Zeynep Kamil Med J 2024;55(2):83–87
DOI: 10.14744/zkmj.2023.60362

ORIGINAL ARTICLE

Relationship between first trimester maternal PAPP-A (pregnancy associated plasma protein-A) and free β-hCG (human chorionic gonadotropin) levels with fetal birth weight

Gökhan KILIÇ
Gülin FEYKAN YEĞİN
Elçin İŞLEK SEÇEN
Hüseyin LEVENT KESKİN
Ayşe Filiz YAVUZ

Department of Obstetrics and Gynecology, Yıldırım Beyazıt University, Atatürk Training and Research Hospital, Ankara, Turkey

ORCID ID
GK : 0000-0002-9940-7139
GFY : 0000-0001-8006-5055
EİS : 0000-0002-0892-8589
HLK : 0000-0002-2268-3821
AFY : 0000-0003-3699-7757

ABSTRACT

Objective: The aim of this study was to evaluate the relationship between maternal serum PAPP-A (pregnancy-associated plasma protein A) and free β-hCG (human chorionic gonadotropin) values with fetal birth weight.

Material and Methods: 554 patients who applied to Yıldırım Beyazit University Atatürk Training and Research Hospital Obstetrics Clinic between January 2009 and December 2016 for first trimester combined screening tests were included in the study. Antenatal follow-up and pregnancy outcomes were examined. The relationship between adjusted multiples of median (MoM) values of maternal serum PAPP-A and free β-hCG levels and fetal birth weight (FBW); small for gestational age (SGA—fetal birth weight <10th percentile) and large for gestational age (LGA—fetal birth weight > 90th percentile) were analyzed.

Results: Maternal serum PAPP-A level was found to have a relationship with SGA development (p=0.03). Every decrease per unit in the adjusted MoM value of maternal serum PAPP-A level increases the risk of SGA development three times (RR, 1/0.333; 95% CI, 0.1–0.8, p=0.030).

Conclusion: Correlation between PAPP-A value and SGA was found to be statistically significant. However, a similar prediction was not eligible between maternal serum PAPP-A level and LGA fetuses. On the other hand, maternal serum free β-hCG level did not have a statistical significance as a predictor for both SGA and LGA fetuses.

Keywords: β-hCG, fetal birth weight, first trimester screening, LGA, PAPP-A, SGA.

Cite this article as: Kılıç G, Feykan Yeğin G, İşlek Seçen E, Keskin HL, Yavuz AF. Relationship between first trimester maternal PAPP-A (pregnancy associated plasma protein-A) and free β-hCG (human chorionic gonadotropin) levels with fetal birth weight. Zeynep Kamil Med J 2024;55(2):83–87.

Received: July 01, 2023 **Revised:** August 26, 2023 **Accepted:** October 25, 2023 **Online:** May 07, 2024
Correspondence: Gökhan KILIÇ, MD. Yıldırım Beyazıt Üniversitesi, Atatürk Eğitim ve Araştırma Hastanesi, Kadın Hastalıkları ve Doğum Kliniği, Ankara, Türkiye.
Tel: +90 312 595 30 00 **e-mail:** gokkilic@yahoo.com

INTRODUCTION

One of the main purposes of antenatal screening tests has been accepted as to detect pregnant women at risk for developing pregnancy complications and to reduce the morbidity and mortality rates with the use of preventive policies. For this reason, the majority of studies have focused on early pregnancy. In the first trimester, maternal serum free beta human chorionic gonadotropin (β-hCG) and pregnancy-associated plasma protein A (PAPP-A) levels have been proved to predict the risk of aneuploidies. Also, the association between first trimester maternal serum free β-hCG and PAPP-A levels and adverse pregnancy outcomes has been investigated by different studies.

Placental insufficiency has been suggested as the underlying mechanism for adverse pregnancy outcomes such as spontaneous preterm birth, pre-eclampsia, preterm prelabor rupture of membranes, and intrauterine growth restriction.[1] The relationship between first trimester biomarkers of placental function and adverse pregnancy outcomes is controversial.[2–4]

The aim of this study is to evaluate maternal serum free β-hCG and PAPP-A levels as components of combined screening tests at 11–14 weeks of gestation and to determine that these markers are predictors for fetal development abnormalities; small for gestational age (SGA) and large for gestational age (LGA).

