ASSOCIATION BETWEEN FIRST-TRIMESTER ANEUPLOIDY MARKERS AND BIRTH WEIGHT

İLK TRİMESTER ANÖPLOİDİ BELİRTEÇLERİ VE DOĞUM KİLOSU ARASI İLİŞKİ

FIRST-TRIMESTER SCREENING AND BIRTH WEIGHT

Demet Kokanalı, Buğra Coşkun, Mahmut Kuntay Kokanalı, Yasemin Taşçı
Zekai Tahir Burak Woman's Health Education and Research Hospital, Ankara, Turkey

Öz

Amaç: İlk trimester ultrasonografik ve biyokimyasal anöploidi belirteçleri ile doğum kilosu arasında ilişki olup olmadığını ve bu belirteçlerin gebelik yaşına göre küçük (SGA) ve büyük (LGA) yenidoğanları öngörmedeki rolünü belirlemeyi amaçladık. Gereç ve Yöntem: Nukal translusensi (NT) kalınlığı, anne serum serbest beta-human koryonik gonadotropin (fβ-hCG) ve gebelikle ilişkili plazma protein-A (PAPP-A) ölçümü ile ilk trimester anöploidi taraması yapılan, tekil gebeliğe sahip 1356 kadın çalışmaya dahil edildi. Yenidoğanları, doğum ağırlığı ≤ 10. persentil ise SGA ve ≥90. persentil ise LGA olarak tanımlandı. Bulgular: Serum PAPP-A düzeyi anlamlı ancak zayıf şekilde doğum kilosu ile ilşkili iken fβ-hCG düzeyi ve NT ölçümü ilişkili değildi. <0.795 MoM luk PAPP-A değeri 73.9%'luk duyarlılık, 63.1%'lik özgüllük, 18.5%'lik PPV, 95.5%'lik NPV ve 64.2%'lik doğruluk ile SGA yenidoğanı öngördü. Diğer taraftan, PAPP-A için 1.005 MoM'luk eşik değer, LGA yenidoğanı öngörmede 61.0%'lık duyarlılığa, 62.7%'lik özgüllüğe, 26.6%'lik PPVye, 87.9%'lik NPVye ve 62.4%'lik doğruluğa sahipti. Tartışma: İlk trimester PAPP-A düzeyi doğum kilosunu öngörmede katkı sağlayabilir. Ancak düşük duyarlılıktan dolayı, SGA ya da LGA yenidoğanları öngörmede klinik uygulamada uygun bir tarama testi değildir.

Anahtar Kelimeler

Doğum Ağırlığı; Serbest Beta-Human Koryonik Gonadotropin; Gebelikle İlişkili Plazma Protein-A

Abstract

Aim: We aimed to investigate whether first trimester ultrasound and biochemical markers of aneuploidy were related to birth weight and to determine the predictive role of these parameters for small for gestational age (SGA) and large for gestational age (LGA) newborns. Material and Method: 1356 women with singleton pregnancy who had undergone first-trimester aneuploidy screening by nuchal translucency (NT) thickness, maternal serum free beta-human chorionic gonadotropin (fβ-hCG), and pregnancy-associated plasma protein-A (PAPP-A) were retrospectively included. Newborns with a birth weight of ≤ 10th percentile were defined as SGA and ≥90th percentile as LGA, respectively. Results: Serum PAPP-A level was significantly but weakly (r=0.168; p=0.011) correlated to birth weight whereas maternal serum fβ-hCG levels and NT measurements were not significantly correlated. A single PAPP-A level of <0.795 MoM predicted SGA newborn with a sensitivity of 73.9%, specificity of 63.1%, PPV of 18.5%, NPV of 95.5%, and accuracy of 64.2%. On the other hand, a PAPP-A level of 1.005 MoM was identified as the optimal cut-off point for the prediction of LGA newborn with a sensitivity of 61.0%, specificity of 62.7%, PPV of 26.6%, NPV of 87.9%, and accuracy of 62.4%. Discussion: First-trimester PAPP-A levels may contribute to the prediction of birth weight. However, due to low sensitivity, it is not a clinically relevant screening test for prediction of SGA or LGA newborn.

