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The relation of first trimester PaPP-A level and vaginal birth complications in large for gestational age fetuses

Anil Erturk, Nergis Kender Erturk*

Department of Obstetrics and Gynecology, Bursa Yuksek Ihtisas Training and Research Hospital, Bursa, Türkiye

ABSTRACT

Aim: To investigate the association of vaginal birth complications with first trimester pregnancy associated plasma protein A (PaPP-A) level in LGA vaginal deliveries of non-diabetic mothers.

Methods: This is a retrospective study conducted in a tertiary hospital between May 2020 and July 2022. A total of 9,184 singleton pregnancies with normal vaginal delivery between 37 and 42 weeks were reviewed. Non- diabetic patients who gave birth to LGA infants were grouped according to the presence of vaginal birth complications and compared in terms of first trimester aneuploidy screening results. Regression analysis was used to investigate the effect of variables on complications. Receiver operating characteristic (ROC) analysis was performed for the threshold PaPP-A value to predict birth complications.

Results: Of the 357 patients, 68 (19.0%) had at least one complication, remaining 289 (81.0%) had no complications. First trimester serum PaPP-A level was significantly higher in complicated group than patients without complications (20.85 ± 19.73 vs 15.18 ± 15.81, p= 0.046). First trimester NT, β-hCG and PaPP-A are significantly associated with perinatal complications in LGA vaginal deliveries. The cut-off value of first trimester PaPP-A level was 10.46 mIU/mL to predict the complications with a sensitivity of 54.4% and a specificity of 54.3%.

Conclusions: First trimester PaPP-A level may be associated with vaginal birth complications in LGA infants from non-diabetic mothers.

Key words: Pregnancy, prenatal care, placenta, labor complications, PaPP-A.

✉ * *Dr. Nergis Kender Erturk,*
Department of Obstetrics and Gynecology, Bursa Yuksek Ihtisas Training and Research Hospital, Bursa, Türkiye
E-mail: nergiskender@gmail.com
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Introduction

Infants with a birth weight greater than the 90th percentile for gestational age are defined as Large for gestational age (LGA) newborns. LGA babies are at increased risks of adverse perinatal outcomes such as instrumental vaginal delivery, shoulder dystocia, perinatal asphyxia and neonatal mortality [1]. Although the mechanisms controlling fetal weight gain and growth are not well understood, it can be mentioned that genetic, maternal, placental and intrauterine environmental factors are effective in excessive fetal growth.

Pregnancy associated plasma protein A (PaPP-A) and freeβ-human chorionic gonadotropin (β-hCG) both released from placental syncytiotrophoblasts are components of first trimester aneuploidy screening with ultrasonographic measurement of fetal nuchal

translucency (NT) thickness [2]. PaPP-A leads to increased secretion of insulin-like growth factors and thus plays a role in fetal growth [3]. High maternal serum PaPP-A in the first trimester was reported to be associated with the risk of fetal LGA [4,5]. In addition, free beta-Hcg levels have been shown to be associated with birth weight [6].

The associations of PaPP-A with birth weight and complications related to LGA have been investigated especially in diabetic pregnancies [7,8]. However, the role of these first trimester screening markers in perinatal outcomes of LGA infants from non-diabetic mothers is unclear. It is important to predict possible complications in order to improve perinatal outcomes in LGA deliveries.

Given this background, the aim of the study was to investigate the association of adverse perinatal outcomes due to macrosomia with first trimester PAPP-A level in LGA vaginal deliveries of non-diabetic mothers.

Materials and metods

This is a retrospective study conducted in a university affiliated tertiary hospital between May 2020 and July 2022. Local ethics committee approval was obtained (2011-KAEK-25 2022/10-9) and the study was carried out in accordance with the Declaration of Helsinki.

A total of 9,184 singleton pregnancies with normal vaginal delivery between 37 and 42 weeks were reviewed. Demographic data, maternal comorbidities, laboratory results, newborn data and delivery complications were obtained from electronic and manual patient files. Those who gave birth to LGA infants, those who were screened for aneuploidy in the first trimester and those whose pregnancy follow-up visits were performed in our hospital were included in the study. Those who were obese, with pre- or gestational diabetes diagnosis, those with hypertensive disorders, preterm pregnancies, small for gestational age (SGA) infants, cesarean deliveries, fetal genetic or congenital anomalies, and missing records were excluded from the study. Those with abnormal results of 75g/100 g glucose tolerance tests were defined as gestational diabetes. Birth weight was defined as SGA if it was <10th percentile, AGA if it was between 10-90th percentile, and LGA if it was >90th percentile.