MATERIAL AND METHODS

The entire study group consisted of 1378 patients who applied to Yıldırım Beyazıt University Atatürk Training and Research Hospital Gynecology and Obstetrics Clinic for first trimester combined screening tests between January 2009 and December 2016. Six hundred seventy-three patients were lost to follow-up. Twin pregnancies (n=46), post-term pregnancies, patients with diabetes mellitus and chronic hypertension, fetal chromosomal anomalies, and major fetal anomalies were excluded from the study group. Also, patients who developed intrauterine growth restriction (IUGR) due to placental insufficiency were excluded. Finally, the study included 554 singleton pregnancies. Data related to patients were obtained from retrospective research in the Gynecology and Obstetrics Clinic's electronic database system and patients' files. Ethical approval was obtained by the local Ethics Committee of Yıldırım Beyazıt University Faculty of Medicine (26379996/312/268 date: 19.12.2018) in view of the retrospective nature of the study and all the procedures being performed were part of the routine care. Thus, the requirement to obtain informed consent was waived. The study was conducted in concordance with the Declaration of Helsinki—Ethical Principles for Medical Research Involving Human Subjects.

Maternal serum PAPP-A and free β-hCG levels were measured using the chemiluminescence method in the hospital's biochemistry laboratory Immulite 2000 analyzer. Adjusted multiples of median (MoM) values were calculated by the PRISCA package software program with patients' information gathered from outpatient clinical forms. Adjusted MoM values of maternal serum PAPP-A and free β-hCG levels were classified according to the 5th, 10th, 90th, and 95th percentiles. The relationship between these groups and fetal birth weight percentile groups (SGA, LGA) was evaluated. SGA was defined as fetal birth weight (FBW) under the 10th percentile and LGA was defined as FBW over the 90th percentile. For the evaluation of SGA vs. non-SGA; FBW under the 10th percentile and FBW over the 10th percentile (FBW<10p and FBW=10-90p) groups were compared. For the evaluation of LGA vs. non-LGA; FBW over the 90th percentile and FBW under the 90th percentile (FBW>90p and FBW=10-90p) groups were compared.

Table 1: Patients' demographical, clinical features and pregnancy outcomes

Study group (n=554)	Mean±SD (min–max)
Age (years)	26±4.9 (16–43)
Gravida	1.9±1.1 (1–8)
Parity	0.6±0.7 (0–4)
Abortion	0.19±0.4 (0–3)
BMI (kg/m^2)	24±2.3 (19–34)
Delivery mode, n (%)	
Vaginal	377 (68%)
Caesarean	177 (32%)
Gestation week at delivery, n (%)	
Preterm	68 (13.9%)
Term	486 (86.1%)
Gender, n (%)	
Male	285 (51.4%)
Female	269 (48.6%)
Fetal birth weight (gr)	3324±491 gr
(630–5265)	
Percentile (n;%)	
<10%	50 (9%)
10–90%	474 (85.6%)
>90%	30 (5.4%)

BMI: Body mass index.

Statistical Analysis

SPSS 21.0 (SPSS Inc., Chicago, IL) software package was used for data management and statistical analysis. Analysis of nominal variables was performed using the χ^2 test, Student-T test, Mann-Whitney U test, or the Fisher-exact test where appropriate. The Kolmogorov-Smirnov test was used to crosscheck the distribution of variables. Descriptive statistics were expressed as mean±standard deviation or median (min–max) for continuous variables and number/percentage for categorical variables. All variables with a p-value <0.05 in the univariate analysis were included in the multivariate analysis. Multivariate analysis was performed using the stepwise logistic regression model, and relative rates of variables were calculated. Odds ratios with 95% confidence intervals were calculated. P-values less than 0.05 were considered significant.

