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First trimester maternal serum PAPP-A levels and macrosomia in nondiabetic mothers

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Aim: To determine whether or not there is a relationship between first-trimester maternal serum pregnancy-associated placental protein (PAPP-A) levels and fetal macrosomia in nondiabetic mothers.

Materials and methods: In this study, 63 consecutive term macrosomic neonates (Group 1) (birth weight ≥ 4000 g) and 100 consecutive appropriate-for-gestational-age (AGA) term neonates (Group 2) were included. Transabdominal ultrasound examinations were performed to diagnose any major fetal defects and to measure crown-rump length (CRL) and fetal nuchal translucency (NT) thickness. Blood samples were drawn from each woman in order to obtain fasting blood glucose, PAPP-A, and free beta-human chorionic gonadotropin (beta-hCG) levels. Ultrasound measurements of the fetal biparietal diameter, abdominal circumference, and femur length were obtained at 29-34 weeks of gestation.

Results: The two groups were similar with respect to maternal age, parity, and gestational age in the first trimester. There were no significant differences between the groups in terms of the mean plasma levels of PAPP-A, free beta-HCG (as MoM values), mean CRL, and NT measurements. First-trimester PAPP-A levels were not correlated with birth weight (r = –0.116, P = 0.146), maternal age (r = 0.137, P = 0.089), maternal body mass index (BMI) in the first trimester (r = –0.037, P = 0.641) or at delivery (r = 0.042, P = 0.620), fasting blood glucose in the first trimester (r = –0.019, P = 0.816), macrosomia (r = –0.092, P = 0.249), or the occurrence of male sex (r = –0.074, P = 0.358) by the Pearson and Spearman correlations. In addition, first-trimester PAPP-A levels were not correlated with ultrasonographic measurements at 29-34 weeks of gestation.

Conclusion: Although PAPP-A may promote fetal growth and development through metabolic and differentiation pathways, it seems that there is no relationship between PAPP-A levels and macrosomia.

Key words: PAPP-A, macrosomia, first-trimester screening

Diyabeti olmayan annelerde gebeliğin ilk üç ayında maternal serum PAPP-A düzeyleri ve makrozomi

Amaç: Bu çalışmadaki amacımız gebeliğin ilk üç ayındaki maternal serum PAPP-A (gebelikle ilişkili plasental protein) ve makrozomi arasında ilişkinin olup olmadığını araştırmaktır.

Yöntem ve gereç: Termde doğan 63 makrozomik bebek (doğum kiloları ≥ 4000 g) (Grup 1) ve 100 normal kiloya sahip bebek (Grup 2) çalışmaya alındı. Fetal major anomalilerin varlığı, baş-popo mesafesi ve ense kalınlıkları ölçümü için transabdominal ultrasonografi yapıldı. Her kadından kanda açlık kan şekeri, PAPP-A ve serbest beta-hCG düzeyleri bakıldı. Gebeliğin 29- 34. haftalarında biparietal çap, abdominal çevre ve femur ölçümleri elde edildi.

Bulgular: İki grup arasında anne yaşı, parite ve ilk üç aydaki ultrasonografik gebelik yaşı bakımından fark yoktu. Gruplar arasında maternal serum PAPP-A, serbest beta-hCG düzeyleri ile fetal baş-popo mesafesi ve ense kalınlıkları ölçümü yönünden fark izlenmedi. Pearson ve Spearman korelasyon testlerinde; birinci trimester PAPP-A düzeyleri doğum kilosu (r = –0,116, P = 0,146), maternal yaş (r = 0,137, P = 0,089), annenin birinci trimesterde (r = –0,037, P =

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0,641) ve doğumda (r = 0,042, P = 0,620) vücut kitle indeksi, birinci trimesterde açlık kan glukozu (r = –0,019, P = 0,816) makrozomi (r = –0,092, P = 0,249) ve erkek cinsiyet (r = –0,074, P = 0,358) ile ilişkili bulunmadı. Ek olarak; birinci trimester PAPP-A düzeyleri gebeliğin 29-34. haftalarındaki ultrasonografi ölçümleri ile de korelasyon göstermedi.

Sonuç: PAPP-A fetal büyüme ve gelişmeyi metabolik ve farklılaşmayı içeren yollar üzerinden arttırsa da, PAPP-A düzeyleri ve fetal makrozomi arasında bir ilişki yok gibi görünmektedir.

Anahtar sözcükler: PAPP-A, makrozomi, ilk üç ay tarama

Introduction

Pregnancy-associated placental protein A (PAPP-A), a placental hormone that increases in the maternal circulation throughout human pregnancy, has long been recognized as a useful first-trimester marker for Down's syndrome (1). PAPP-A exhibits insulin-like growth factor binding protein 4 (IGFBP-4) protease activity and it regulates the bioavailability of IGF-II in the local environment (2). Low levels of PAPP-A are associated with high levels of IGFBP-4 and, consequently, with low levels of free IGF-II (3). IGF-II regulates fetal growth by controlling the uptake of glucose and amino acids in cultured trophoblasts. It also plays a significant role in the autocrine and paracrine control of trophoblast invasion (4,5).