Keywords

Birth Weight; Free Beta-Human Chorionic Gonadotropin; Pregnancy-Associated Plasma Protein-A

DOI: 10.4328/JCAM.4894 Received: 25.12.2017 Accepted: 17.03.2017 Printed: 01.04.2017 J Clin Anal Med 2017;8(suppl 2): 125-8
Corresponding Author: Demet Kokanalı, Güzeltepe Mah. Halide Nusret Zorlutuna Sok, No: 6/4, Cankaya, Ankara, Türkiye.
GSM: +905056737924 F.: +90 3123124931 E-Mail: d.ozturkkan@yahoo.com.tr

Introduction

There are many factors regulating birth weight, including gestational age at delivery, maternal age, body mass index (BMI), parity, ethnicity, habits (smoking, etc.), and medical (diabetes mellitus, etc.) conditions [1-3]. Abnormal fetal growth may increase neonatal morbidity and mortality. The risks of stillbirth, chronic lung disease, necrotizing enterocolitis, and neurodevelopmental problems in childhood, as well as hypertension, vascular disease, and diabetes in adulthood increase in small for gestational age (SGA) newborns (defined as less than 10th percentile birth weight) [4,5]. Similarly, large for gestational age (LGA) newborns (defined as greater than 90th percentile birth weight) have an increased risk of delivery complications such as shoulder dystocia, other birth injuries, and cesarean delivery, as well as obesity, cardiovascular disease, and metabolic complications in adulthood [6,7]. Early determination of fetal growth abnormalities may be beneficial for obstetricians in order to take essensial precautions. However, today's screening modalities are limited by varying sensitivities and high false positive rates. Thus early prediction of fetal growth abnormalities is still challenging.

Placental volume and maternal biochemistry reflecting placental function at 11-13 weeks of gestation have been studied in order to determine whether they have any predictive role for birth weight abnormalities [8-10]. But the results are highly variable and controversial.

In our study, we aimed to investigate whether first trimester biochemical parameters used to screen for Down syndrome were related to birth weight in a Turkish population and to determine the prediction accuracy of these parameters for SGA and LGA newborns.

Material and Method

This retrospective study was approved by the instituional review board of Zekai Tahir Burak Woman's Health Education and Research Hospital, a tertiary referral research hospital located in the central region of Turkey. Pregnant women who had undergone first-trimester aneuploidy screening by nuchal translucency (NT) thickness, maternal serum free beta-human chorionic gonadotropin (fβ-hCG), and pregnancy-associated plasma protein-A (PAPP-A) between January 2014 and January 2015 at the Obstetrics Department of the hospital participated. Women who had multiple gestation pregnancy, preexisting diabetes, detected fetal chromosomal or major structural defects, miscarriage or fetal death before 24 weeks, diagnosed gestational diabetes, or intrauterine growth restriction in their follow-up and those with insufficient data were excluded.

All data were collected from hospital records. Between the 11th and 14th week of gestation, transabdominal or transvaginal (if necessary) ultrasonographic assessment of all pregnancies was performed for the measurements of fetal crown-rump length (CRL). When a CRL between 45 and 84 mm was detected, NT thicknesses were also measured by trained obstetricians. Furthermore, at that time maternal serum PAPP-A and fβ-hCG levels were measured by automatic fluorometric immunoassays. Results were reported as multiples of the median (MoM) adjusted for gestational age, maternal weight, and smoking status. Smokers were defined as those who had smoked at a continuous rate of at least one cigarette per day, starting at conception or earlier.

At delivery, birth weight was converted into a percentile for gestational age at delivery and by gender according to the Turkish population data [11]. Gestational ages at delivery were adjusted using the gestational age and CRL obtained during NT measurement. Newborns with a birth weight of ≤ 10th percentile were identified as SGA, newborns with a birth weight ≥ 90th percentile as LGA, and those in the 10th-90th percentile as average for gestational age (AGA).