Table 2: Association of PAPP-A percentile groups and SGA (fetal birth weight <10p)

PAPP-A percentile (n, %)	FBW <10p	FBW >10p	RR (95% CI)	p
<5p	3 (10%)	21 (4%)	1.4 (0.2–8)	0.063
<10p	5 (16.6%)	47 (9%)	1.1 (0.3–4.3)	0.060
>90p	4 (13%)	58 (11%)	0.7 (0.1–1.1)	0.737
>95p	2 (6.6%)	26 (5%)	0.5 (0–0.8)	0.801
PAPP-A (MoM) (mean±SD)	0.96±0.61	1.08±0.59	0.3 (0.1–0.8)	0.030

SD: Standard deviation; PAPP-A: Pregnancy associated plasma protein - A; SGA: Small for gestational age; FBW: Fetal birth weight; RR: Relative ratio; CI: Confidence interval; MoM: Multiples of median.

Table 3: Association of free β-hCG percentile groups and SGA (fetal birth weight <10p)

β-hCG percentile (n, %)	FBW <10p	FBW >10p	RR (95% CI)	p
<5p	2 (6%)	26 (5%)	0.9 (0.3–3.3)	0.938
<10p	3 (10%)	52 (10%)	1 (0.2–4.4)	0.778
>90p	5 (17%)	53 (10%)	0.8 (0.2–2.5)	0.596
>95p	2 (7%)	28 (5%)	0.7 (0.1–2.5)	0.666
PAPP-A (MoM) (mean±SD)	0.99±0.47	1.27±0.86	0.9 (0.8–1)	0.542

SD: Standard deviation; β-hCG: Human chorionic gonadotropin; SGA: Small for gestational age; FBW: Fetal birth weight; RR: Relative ratio; CI: Confidence interval; MoM: Multiples of median.

RESULTS

The mean age of the study group was 26±4.9 (range 16–43) years. The mean number of gestations was 1.9±1.1 (ranged between 1 and 8 gestations) and the mean number of parities was 0.6±0.7 (ranged between 0 and 4 parities). The median time for first trimester screening was 85.9±5.2 days. The median fetal birth weight was 3324±491 g and ranged between 630 and 5265 g. Demographical, clinical features, and pregnancy outcomes of the study population are shown in Table 1.

Three hundred seventy-seven (68%) pregnancies resulted in vaginal birth and 177 (32%) with cesarean section (CS). Seventy-seven (14%) patients underwent surgery for previous CS, 40 (7%) patients for fetal distress, 22 (4%) patients for cephalopelvic disproportion, and 40 (7%) patients for other reasons (placenta previa, abruptio placenta, maternal morbidity, etc.). There was no statistical significance between FBW and mode of delivery (p>0.05). There were 285 (51.4%) male newborns and 269 (48.6%) female newborns. Tobacco use was positive in 86 (6.2%) pregnancies. The duration of pregnancy was under 37 weeks in 68 (13.9%) patients and equal to or more than 37 weeks in 486 (86.1%) patients.

Mean adjusted MoM values of maternal serum PAPP-A level was 0.96 and ranged between 0.1 and 5.8 in entire study group. Patients with FBW <10th percentile and FBW ≥10th percentile were compared and mean maternal serum PAPP-A level was found to have a relationship with SGA development by using backward regression analysis (p=0.03). It was calculated that every decrease per unit in adjusted MoM value of maternal serum PAPP-A level increases the risk of SGA development 3 times (RR, 1/0.333; 95% CI, 0.1–0.8, p=0.030). Adjusted maternal serum PAPP-A levels were investigated for <5p, <10p, >90p and >95p groups with regression analysis however the association of PAPP-A levels and SGA risk did not reach a statistical significance (Table 2).

Mean maternal serum PAPP-A levels between FBW >90th percentile and FBW ≤90th percentile (LGA vs non-LGA) fetuses were not statistically significant (p>0.05).

Mean maternal serum free β-hCG adjusted MoM level was 1.26±0.8 and ranged between 0.2 and 7.4. FBW <10th percentile and ≥10th percentile (SGA vs. non-SGA) fetuses were compared and mean maternal serum free β-hCG levels were not statistically significant between these groups (p>0.05) (Table 3). Additionally, FBW >90th percentile and FBW ≤ 90th percentile (LGA vs non-LGA) fetuses did not have a statistical significance for mean maternal serum free β-hCG levels (p>0.05).