Decreased levels of first-trimester maternal serum PAPP-A have been found to be predictive for adverse pregnancy outcome in many studies (3,6-8). Secondary analysis of the FASTER trial demonstrated that extremely low levels of PAPP-A were significantly associated with adverse pregnancy outcomes (9).

Fetal macrosomia is associated with increased numbers of perinatal complications, such as prolonged labor, perinatal mortality, asphyxial injuries, meconium aspiration, shoulder dystocia, soft tissue trauma, humeral and clavicular fractures, brachial plexus, and facial palsies (10-13). However, the accuracy of sonographic estimations of fetal weight in macrosomia is suboptimal, with a positive predictive value of just 38%-67% (12).

It is commonly assumed that first-trimester biological variations in fetal size are minimal and that variations in size do not emerge until the second half of pregnancy (14). As macrosomia remains a significant contributor to perinatal morbidity and mortality, however, early identification of fetuses at risk for developing growth disorders may assist in targeting those that warrant more intensive antenatal surveillance.

In this retrospective study, we investigate the potential relationship between first-trimester maternal serum PAPP-A levels and fetal macrosomia.

Materials and methods

This study was conducted at Başkent University, Adana, Turkey, between January 2008 and June 2009. Approval for the study was granted by the local ethics committee. Exclusion criteria included patients with multiple gestation, preterm delivery, maternal hypertension or proteinuria, pregestational diabetes, gestational diabetes, and known genetic or congenital malformations.

The studied group comprised 63 consecutive term macrosomic neonates (birth weight ≥ 4000 g) (Group 1), while the control group was made up of 100 consecutive appropriate-for-gestational-age (AGA) term neonates (Group 2) (10th percentile < birth weight < 90th percentile). Based on an effect size of 0.20, a power level of 0.80, and an alpha level of 0.05, the minimum sample size was determined as 63 for each group.

Major fetal defects, crown-rump length (CRL), and nuchal translucency (NT) thickness were determined by transabdominal ultrasound examination using the Prosound Alpha 10 (Aloka™) system (15). Gestational age was based on the mother's last menstrual period and ultrasonographic measurements of CRL before 12 weeks of gestation. Ultrasound measurements of the fetal biparietal diameter, abdominal circumference, and femur length were obtained at 29-34 weeks of gestation. The Hadlock nomogram was used to estimate fetal growth in the third trimester based

on ultrasonographic measurements of biparietal diameter (BPD), abdominal circumference (AC), and femur length (FL) (16,17).

A Kryptor analyzer (Brahms AG, Berlin, Germany) was used to measure maternal serum levels of PAPP-A and serum free beta-human chorionic gonadotropin (beta-hCG). Biochemical analysis was done on the same day as the NT measurements. Serum analyte levels were then converted to multiples of the median (MoM) adjusted for gestational age, ethnicity, and body mass index (BMI). The screening for gestational diabetes was done according to the criteria of Carpenter and Coustan between 24 and 28 weeks of gestation (18).

Data are expressed as mean ± SD. Differences between the 2 groups were analyzed using the independent Student's t-test and the Mann-Whitney U test. The homogeneity of variances was calculated by Levene's test and the Liliefors significance correction test. Correlations between the groups were assessed with Pearson and Spearman correlation coefficient and linear regression analyses. All statistical calculations were performed using the program SPSS for Windows, version 9.05 (SPSS Inc., Chicago, IL, USA). Differences were considered statistically significant at levels of $P < 0.05$.

Results

Some clinical and demographic characteristics of the 2 groups are shown in Table 1. The mean birth weights of the macrosomic babies were 4173 ± 176 g, compared to 3350 ± 328 g for control group (P = 0.000). The groups were similar with respect to maternal age, parity, BMI at the first trimester, and gestational weeks at delivery. In contrast with these similarities, BMI at the time of delivery (31.20 ± 3.29 in Group 1 and 29.86 ± 3.59 in Group 2, P = 0.019) and the percentage of male neonates (71% in Group 1 and 48% in Group 2, P = 0.003) were significantly higher in the macrosomic group (Table 1).

There were no significant differences between the groups with respect to gestational age (weeks) in the first trimester, the mean plasma levels of PAPP-A, free beta-hCG (as MoM values), the mean CRL, NT measurements, or mean fasting blood glucose levels (Table 2).

The linear correlation between PAPP-A levels and macrosomia, birth weight, and other variables was calculated. In the Pearson correlation, first-trimester PAPP-A levels were not correlated with birth weight (r = –0.116, P = 0.146), maternal age (r = 0.137, P = 0.089), maternal BMI in the first trimester (r

Table 1. Demographic data of the 2 groups included in the study.