A total of 357 patients were analyzed. For these patients, maternal age, gestational week, BMI, gravida, parity, time from active phase to delivery, need for induction, first trimester serum Papp-A, free β-hCG and nuchal translucency (NT) thickness values and perinatal complications were recorded.

Vacuum or forceps delivery, 3-4 perineal tears, cervical laserations, neonatal APGAR score below 7, dystocia, clavicle fracture, caput succedaneum, postpartum atony were considered as adverse perinatal outcomes. According to the records, patients who underwent the Mc roberts maneuver and suprapubic compression during delivery or clavicle fracture were defined as dystocia, and patients who needed additional uterotonics in the third stage of labor, who underwent intrauterine balloon tamponade or surgical approach were defined as postpartum atony.

Statistical analysis

SPSS 21 software (SPSS Inc Chicago,IL) program was used for statistical analysis. Normality of distribution was evaluated with the Shapiro Wilk test. Parametric data were given as mean±SD, non-parametric data as median (min-max). Student t test or Mann Whitney u test was used to compare the groups according to distribution. Categorical data were analyzed with the chi-square test. Multi-nominal logistic regression analysis was performed to evaluate

the effects of independent variables on complications. ROC analysis was performed to find out the cut-off value of first trimester PaPP-A level to predict the complications of LGA vaginal deliveries. p <0.05 was considered as statistically significant.

Results

The mean age of the patients was 27.89±5.49 and ranged between 17-45 years. The mean birth weight of infants was 4010.20±199.42 and ranged between 3700-5315 gr. The mean gestational week was 39.08±1.18 and ranged between 37-42 weeks. Of the 357 patients, 68 (19.0%) had at least one complication, remaining 289 (81.0%) had no complications. Demographic and clinical characteristics of the groups were given in Table 1. First trimester serum PaPP-A level was significantly higher in complicated group than patients without complications (20.85 ± 19.73 vs 15.18 ± 15.81, p= 0.046) (Table 1).

The overall complication rate of LGA vaginal deliveries was 19.0%. The rates of each complications were given in Table 2. Vacuum was used in all eight patients who delivered operatively. Among patients with postpartum atony intrauterine balloon tamponed was applied to seven subjects, hysterectomy was performed in one patient.

Table 1. Demographic and clinical features of the groups.

Parameters	**Patients Wo complications (n=289)**	**Patients w complications (n=68)**	***p***
Age (y)	27.86 ±5.62	28.00 ±4.95	*0.618*
Gravida*	3 (1-12)	3 (1-7)	*0.354*
Parity*	2 (0-10)	2 (0-6)	*0.152*
BMI (kg/m2)	24.00 ±2.58	24.15 ±2.95	*0.713*
Gestational week of birth (w)	39.04 ±1.18	39.29 ±1.15	*0.093*
Induction need, n(%)	201 (69.6)	55 (80.9)	*0.062[a]*
Labor length (h)	6.00 ±5.13	5.60 ±4.26	*0.893*
Birth Weight (gr)	4004.69 ±200.24	4033.61 ±195.65	*0.259*
APGAR score 1st minute*	9 (5-9)	9 (5-9)	*0.219*
First trimester screening tests			
Nuchal translucency (mm)	1.30 ±0.36	1.39 ±0.29	*0.054*
PaPP-A (mIU/mL)	15.18 ±15.81	20.85 ±19.73	*0.046*
Free B-hCG (ng/mL)	79.41 ±65.69	65.57 ±44.94	*0.157*

Wo: without, w: with, y: years, BMI: body mass index, w: weeks, h: hours. Values are given as mean ±SD and Mann Whitney U test was performed, unless otherwise mentioned. A p value <0.05 was considered as significant.
**Values are given median (min-max). [a] Chi square test was performed.*

Table 2. The rates of each perinatal complication in total patients (n=357).

Complications	n (%)
Dystocia	31 (8.7)
Operative delivery	8 (2.2)
3-4 degree perineal tear	7(2.0)
Cervical laceration	12 (3.4)
Postpartum atony	13 (3.6)
Clavicle fracture	6 (1.7)
Brachial plexus injury	2 (0.6)
Caput succedaneum	3 (0.8)
1st min APGAR score < 7	4 (1.1)