DISCUSSION

In the first trimester of pregnancy, maternal serum free β-hCG and PAPP-A levels, combined with nuchal translucency (NT) measurement, were proved to diagnose fetuses with Down syndrome (Trisomy 21) with 89% positivity and 5% false positivity. Also, these biochemical markers were evaluated as predictors for adverse

pregnancy outcomes.[5] PAPP-A is a protease for insulin-like growth factor-binding protein-4 (IGFBP-4).[6] Therefore, low serum PAPP-A levels cause high IGFBP-4 levels resulting in low levels of maternal serum free insulin-like growth factor (IGF). IGF plays a major role in fetal growth regulation by controlling glucose and amino acid intake to trophoblasts.[7,8] For this reason, conditions with trophoblast invasion anomalies such as spontaneous fetal loss, SGA, IUGR, and preeclampsia could have low maternal serum PAPP-A levels in the first trimester. Westergaard et al.[9] were the first authors to suggest that low maternal serum PAPP-A levels predict adverse pregnancy outcomes 25 years ago. In their study, pregnancies with low PAPP-A levels had a tendency to develop miscarriages within days or weeks. These results were confirmed by other investigators with different reports.[9,10]

Patients with low maternal serum PAPP-A levels have a risk for developing spontaneous preterm delivery, pregnancy-induced hypertension, spontaneous abortion, SGA, and gestational diabetes mellitus.[11,12] Also, different investigators reported that pregnancies with SGA fetuses have low maternal serum PAPP-A levels and pregnancies with LGA fetuses have high maternal serum PAPP-A levels in early pregnancy.[13,14] A maternal serum PAPP-A level <5th percentile increases the risk for SGA, preeclampsia, spontaneous abortion, and intrauterine fetal death.[15,16] However, there are some authors suggesting that low first trimester maternal serum PAPP-A levels are not related to IUGR. These authors reported that insufficient placentation induces a maternal systemic inflammatory response syndrome and releases different mediators, which enhances PAPP-A production from other non-placental tissues.[17,18]

We found that a decrease per unit in adjusted maternal serum PAPP-A levels increases SGA risk three times in 10–14th weeks of gestation (RR, 1/0.333; 95% CI, 0.1–0.8, p=0.030). Our findings correlate with the literature review. First trimester free β-hCG levels did not affect fetal growth in our study. On the other hand, different studies assessed the relationship between low free β-hCG levels and pregnancy complications. The FASTER (First and Second Trimester Evaluation of Risk Trial) study was expanded by Dugoff et al.,[15] and a total of 34,271 pregnant women were enrolled in a larger study cohort. In their study, first trimester maternal serum free β-hCG level <1st percentile (0.24 MoM) increased the risk of fetal loss before the 24th week of pregnancy. They concluded that first trimester maternal serum free β-hCG level <5th percentile (0.42 MoM) indicates a low FBW with <10th percentile. As a result, insufficient placentation and low placental volume were considered responsible for decreased maternal serum free β-hCG levels in 10–14th weeks of gestation. In the second trimester of pregnancy, hypoperfusion-induced hormone production was admitted as the cause of high maternal serum free β-hCG levels.[12,19] Different investigators established their findings that support the role of first trimester maternal serum free β-hCG levels as predictors for pregnancy complications.[11,12,15,20,21] However, several studies, including our study, suggest that first trimester maternal serum free β-hCG levels have no impact on fetal development and fetal birth weight.[12,15,22]

A Cochrane Library review between the years 1966 and 2007 was carried out by the Society of Obstetricians and Gynaecologists of Canada Genetics Committee in 2008.[23] According to this algorithm, maternal serum markers are not recommended for predicting pregnancy complications due to low sensitivity and high false positivity. During ordinary antenatal screening procedures such as screening for chromosomal anomalies, abnormal results in maternal serum markers could be investigated for pregnancy complications. Unexplained low maternal serum PAPP-A (<0.4 MoM) and/or low free β-hCG (<0.5 MoM) levels in the first trimester are associated with adverse pregnancy outcomes. However, a specific follow-up protocol could not be defined. Uterine artery Doppler Ultrasonography (USG) estimates might be suitable for the evaluation of abnormal and unexplained maternal serum markers. An abnormality in uterine artery Doppler USG along with low first trimester maternal serum PAPP-A levels and high second trimester alpha-feto protein (AFP), β-hCG, inhibin-A levels carry an elevated risk for IUGR and preeclampsia. Thus, obstetricians can rearrange antenatal visits according to the patient's symptoms, follow-up signs (fetal growth, amniotic fluid volume, fetal biophysical profile, uterine artery Doppler USG, cervical measurement), or the patient's education status.