	Group 1 (n = 63)	Group 2 (n = 100)	P
Age*	28.39 ± 5.09	29.42 ± 4.11	0.161
Parity ≥ 1, n (%)	36 (57.1)	49 (49)	0.336
BMI in the first trimester*	24.86 ± 3.40	23.77 ± 3.60	0.057
BMI at the time of delivery*	31.20 ± 3.29	29.86 ± 3.59	**0.019**
Gestational weeks at delivery*	39.30 ± 0.94	39.06 ± 0.91	0.109
Male neonates, n (%)	45 (71 %)	48 (48 %)	**0.003**

*presented as mean ± SD

Table 2. Comparison of the groups according to the gestational age in the first trimester, fetal CRL and NT measurements, maternal serum PAPP-A, free beta-hCG, and fasting glucose levels.

	Group 1 (n = 63)	Group 2 (n = 100)	P
Gestational age (weeks) at the first trimester*	12.59 ± 0.67	12.45 ± 0.59	0.184
CRL (mm)*	63.76 ± 8.64	62.40 ± 8.05	0.311
PAPP-A (MoM)*	0.94 ± 0.51	1.05 ± 0.57	0.211
PAPP-A (mIU/mL)*	2.28 ± 1.59	2.51 ± 1.80	0.407
Free b-hCG (MoM)*	1.19 ± 0.94	1.14 ± 0.66	0.659
NT (mm)*	1.73 ± 0.45	1.83 ± 0.33	0.098
Fasting glucose (mg/dL)*	83.62 ± 9.87	81.152 ± 7.29	0.069

*presented as mean ± SD

= –0.037, P = 0.641) or at delivery (r = 0.042, P = 0.620), or fasting blood glucose in the first trimester (r = –0.019, P = 0.816). First-trimester PAPP-A levels were also not correlated with macrosomia (r = –0.092, P = 0.249) or the occurrence of male sex (r = –0.074, P = 0.358) by the Spearman correlation.

In addition, first-trimester PAPP-A levels were not correlated with BPD (r = 0.003, P = 0.976), AC (r = 0.037, P = 0.663), or FL measurements (r = 0.084, P = 0.320) by the Pearson correlation (Table 3).

Table 3. Pearson correlation analysis of PAPP-A levels with different ultrasonographic parameters in the third trimester.

	r	P
BPD (mm)	0.003	0.976
BPD (weeks)	0.007	0.928
AC (mm)	0.037	0.663
AC (weeks)	0.025	0.763
FL (mm)	0.084	0.320
FL (weeks)	0.028	0.731

Discussion

Excessive fetal growth can occur because of genetic factors or because of an increased supply of nutrients. Fetal hyperglycemia and hyperinsulinemia promote growth in infants of diabetic mothers (IDMs) and infants with Beckwith-Wiedemann syndrome. Macrosomic infants who are not IDMs exhibit high levels of C-peptide, indicating that increased insulin secretion in nondiabetic disorders may also contribute to enhanced fetal growth (19).

Our study showed that neither PAPP-A nor free beta-hCG levels are associated with an increased risk of macrosomia in infants born to nondiabetic patients. This finding contrasts with that of Peterson and Simhan, who demonstrated an association of >90th percentile PAPP-A with macrosomia (20). Canini et al. also found that maternal serum PAPP-A levels in the late first trimester of pregnancy were associated with subsequent fetal growth, both in the form of physiologic variations and in abnormal growth (21). This is in contrast to the findings of Habayeb et al., however, which showed that first-trimester fetal growth rate was not related to birth weight percentile or first-trimester PAPP-A levels (22).

Alterations in the level of PAPP-A are associated with adverse pregnancy outcomes in chromosomally normal fetuses. PAPP-A also plays an important role in biological pathways that promote effective placentation and fetal growth (7). Low levels of PAPP-A adversely affect fetal growth due to the resulting reduction in the levels of free or soluble IGF in fetal circulation (23). Both clinical and research evidence has suggested that there is a relation between IGFs and human fetal growth. (24-26)

Leung et al. found that first-trimester PAPP-A and free beta-hCG were independent factors that influence subsequent fetal growth. In that study, PAPP-A level was positively correlated with femur length and abdominal circumference in the second trimester, while free beta-hCG level was negatively correlated with them. Biparietal diameter was not affected by either of the hormones, however (27). In our own study, we were unable to find any correlation between PAPP-A levels and ultrasonographic measurements at 29-34 weeks of gestation.

Our findings are limited by the retrospective design of the study. As the data were collected from chart reviews, the findings are dependent on correct entry of the serum analyte levels, maternal characteristics, and neonatal outcomes.

We conclude by underlining the fact that fetal growth is a complex process influenced by various determinants, such as genetics, maternal factors, the uterine environment, and maternal and fetal hormones. It appears that many growth factors (IGF-I, epithelial growth factor, and fibroblast growth factor-2) and their receptors influence materno-fetal communication, a communication that might be implicated in the fetal weight gain of macrosomic babies (28). Although PAPP-A may promote fetal growth and development through metabolic and differentiation pathways, it seems that there is no relationship between PAPP-A levels and macrosomia. Further studies are still required to fully elucidate the interaction between growth factors and their receptors in macrosomic infants.

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