclampsia. The rate of preeclampsia was 2.6 times higher in the high-risk group with PAPP-A values below 0.4 MoM (p: 0.001). There was no significant relationship between PAPP-A values and GDM. There was a significant relationship between PAPP-A values and preterm birth. The rate of preterm birth was 3.2 times higher in the high-risk group with PAPP-A values below 0.4 MoM (p: 0.0001). There was no significant relationship between PAPP-A and SGA or PROM. The findings are summarized in Table 3.

In our study, there was no significant relationship between B-HCG values and 5-minute APGAR scores. There was a significant relationship between B-HCG values and preeclampsia. The rate of preeclampsia was 2 times higher in the high-risk group with B-HCG values below 0.5 MoM (p: 0.023). There was no significant relationship between B-HCG values and GDM, also

**Table 3.** Relationship between first trimester β-HCG and perinatal complications.

	N	n(%)	p value	OR
Apgar at 5 min <7		123		
B-hCG < 0.5	70	16 (23)	0.632	1.117
B-hCG ≥ 0.5	419	107 (26)		
Newborn weight				
B-hCG < 0.5	70	3022.8 ± 522.4	0.414	
B-hCG ≥ 0.5	419	3078.2 ± 526.2		
Neonatal ICU		117		
B-hCG < 0.5	70	19 (27)	0.497	1.220
B-hCG ≥ 0.5	419	98 (24)		
Preeclampsia		69		
B-hCG < 0.5	70	16 (22.9)	0.023*	2.046*
B-hCG ≥ 0.5	419	53 (12.6)		
GDM		68		
B-hCG < 0.5	70	12 (17.1)	0.398	1.341
B-hCG ≥ 0.5	419	56 (13.4)		
Preterm Delivery		61		
B-hCG < 0.5	70	11 (15.7)	0.375	1.376
B-hCG ≥ 0.5	419	50 (11.9)		
PROM		23		
B-hCG < 0.5	70	1 (1.4)	0.227	0.262
B-hCG ≥ 0.5	419	22 (5.3)		
SGA		38		
B-hCG < 0.5	70	7 (10)	0.452	1.391
B-hCG ≥ 0.5	419	31 (7.4)		

Small for gestational age (SGA), preterm labor, premature rupture of membrane (PROM), Appearance, Pulse, Grimace, Activity, and Respiration (APGAR)

between B-HCG values and preterm birth. There was no significant relationship between B-HCG MoM values and SGA, PROM, and the need for neonatal intensive care. The findings are summarized in Table 3.

**Discussion**

PAPP-A is produced by syncytiotrophoblasts and is the largest glycoprotein associated with pregnancy [6]. PAPP-A is a metalloproteinase that cleaves insulin-like growth factor-binding protein-4 (IGFBP-4) and serves as an important regulator of IGF bioavailability and cell growth. Concentrations of PAPP-A in the blood of pregnant women often decrease in fetal aneuploidy, and low concentrations can be associated with intrauterine growth restriction, preterm birth, preeclampsia, and placental abruption [7]. PAPP-A has been characterized as an IGF-dependent IGFBP-4 protease. In a study, IGFBP-4 was identified as a potent IGF inhibitor in vitro, and the cleavage of IGFBP-4 eliminated the inhibitory effect of IGF on various systems. This suggests that IGFBP-4 proteolysis functions as a positive regulator of IGF bioavailability [8].

Due to the intriguing nature of the topic, there are numerous articles available in the literature. In a recent study, uterine artery Doppler pulsatility index (UtA-PI), serum pregnancy-associated plasma protein-A (PAPP-A), and free beta-human chorionic gonadotropin (fβ-hCG) levels were investigated individually or in combination for predicting the development of

preeclampsia. However, the addition of these markers to first-trimester screening tests was not found to be beneficial for predicting preeclampsia [9]. Similarly, in another recent study, it was concluded that placental growth factor (PLGF) is a more useful marker for predicting preeclampsia in the first-trimester screening compared to PAPP-A [10]. Another study found that low maternal serum PAPP-A in the first trimester is associated with adverse pregnancy outcomes, but the predictive values are weak [11]. In another study, the addition of placental volume to first-trimester screening tests has been found to be useful in predicting the risk of small for gestational age (SGA) [12]. In our study, PAPP-A values below 0.4 MoM and B-HCG values below 0.5 MoM were found to be associated with preeclampsia, miscarriage, and preterm delivery.