CONCLUSION

Our study suggested that low levels of first trimester maternal serum PAPP-A and free β-hCG values could predict adverse pregnancy outcomes. A decrease per unit in adjusted maternal serum PAPP-A level tripled the risk of SGA in our study (RR, 1/0.333; 95% CI, 0.1–0.8, p=0.030). However, a similar prediction was not viable between maternal serum PAPP-A level and LGA fetuses. On the other hand, maternal serum free β-hCG level did not have statistical significance as a predictor for both SGA and LGA fetuses.

The results of routine first trimester screening tests might be extended to get an anticipation for pregnancy complications. Thus, the cost-effective power of these tests would be enhanced, and the morbidity of pregnancy complications could be reduced. The most important limitation of this study is its retrospective design. On the other hand, a high number of patients is an advantage. Besides, inclusion and exclusion criteria strengthen study homogenization. However, precise conclusions could not be made for using antenatal routine screening tests as predictors of pregnancy outcomes. For more accurate results, more randomized controlled trials should be conducted in this patient group.

Statement

Ethics Committee Approval: The Yıldırım Beyazıt University Clinical Research Ethics Committee granted approval for this study (date: 19.12.2018, number: 26379996/312/268).

Author Contributions: Concept – GK, HLK, AFY; Design – GK, AFY; Supervision – HLK, AFY; Data Collection and/or Processing – GK, GFY, EİS; Analysis and/or Interpretation – GK, EİS; Literature Search – GK, GFY, EİS; Writing – GK, GFY, HLK; Critical Reviews – HLK, AFY.

Conflict of Interest: The authors have no conflict of interest to declare.

Informed Consent: Informed consent was waived because of the retrospective nature of the study.

Use of AI for Writing Assistance: Not declared.

Financial Disclosure: The authors declared that this study has received no financial support.

Peer-review: Externally peer-reviewed.

