Association of first trimester low PAPP-A levels with adverse pregnancy outcomes

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Summary

Objective: To investigate whether first trimester low PAPP-A levels are associated with adverse pregnancy outcomes. *Methods:* A case control retrospective study including 663 pregnant women whose gestational age ranged between 11 and 14 weeks attending prenatal care at Akdeniz University Hospital was carried out. Chromosomal abnormalities, spontaneous abortions, and multiple pregnancies were excluded from the study. Finally 318 singleton pregnancies were included in this study. Pregnant women whose PAPP-A levels were ≤ 10th percentile were compared with PAPP-A levels > 10th percentile for the frequency of pregnancy complications such as SGA, preeclampsia, preterm delivery, gestational diabetes mellitus and gestational hypertension. *Results:* The most common complication of pregnancy was SGA (9.4%, n = 30). There was no significant association between low PAPP-A levels and incidence of subsequent pregnancy outcomes. Maternal age was found to be a risk factor for gestational diabetes (p = 0.00). Small for gestational age was significantly associated with nulliparity and smoking during pregnancy (p = 0.03 and p = 0.01, respectively). *Conclusion:* First trimester of low PAPP-A level (≤ 10th percentile) was not associated with SGA, preeclampsia, preterm delivery, gestational hypertension or gestational diabetes mellitus.

Key words: First trimester serum screening; PAPP-A; Pregnancy complications.

Introduction

Pregnancy-associated plasma protein-A (PAPP-A) and free human chorionic gonadotropin (β-hCG) are increasingly being used as a part of screening programs for the detection of fetal aneuploidy in early pregnancy [1-7[. Recent studies have focused on the relation between PAPP-A and low levels of this marker with negative obstetrics results. These negative results are related to intrauterine growth restriction (IUGR), gestational hypertension, gestational diabetes, preeclampsia, fetal death, spontaneous abortus and preterm delivery [8-13]. PAPP-A is produced by trophoblasts, thereby abnormal levels of this protein detected as early as possible in the first trimester are considered to be related to abnormal placentation and to cause the mentioned pathological situations [10-14]. The relation of fetal growth with PAPP-A is based on insulin-like growth hormone activity which is considered to have an important role in trophoblast invasion [15]. PAPP-A is a protease produced from syncytiotrophoblasts for insulin-like growth factor binding protein-4, and its protease activity divides complex growth factor binding protein and release growth factors in mitogenic signal channels [16, 17]. High concentrations of PAPP-A release more insulin-like growth hormones for bioactivity, and this could result in advanced growth. On the other hand, low concentrations of PAPP-A results in a limited amount of growth factor which causes reduced development. Growth retardation was detected in homozygote mice in which the PAPP-A gene was affected [18]. A number of screening studies reported the relation between PAPP-A and reduced fetal development [9, 19, 20].

The present study aimed to investigate the relation between PAPP-A values observed in the first trimester and birth weight, as well as the predictability of pregnancy complications like IUGR, preeclampsia, gestational hypertension, gestational diabetes, and preterm labor by using low PAPP-A values.

Materials and Methods

In the study, the files of 663 pregnant women who underwent first trimester screening between December 2008 and September 2009 at the Akdeniz University Obstetrics Unit were retrospectively investigated. Subjects with no record, multiple pregnancies, fetal anomaly detection in the follow-up period and pregnancies resulting in abortus were excluded from the study. A total of 318 pregnant women were included.

PAPP-A multiple of median (MoM) values used in the study were taken from the records of Biochemistry Clinics. Immunassays were performed according to the manufacturer's protocol (Roche Diagnostics GmbH, Mannheim).

The PAPP-A MoM values were reported routinely after adjusting for maternal weight, smoking status, ethnicity and diabetes.

Obstetric outcomes were obtained from file records or by reaching them via phone contact. Gestational hypertension was diagnosed in cases with >140/90 mm/Hg blood pressure of two measurements at 6-hour intervals, no chronic hypertension and no significant sign of proteinuria. Preeclampsia was defined as the existence of gestational hypertension developing proteinuria. Proteinuria was defined as 0.1 g/l (> 2+ at dipstick) in at least two samples taken at an interval ≥ 6 h or > 300 mg total protein on 24 h urine collection. Preterm birth was defined as

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delivery before the 37th week of gestation. Small for gestational age (SGA) was defined as birth weights below the ≤ 5th and ≤ 10th percentile birth weights. Gestational diabetes is diagnosed when at least two values exceed the limits in a 100 g oral glucose tolerance test.