Statistical analysis was performed using the using SPSS software version 17.0 (SPSS Inc., Chicago, IL). Kolmogorov–Smirnov test was performed to determine whether the data were sampled from a normal distribution. Continuous variables with normal distribution are presented as mean±standard deviation. For these variables, the difference between the groups was evaluated by one-way analysis of variance test. When the p value from the variance analysis was statistically significant, post-hoc Tukey test was used to determine which group differed from which others. Categorical variables were analyzed with the Chi-square test. Receiver-operating characteristic (ROC) curves were constructed to calculate the sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy for different measures of maternal serum PAPP-A levels in predicting SGA and LGA newborns. Correlations between birth weight and first trimester markers were estimated using the Spearman's correlation coefficient. $p<0.05$ was considered statistically significant.

Results

For this study, 1558 singleton pregnancies with a live fetus who had undergone first trimester aneuploidy screening were reviewed. Because of miscarriage and fetal death before 24 weeks of gestation, 45 women were excluded. 33 women were excluded because of detected fetal chromosomal or major structural defects. 124 women were excluded due to insufficient data. The final study population included 1356 screened singleton pregnancies with their live born infants. Of these newborns, 138 (10.2%) were SGA, 246 (18.1%) were LGA, and 972 (71.7%) were AGA.

The characteristics of SGA, LGA, and AGA groups are listed in Table 1. In the SGA group, maternal serum PAPP-A level and birth weight were significantly lower than the other groups. In contrast, the LGA group had statistically higher serum PAPP-A levels and birth weights than the AGA group. Maternal serum fβ-hCG level was lower in the SGA group than the AGA and LGA groups, but the differences between the groups were not statistically significant. There was also no difference between the groups with regard to other variables listed in Table 1.

The correlations between the first trimester markers and birth weight are shown in Table 2. Maternal serum PAPP-A level was significantly but weakly correlated to birth weight, whereas maternal serum fβ-hCG levels, NT, and CRL measurements were not significantly correlated.

ROC curve for maternal serum PAPP-A level in predicting SGA newborn is displayed in Figure 1. The curve constructed for measured PAPP-A level was above the 45° line, showing that there was a significant relationship between these two vari-

Table 1. Characteristics of the groups

	SGA group (n=138)	AGA group (n=972)	LGA group (n=246)	P
Maternal age (years)	27.13±7.09	27.80±5.73	27.88±6.25	0.871
Maternal weight at screening (kg)	65.08±6.34	64.51±5.48	66.65±6.78	0.365
Maternal height (cm)	160.30±3.40	159.86±3.64	160.32±2.98	0.885
Smoking	20 (14.4)	119 (12.2)	29 (11.8)	0.356
Gestational age at screening (week)	12.18±0.33	12.26±0.56	12.44±0.30	0.405
Weight gain during pregnancy (kg)	11.55±1.88	11.00±1.38	11.32±1.16	0.505
CRL (mm)	58.17±7.58	58.70±9.43	61.56±10.20	0.194
NT (MoM)	0.87 (0.47-1.69)	0.83 (0.48-1.57)	0.84 (0.41-1.30)	0.855
PAPP-A levels (MoM)	0.64 (0.12-0.97)	0.94 (0.14-3.18)	1.16 (0.23-3.10)	<0.001
fβ-hCG levels (Mom)	0.71 (0.20-2.10)	0.96 (0.18-4.21)	0.97 (0.11-4.33)	0.087
Gestational age at delivery (week)	39.0 (35.5-41.2)	39.2 (35.5-42.0)	39.4 (37.3-41.5)	0.163
Birth weight (gram)	2566.52± 204.71	3357.78± 313.09	4089.75±199.49	<0.001
Male newborn gender	67 (48.6)	488 (50.2)	123 (50.0)	0.686

Values were given as mean±standard deviation; median (minimum-maximum) or number (%)
SGA: Small for gestational age; AGA: Appropriate for gestational age; LGA: Large for gestational age; CRL: Crown-rump length; NT: nuchal translucency; fβ-hCG:free beta-human chorionic gonadotropin; PAPP-A: Pregnancy associated plasma protein-A ; Mom: Multiples of the expected median
p<0.05 was considered statistically significant.