#### Limitation

The limitations of the study stem from its retrospective nature; however, the complete patient records within the hospital system strengthened our study. Over the years, the discovery of new biomarkers will contribute to further advancements in research. Undoubtedly, the quest for markers that can predict the later weeks of pregnancy during the intrauterine course has always intrigued researchers. It is expected that in the coming years, with the continuous advancement of technology, these topics will diversify.

#### Conclusion

It has been observed that PAPP-A and HCG levels examined in the first trimester are associated with adverse pregnancy outcomes in the later weeks of pregnancy

#### Scientific Responsibility Statement

The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

#### Animal and human rights statement

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. No animal or human studies were carried out by the authors for this article.

#### Funding: None

#### Conflict of interest

None of the authors received any type of financial support that could be considered potential conflict of interest regarding the manuscript or its submission.

#### References

- Elmas B, Laleli Koç B, Tuğrul Ersak D, Zorlu U, Aydoğdu E, Yılmaz G, et al. The relationship between the first trimester maternal serum PAPP-A and  $\beta$ -hCG values and newborn intensive care needs in low-risk pregnancies. *Turk J Obstet Gynecol.* 2022;19(4):287-94.
- Guo X, Wang F, Li J, Guo Z, Wang J. Prediction performance of serum placental growth factor (PLGF) human chorionic gonadotropin  $\beta$  ( $\beta$ -hCG) and PAPP-A levels in early pregnancy for pregnancy outcomes. *Pak J Med Sci.* 2022;38(7):1877-82.
- Honarjoo M, Zarean E, Tarrahi MJ, Kohan S. Role of pregnancy-associated plasma protein A (PAPP-A) and human-derived chorionic gonadotrophic hormone (free  $\beta$ -hCG) serum levels as a marker in predicting of Small for gestational age (SGA): A cohort study. *J Res Med Sci.* 2021;26:104.
- Caron L, Fillion A, Giguère Y, Audibert F, Forest JC, Gasse C, et al. First-trimester screening for Down syndrome using quadruple maternal biochemical markers. *Clin Chem Lab Med.* 2023;61(9):1630-5.
- Genc S, Ozer H, Emeklioglu CN, Cingillioglu B, Sahin O, Akturk E, et al. Relationship between extreme values of first trimester maternal pregnancy associated plasma Protein-A, free- $\beta$ -human chorionic gonadotropin, nuchal translucency and adverse pregnancy outcomes. *Taiwan J Obstet Gynecol.* 2022;61(3):433-40.
- Pasińska M, Balcerk E, Repczyńska A, Łazarczyk E. The Levels of Pregnancy-Associated Plasma Protein (PAPP-A) and Chorionic Gonadotropin ( $\beta$ -hCG) in the Blood Serum of Women with Hypothyroidism in the 1st Trimester of Pregnancy.

*Int J Womens Health.* 2023;15:167-76.

7. Cruañes-Monferrer J, Gil Liñan A, Ramírez Andreo A. [Translated article] Edematous Infraumbilical Plaque in a Pregnant Woman. *Actas Dermosifiliogr.* 2023;114(3):T257-8.

8. Oxvig C, Conover CA. The Stanniocalcin-PAPP-A-IGFBP-IGF Axis. *J Clin Endocrinol Metab.* 2023;108(7):1624-33.

9. Khanam Z, Mittal P, Suri J. Does the Addition of Serum PAPP-A and  $\beta$ -hCG Improve the Predictive Value of Uterine Artery Pulsatility Index for Preeclampsia at 11-14 Weeks of Gestation? A Prospective Observational Study. *J Obstet Gynaecol India.* 2021;71(3):226-34.

10. Mazer Zumaeta A, Wright A, Syngelaki A, Maritsa VA, Da Silva AB, Nicolaides KH. Screening for pre-eclampsia at 11-13 weeks' gestation: use of pregnancy-associated plasma protein-A, placental growth factor or both. *Ultrasound Obstet Gynecol.* 2020;56(3):400-7.

11. 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):253-5.

12. Kim YR, Park G, Joo EH, Jang JH, Ahn EH, Jung SH, et al. First-trimester screening model for small-for-gestational-age using maternal clinical characteristics, serum screening markers, and placental volume: prospective cohort study. *J Matern Fetal Neonatal Med.* 2022;35(25):5149-54.

#### How to cite this article:

Fatih Şahin, Fatma yazıcı yılmaz. The role of PAPP-A and free B-HCG, which are among the first trimester tests, in predicting pregnancy complications. *Ann Clin Anal Med* 2023;14(Suppl 2):S176-179

This study was approved by the Ethics Committee of Sişli Etfal Training and Research Hospital (Date: 2014-09-02, No: 356)