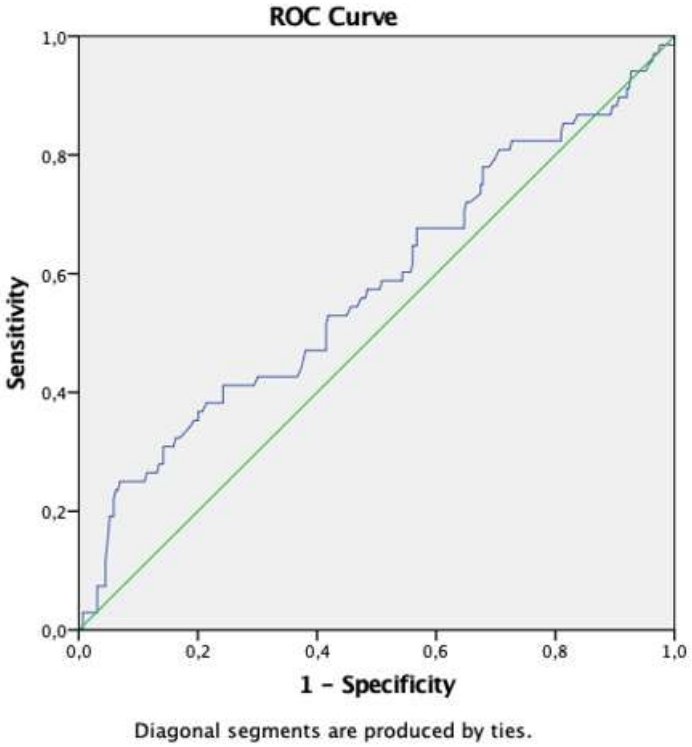

Figure 1. Receiver operating characteristic (ROC) curve of first trimester Pregnancy associated plasma protein A (PaPP-A) for the the prediction of birth complications. The estimate of the area under curve (AUC) and its 95 % confidence interval is shown. Cut-off value of PaPP-A was 10.46 mIU/mL (sensitivity 54.4% and specificity 54.3%) for prediction of LGA birth compliactions. (AUC: 0.578; 95% CI (0.497- 0.658), p<0.05).

The Spearman correlation coefficients between first trimester markers (PaPP-A and β-hCG) and birth weight were -0.022 and 0.096 respectively (p=0.685 and p=0.71, respectively). According to logistic regression analysis, first trimester NT, β-hCG and PaPP-A are significantly associated with perinatal complications in LGA vaginal deliveries (p = 0.019, R2 =0.04). The odds ratio of PaPP-A was 1.016, 95% CI (1.001-1.031) (p=0.035). According to the ROC analysis, the cut-off value of first trimester PaPP-A level was 10.46 mIU/mL to predict the complications in LGA vaginal deliveries with a sensitivity of 54.4% and a specificity of 54.3% (Area under curve (AUC): 0.578; 95% CI (0.497- 0.658), p=0.046) (Figure 1).

Discussion

In this study, we examined the relationship between perinatal complications that may occur in LGA vaginal deliveries and first trimester aneuploidy screening tests. First trimester NT, β-hCG and PaPP-A were associated with perinatal complications. In the complicated group, the level of PaPP-A was significantly higher than those without complications.In addition, a PaPP-a level above 10.46 mIU/mL was calculated to predict the risk of complications in LGA-vaginal deliveries.

The prevalence of LGA fetuses, which is important in prenatal care, is increasing. Newborns with a birth weight above the 90th percentile for gestational age are defined as LGA (9). The risks of maternal and perinatal morbidity and even mortality are increased in pregnancies with LGA fetuses (1). Birth weight can be affected by many maternal factors such as ethnicity, age, body mass index, nutritional status

and medical conditions (10). In addition to these, placental function in early pregnancy may also be associated with birth weight. PaPP-A and hCG are placenta-derived factors. Many reports have been published showing that adverse perinatal outcomes may be associated with maternal β-hCG and PaPP-A levels measured in the first trimester of pregnancy (4,6, 11, 12). However, the relationship between these markers and perinatal complications in LGA babies in healthy pregnancies is not clear. To the best of our knowledge, this study is the first report in the literature examining this relationship.

According to Beneventi et al, there was a positive correlation between PaPP-A and birth weight in non-diabetic pregnancies (13). Kapustin et al reported that first trimester screening tests could not be used to predict the complications in diabetic pregnancies, they found no link between PaPP-A or hCG and birth weight (7). It could be thought that PaPP-A levels may be lower in diabetic pregnancies than the healthy population due to the impaired placental function. Our subjects were healthy and we could not detect a significant association between PaPP-A or hCG and birth weight. However, first trimester PaPP-A level was analyzed to be associated with complications in LGA deliveries.