Table 2. Correlation between birth weight and first trimester markers

	r	p
PAPP-A levels (Mom)	0.168	0.011
fβ-hCG levels (Mom)	0.101	0.129
NT (Mom)	0.034	0.613
CRL (mm)	0.084	0.210

PAPP-A: pregnancy associated plasma protein-A; fβ-hCG: free beta human chorionic gonadotropin; NT: nuchal tranclucency; CRL: Crown-rump length; MoM: multiples of the expected median
r: Spearman's coefficient
p<0.05 was considered significant

ables (area under the curve 0.752; standard error 0.040; 95% confidence interval 0.673–0.830; p<0.001). The best cut-off value of maternal serum PAPP-A level for the prediction of SGA newborn was 0.795 MoM with a sensitivity of 73.9%, specificity of 63.1%, PPV of 18.5%, NPV of 95.5%, and accuracy of 64.2% (Table 3).

Figure 2 shows the ROC curve for maternal serum PAPP-A level in predicting an LGA newborn. The curve constructed for PAPP-A level was above the 45° line, showing that there was a weak but significant relationship between these two variables (area under the curve 0.611; standard error 0.054; 95%, confidence interval 0.505–0.717; p=0.026). The best cut-off value of maternal serum PAPP-A level for the prediction of LGA newborn was 1.005 MoM with a sensitivity of 61.0%, specificity of 62.7%, PPV of 26.6%, NPV of 87.9%, and accuracy of 62.4% (Table 3).

Table 3. Cut-off points for PAPP-A levels in predicting SGA and LGA newborns

	Cut off PAPP-A (MoM)	Sensitivity (%)	Spesificity (%)	PPV (%)	NPV (%)	Accuracy (%)
For SGA newborn	0.795	73.9	63.1	18.5	95.5	64.2
For LGA newborn	1.005	61.0	62.7	26.6	87.9	62.4

SGA: Small for gestational age; LGA: Large for gestational age; PAPP-A: Pregnancy associated plasma protein-A ; Mom: Multiples of the expected median; PPV: Positive predictive value; NPV: Negative predictive value

Discussion

In our retrospective cohort study, maternal serum PAPP-A levels measured by the first trimester aneuploidy screening was weakly associated with birth weight. ,Pregnant women with low PAPP-A levels were more likely to have an SGA newborn while women with high levels were more likely to have an LGA newborn. However, there were no relationships found between maternal serum fβ-hCG level, ultrasonographic measurement of NT thickness, and birth weight.

PAPP-A is a protease in glycoprotein structure, produced by syncytiotrophoblast during pregnancy; its concentration in the maternal circulation increases as pregnancy progresses [12]. By means of its proteolytic activity, PAPP-A acts as a regulatory protein in the insulin-like growth factor system (IGF) [13]. It has been suggested that the IGF system modulates trophoblast invasion and cell growth [14]. Therefore PAPP-A appears to be important for placental formation and regulation of fetal growth.

In the literature, it has been consistently suggested that low PAPP-A level is a reliable predictor for SGA delivery [8,10,15]. However, studies investigating the association between high PAPP-A levels and birth weight have reported conflicting results. Namely, some reports have indicated that there is a relationship between high PAPP-A level and LGA newborn [9,15], while others have found no association [16,17]. As mentioned above, our results revealed that first trimester PAPP-A level is weakly and positively associated with birth weight in uncomplicated pregnancies. In our study, a single PAPP-A level of <0.795 MoM predicted SGA newborn with a sensitivity of 73.9%, specificity of 63.1%, PPV of 18.5%, NPV of 95.5%, and an accuracy of 64.2%. This high NPV with relatively low sensitivity reflects that measurement of PAPP-A level during the first trimester is beneficial in determining women who are unlikely to deliver SGA newborns. On the other hand, a PAPP-A level of 1.005 MoM was identified as the optimal cut-off point for the prediction of an LGA newborn with a sensitivity of 61.0%, specificity of 62.7%, PPV of 26.6%, NPV of 87.9%, and accuracy of 62.4%. Similarly, this cut-off point with high NPV and low sensitivity is an effective indicator of women who are unlikely to deliver an LGA newborn. The overlap in PAPP-A levels between the AGA group [0.94 (0.14-3.18) MoM] and the LGA group [1.16 (0.23-3.10) MoM] might decrease the sensitivity of maternal serum PAPP-A level in predicting a LGA newborn.