REFERENCES

1. Chiu CPH, Feng Q, Chaemsaithong P, Sahota DS, Lau YY, Yeung YK, et al. Prediction of spontaneous preterm birth and preterm prelabor rupture of membranes using maternal factors, obstetric history and biomarkers of placental function at 11-13 weeks. Ultrasound Obstet Gynecol 2022;60:192–9.
2. Beta J, Akolekar R, Ventura W, Syngelaki A, Nicolaides KH. Prediction of spontaneous preterm delivery from maternal factors, obstetric history and placental perfusion and function at 11-13 weeks. Prenat Diagn 2011;31:75–83.
3. El-Achi V, de Vries B, O'Brien C, Park F, Tooher J, Hyett J. First-Trimester prediction of preterm prelabour rupture of membranes. Fetal Diagn Ther 2020;47:624–9.
4. Soni S, Krantz DA, Blitz MJ, Vohra N, Rochelson B. Elevated maternal serum-free β-human chorionic gonadotropin (β-hCG) and reduced risk of spontaneous preterm delivery. J Matern Fetal Neonatal Med 2019;32:3191–6.
5. Spencer K, Souter V, Tul N, Snijders R, Nicolaides KH. A screening program for trisomy 21 at 10-14 weeks using fetal nuchal translucency, maternal serum free beta-human chorionic gonadotropin and pregnancy-associated plasma protein-A. Ultrasound Obstet Gynecol 1999;13:231–7.
6. Lawrence JB, Oxvig C, Overgaard MT, Sottrup-Jensen L, Gleich GJ, Hays LG, et al. The insulin-like growth factor (IGF)-dependent IGF binding protein-4 protease secreted by human fibroblasts is pregnancy-associated plasma protein-A. Proc Natl Acad Sci USA 1999;96:3149–53.
7. Kniss DA, Shubert PJ, Zimmerman PD, Landon MB, Gabbe SG. Insulin-like growth factors. Their regulation of glucose and amino acid transport in placental trophoblasts isolated from first-trimester chorionic villi. J Reprod Med 1994;39:249–56.
8. Irwin JC, Suen LF, Martina NA, Mark SP, Giudice LC. Role of the IGF system in trophoblast invasion and pre-eclampsia. Hum Reprod 1999;14(Suppl 2):90–6.
9. Westergaard JG, Sinosich MJ, Bugge M, Madsen LT, Teisner B, Grudzinskas JG. Pregnancy-associated plasma protein A in the prediction of early pregnancy failure. Am J Obstet Gynecol 1983;145:67–9.
10. Ruge S, Pedersen JF, Sørensen S, Lange AP. Can pregnancy-associated plasma protein A (PAPP-A) predict the outcome of pregnancy in women with threatened abortion and confirmed fetal viability? Acta Obstet Gynecol Scand 1990;69:589–95.
11. Ong CY, Liao AW, Spencer K, Munim S, Nicolaides KH. First trimester maternal serum free beta human chorionic gonadotrophin and pregnancy associated plasma protein A as predictors of pregnancy complications. BJOG 2000;107:1265–70.
12. Yaron Y, Heifetz S, Ochshorn Y, Lehavi O, Orr-Urtreger A. Decreased first trimester PAPP-A is a predictor of adverse pregnancy outcome. Prenat Diagn 2002;22:778–82.
13. Canini S, Prefumo F, Pastorino D, Crocetti L, Afflitto CG, Venturini PL, et al. Association between birth weight and first-trimester free beta-human chorionic gonadotropin and pregnancy-associated plasma protein A. Fertil Steril 2008;89:174–8.
14. Krantz D, Goetzl L, Simpson JL, Thom E, Zachary J, Hallahan TW, et al. Association of extreme first-trimester free human chorionic gonadotropin-beta, pregnancy-associated plasma protein A, and nuchal translucency with intrauterine growth restriction and other adverse pregnancy outcomes. Am J Obstet Gynecol 2004;191:1452–8.
15. Dugoff L, Hobbins JC, Malone FD, Porter TF, Luthy D, Comstock CH, et al. First-trimester maternal serum PAPP-A and free-beta subunit human chorionic gonadotropin concentrations and nuchal translucency are associated with obstetric complications: A population-based screening study (the FASTER Trial). Am J Obstet Gynecol 2004;191:1446–51
16. Smith GC, Stenhouse EJ, Crossley JA, Aitken DA, Cameron AD, Connor JM. Early pregnancy levels of pregnancy-associated plasma protein A and the risk of intrauterine growth restriction, premature birth, preeclampsia, and stillbirth. J Clin Endocrinol Metab 2002;87:1762–7.
17. Morssink LP, Kornman LH, Hallahan TW, Kloosterman MD, Beekhuis JR, de Wolf BT, et al. Maternal serum levels of free beta-hCG and PAPP-A in the first trimester of pregnancy are not associated with subsequent fetal growth retardation or preterm delivery. Prenat Diagn 1998;18:147–52.
18. Cuckle H, Arbuzova S, Spencer K, Crossley J, Barkai G, Krantz D, et al. Frequency and clinical consequences of extremely high maternal serum PAPP-A levels. Prenat Diagn 2003;23:385–8.
19. Lieppman RE, Williams MA, Cheng EY, Resta R, Zingheim R, Hickok DE, et al. An association between elevated levels of human chorionic gonadotropin in the midtrimester and adverse pregnancy outcome. Am J Obstet Gynecol 1993;168:1852–7.
20. Sorensen TK, Williams MA, Zingheim RW, Clement SJ, Hickok DE. Elevated second-trimester human chorionic gonadotropin and subsequent pregnancy-induced hypertension. Am J Obstet Gynecol 1993;169:834–8.
21. Walton DL, Norem CT, Schoen EJ, Ray GT, Colby CJ. Second-trimester serum chorionic gonadotropin concentrations and complications and outcome of pregnancy. N Engl J Med 1999;341:2033–8.
22. James DK, Steer PJ, Weiner CP, Gonik B. High risk pregnancy. Philadelphia: Saunders; 1995. p. 614–5.
23. Gagnon A, Wilson RD. Obstetrical complications associated with abnormal maternal serum markers analytes. J Obstet Gynaecol Can 2008;30:918–32.