PAPP-A is a metalloproteinase that helps release insulin growth factor (IGF) at the cellular level, thereby contributing to cell growth (14). In the literature, the relationship of first trimester PAPP-A level with the development of maternal metabolic diseases during pregnancy as well as its possible role in predicting long-term maternal complications after pregnancy has been reviewed (15). In a recent analysis, low PAPP-A serum levels in the first trimester of pregnancy were reported to be associated with infant short stature and the development of maternal diabetes mellitus in the mother later in life (15).

According to the "Barker hypothesis", the placenta has a very important role in fetal programming, and the development of diseases that may occur in later life may be related to intrauterine life. Based on this hypothesis, we investigated the predictability of shoulder dystocia, an unavoidable complication of labor, and other complications that may occur in LGA deliveries. As a result, we determined that markers of placental origin measured in the first trimester may be associated with these conditions. It can be thought that birth complications are affected by many maternal and environmental factors. Therefore, maternal systemic diseases, obesity, fetal anomalies were excluded in this study. There was no difference between patients with and without complications in terms of demographic data and labor follow-up data. These are all strengths of the study. In addition to the fact that the delivery induction protocols are not standardized for every patient, the relatively small patient population and the inability to clearly access data on cesarean section with indications of acute fetal distress due to retrospective data can be stated as limitations.

Conclusions

In conclusion, first trimester aneuploidy markers, particularly PaPP-A, may be associated with fetal development and thus vaginal birth complications. In the presence of an estimated large for gestational age fetus, the PaPP-A level measured in the first 3 months of pregnancy can give the clinician an idea about the possibility of birth complications. However, prospective studies are needed for further interpretation on the subject.

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Ethical statement*: Local ethics committee approval was obtained (2011-KAEK-25 2022/10-9) and the study was carried out in accordance with the Declaration of Helsinki.*

References

[1]Xu H, Simonet F, Luo ZC. Optimal birth weight percentile cut-offs in defining small- or large-for-gestational-age. Acta Paediatr. 2010; 99(4):550-55.

[2]Krantz D, Goetzl L, Simpson JL, 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;191:1452–58.

[3]Lawrence JB, Oxvig C, Overgaard MT, 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 U S A. 1999;96(6):3149-53.

[4]Tul N, Pusenjak S, Osredkar J, et al. Predicting complications of pregnancy with first-trimestermaternal serum free-beta-hCG, PAPP-A and inhibin-A. Prenat Diagn. 2003;23: 990 – 96.

[5]Canini S, Prefumo F, Pastorino D, et al. Association between birth weight and first-trimester free beta-human chorionic gonadotropin and pregnancy-associated plasma protein A. Fertil Steril. 2008;89(1):174-78.

[6]Poon LC, Karagiannis G, Stratieva V et al. First-trimester prediction of macrosomia. Fetal Diagn Ther. 2011;29(2):139-47.

[7]Kapustin RV, Kascheeva TK, Alekseenkova EN, et al. 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):1113-19.

[8]Savvidou MD, Syngelaki A, Muhaisen M, et al. First trimester maternal serum free β-human chorionic gonadotropin and pregnancy-associated plasma protein A in pregnancies complicated by diabetes mellitus. BJOG. 2012;119(4):410-16.

[9]Alexander, G. R., Himes, J. H., Kaufman, R. B.et al. United States national reference for fetal growth. Obstet Gynecol. 1996; 87(2): 163–68.

[10]Wen SW, Goldenberg RL, Cutter GR, et al. Smoking, maternal age, fetal growth, and gestational age at delivery. American journal of obstetrics and gynecology, 1990; 162(1), 53–58.

[11]Donovan BM, Nidey NL, Jasper EA, et al. First trimester prenatal screening biomarkers and gestational diabetes mellitus: A

systematic review and meta-analysis. PloS One. 2018; 13(7): e0201319.

[12] Pilalis A, Souka AP, Antsaklis P, et al. Screening for pre-eclampsia and fetal growth restriction by uterine artery Doppler and PAPP-A at 11-14 weeks' gestation. Ultrasound Obstet Gynecol. 2007;29(2):135-40.

[13] Beneventi F, Simonetta M, Lovati E, et al. First trimester pregnancy-associated plasma protein-A in pregnancies complicated by subsequent gestational diabetes. Prenat Diagn. 2011;31(6):523-28.

[14] Monget P, Oxvig C. PAPP-A and the IGF system. Ann Endocrinol (Paris). 2016;77(2):90-96.

[15] Fruscalzo A, Cividino A, Rossetti E, et al. First trimester PAPP-A serum levels and long-term metabolic outcome of mothers and their offspring. Sci Rep. 2020;10(1):5131.