Plasma filtrate from maternal circulation is the main nutrition source of the embryo during the mid-first trimester [18]. As serum PAPP-A level increases, IGF-binding protein-3 levels decreases [13]. IGF-binding protein-3 levels are inversely asssociated with capillary permeability [19]. Thus, due to the increase

of maternal serum PAPP-A level, capillary permeability increases at mid-first trimester, enhancing the plasma filtrate taken by the embryo. This could result in an increase of fetal growth. However, this association still needs to be proven. Some toxic agents such as tobacco smoke might damage the blood flow to the placenta resulting in some placental necrosis areas occurring. This may result in insufficient PAPP-A expression and IGF axis disorders, reduced active transport of essential nutrients to the fetus, and may lead to fetal growth failure. In our study, smoking rates in the groups were statistically similar; we think this eliminates bias about the impact of smoking when comparing PAPP-A levels between the groups.

In obstetrical practice, the predictive role of first trimester maternal serum fβ-hCG level for birth weight is still controversial. Several studies reported a significant relationship between fβ-hCG and birth weight [3,20], whereas others demonstrated none [21,22], possibly because of different variables format (IU/ml, MoM, or percentile). Our findings did not confirm the relationship between these two parameters. Thus, we believe that further studies are needed to clarify this topic.

In our study, we observed no relationship between NT thickness and birth weight, similar to some previous studies [1,3,23] and contrary to others [16,24,25]. We speculate that there may be several factors that affect the NT in a euploid fetus—genetic, structural, and developmental—that cannot be detected during the antenatal period. Therefore, this topic remains to be explained with additional and larger prospective studies.

This study has some limitations. The main limitation is its retrospective design. Given this study design, some clinical details including placental volume, placental sufficiency, and pathological investigation of placenta were not included in the study. This study also has a relatively small study population. And lastly, this study included data from a single center in Turkey, so cannot be generalized to other populations.

In conclusion, among the parameters used for first-trimester aneuploidies screening, only maternal serum PAPP-A levels may contribute to the prediction of birth weight in uncomplicated pregnancies. However, due to low sensitivity, this parameter is not a clinically relevant screening test for prediction of pregnancies at risk of SGA or LGA delivery. Nevertheless, further prospective studies are needed to justify our results and to suggest more definitive recommendations.

Competing interests

The authors declare that they have no competing interests.

References

1. Poon LC, Karagiannis G, Staboulidou I, Shafiei A, Nicolaides KH. Reference range of birth weight with gestation and first-trimester prediction of small-for-gestation neonates. Prenat Diagn 2011;31:58–65.
2. Goetzinger KR, Singla A, Gerkowicz S, Dicke JM, Gray DL, Odibo AO. The efficiency of first-trimester serum analytes and maternal characteristics in predicting fetal growth disorders. Am J Obstet Gynecol 2009;201:412, e1–e6.
3. Plasencia W, González Dávila E, Tetilla V, Padrón Pérez E, García Hernández JA, González González NL. First-trimester screening for large-for-gestational-age infants. Ultrasound Obstet Gynecol 2012;39:389–95.
4. Pallotto EK, Kilbride HW. Perinatal outcome and later implications of intrauterine growth restriction. Clin Obstet Gynecol 2006;49:257–69.
5. de Bie HM, Oostrom KJ, Delemarre-van de Waal HA. Brain development, intelligence and cognitive outcome in children born small for gestational age. Horm Res Paediatr 2010;73:6–14.
6. Berard J, Dufour P, Vinatier D, Subtil D, Vanderstichèle S, Monnier JC et al. Fetal macrosomia: risk factors and outcome. A study of the outcome concerning 100 cases >4500 g. Eur J Obstet Gynecol Reprod Biol 1998;77:51–9.
7. Walsh JM, McAuliffe FM. Prediction and prevention of the macrosomic fetus. Eur J Obstet Gynecol Reprod Biol 2012;162:125–30.
8. Boucoiran I, Djemli A, Taillefer C, Rypens F, Delvin E, Audibert F. First-trimester prediction of birth weight. Am J Perinatol 2013;30:665–72.
9. Plasencia W, Akolekar R, Dagklis T, Veduta A, Nicolaides KH. Placental volume at 11–13 weeks' gestation in the prediction of birth weight percentile. Fetal Diagnosis and Therapy 2011;1:23–8.
10. 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.
11. Salihoglu O, Karatekin G, Uslu S, Can E, Baksu B, Nuhoglu A. New intrauterine growth percentiles: a hospital-based study in Istanbul, Turkey. JPMA 2012;62: 1070-4.
12. Kirkegaard I, Uldbjerg N, Oxvig C. Biology of pregnancy-associated plasma protein-A in relation to prenatal diagnostics: an overview. Acta Obstet Gynecol Scand 2010;89:1118–25.
13. Boldt HB, Conover CA. Pregnancy-associated plasma protein-A (PAPP-A): a local regulator of IGF bioavailability through cleavage of IGFBPs. Growth Horm IGF Res 2007;17:10–8.
14. Irwin JC, Suen LF, Martina NA, Mark SP, Giudice LC. Role of the IGF system in trophoblast invasion and pre-eclampsia. Hum Reprod 1999;14:90–6.
15. Peterson SE, Simhan HN. First-trimester pregnancy-associated plasma protein A and subsequent abnormalities of fetal growth. Am J Obstet Gynecol 2008;198:e43–5.
16. 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;19:1446–51.
17. Giudice I, Benintende G, Di Nicolo AM, Mangiameli D, Carrara G, Randazzo C, et al. Correlation of neonatal weight with maternal serum levels of pregnancy-associated plasma protein-A during the first trimester of pregnancy: a retrospective study. J Perinat Med 2015;43: 227–32.
18. Burton GJ, Hempstock J, Jauniaux E. Nutrition of the human fetus during the first trimester—a review. Placenta 2001;22:70–7.
19. Brausewetter F, Jehle PM, JungMF, Boehm BO, Brueckel J, Hombach V, et al. Microvascular permeability is increased in both types of diabetes and correlates differentially with serum levels of insulin-like growth factor I (IGF-I) and vascular endothelial growth factor (VEGF). HormMetab Res 2001;33:713–20.
20. Cignini P, Maggio Savasta L, Gulino FA, Vitale SG, Mangiafico L, et al. Predictive value of pregnancy-associated plasma protein-A (PAPP-A) and free beta-hCG on fetal growth restriction: results of a prospective study. Arch Gynecol Obstet. 2016;293:1227-33.
21. 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.
22. Montanari L, Alfei A, Albonico G, Moratti R, Arossa A, Beneventi F, et al. The impact of first-trimester serum free beta-human chorionic gonadotropin and pregnancyassociated plasma protein A on the diagnosis of fetal growth restriction and small for gestational age infant. Fetal Diagn Ther 2009;25:130–5.
23. Poon LC, Karagiannis G, Stratieva V, Syngelaki A, Nicolaides KH. First-trimester prediction of macrosomia. Fetal Diagn Ther 2011; 29:139–47.
24. 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.
25. Pihl K, Sørensen TL, Nørgaard-Pedersen B, Larsen SO, Nguyen TH, Krebs L, et al. First-trimester combined screening for Down syndrome: prediction of low birth weight, small for gestational age and pre-term delivery in a cohort of non-selected women. Prenat Diagn. 2008;28:247-53.

How to cite this article:
Kokanalı D, Coşkun B, Kokanalı MK, Taşçı Y. Association Between First-Trimester Aneuploidy Markers and Birth Weight. J Clin Anal Med 2017;8(suppl 2): 125-8.