Pregnant women with PAPP-A > 10th percentile and PAPP-A ≤ 10th percentile were compared for pregnancy outcomes. The differences between the two groups were analyzed by chi-square or Fisher exact tests. The Mann-Whitney U test was used in the comparison of birth weight, age, and PAPP-A ≤ 10th percentile at delivery week. Multiple logistic regression models were fit to estimate the risk association between PAPP-A ≤ 10th percentile MoM and the risk for adverse pregnancy outcomes (SGA, preeclampsia, gestational diabetes, gestational hypertension, preterm birth) while adjusting for potentially confounding factors. Receiver-operator analyses were performed, including significant variables identified in the regression models, and the area under the curve (AUC) was used to estimate the ability of PAPP-A ≤ 10th percentile to predict adverse obstetric outcomes. SPSS (18.0 version) software was used in the analysis of the obtained data and $p < 0.05$ was accepted as significance level.

Results

Between December 2008 and September 2009, 663 pregnant women underwent first trimester screening tests for aneuploidy. A total of 318 pregnant women met inclusion criteria for the study analysis. The mean age of the 318 pregnant women was 29 ± 5.1. The mean gestational week for first-trimester screening test was 11.9 ± 0.6, while mean crown-rump-length (CRL) was 59.3 ± 8.4 mm. The mean nuchal translucency (NT) value was 1.45 ± 0.4 mm.

Among 318 pregnant women, 11 (3.5%) pregnant women had a history of smoking during pregnancy, 151 (47.5%) were nulliparous, and three (0.94%) had Type1 diabetes mellitus (DM), while six (1.8%) had thalassemia trait. Among 318 deliveries, there were six preterm deliveries < 35 weeks and 15 preterm deliveries < 37 weeks. The median PAPP-A MoM in the patient NT ≤ 10th percentile group was 1.53 versus 1.40 in the NT >10th percentile group.

The 5th, 10th, 90th and 95th percentiles of PAPP-A MoM values were 0.36, 0.45, 2.05 and 2,55 respectively. The PAPP-A MoM values of 35 patients were ≤ 10th percentile.

The median PAPP-A MoM values in the SGA and control group were 0.74 and 0.99, respectively (p = 0.055). The median PAPP-A MoM in preterm birth (PTB) < 35 weeks was 0.81 versus 0.97 in the group who delivered > 35 weeks (p = 0.441). The median PAPP-A MoM in PTB < 37 weeks was 1.04 versus 0.97 in the group who delivered > 37 weeks.

Compared to 35 women with a PAPP-A ≤ 10th percentile MoM (0.45), the 283 women with PAPP-A > 10th percentile MoM had similar age, parity and smoking status (Table 1). No significant difference was determined between patients with ≤ 10th percentile MoM value and with PAPP-A > 10th percentile in terms of pregnancy complications and characteristics (Table 1).

Table 1. — *Pregnancy complications and characteristics of patients with ≤ 10 percentile MoM value and with PAPP-A > 10 percentile.*

	PAPP-A ≤ 10th percentile MoM (n = 35)	PAPP-A > 10th percentile MoM (n = 283)	*p* value
Maternal age	29.4 ± 3.8	29.01 ± 5.2	0.58
Nulliparity	57.1% (20)	46.3% (131)	0.22
Smoking	2.9% (1)	3.5% (10)	0.99
Gestational hypertension	–	1.8% (5)	0.99
Preeclampsia	2.9% (1)	1.1% (3)	0.37
Gestational diabetes	2.9% (1)	4.9% (14)	0.99
Preterm < 35 wks	2.9% (1)	1.8% (5)	0.50
Preterm < 37 wks	2.9% (1)	4.9% (14)	0.99
SGA < 10th percentile	17.1% (6)	8.5% (24)	0.12
Polyhydramnios	5.7% (2)	2.1% (6)	0.21
Oligohydramnios	5.7% (2)	1.8% (5)	0.17
Birth weight	3206 (± 495)	3261 (± 551)	0.41

Age was determined to be an independent predictive factor for gestational diabetes (p = 0.00), while no relation was detected with PAPP-A ≤ 10th percentile (AUC 0.55, 95% CI 0.45-0.69). PAPP-A ≤ 10th percentile was also not predictive of preeclampsia (AUC 0.58, 95% CI 0.29- 0.86), SGA (AUC 0.60, 95% CI 0.50-0.71), preterm delivery (≤ 37 weeks) (AUC 0.52 95% CI 0.39-0.64) and preterm delivery (≤ 35 weeks) (AUC 0.59 95% CI 0.38-0.80). Nulliparity and smoking were predictive for SGA (p = 0.03 and p = 0.01, respectively).

Discussion

In our study, no significant relation was determined between low PAPP-A values and pregnancy complications (SGA, preeclampsia, preterm birth, gestational hypertension, gestational diabetes, oligohydramnios, polyhydramnios). Similarly, in a retrospective case-control study evaluating the role of serum free β-hCG and PAPP-A levels in SGA and preterm birth, no statistically significant difference was reported between case and control groups [21]. Conversely, in a study investigating the relation between gestational diabetes, gestational hypertension, preeclampsia, spontaneous abortus, PTB, and IUGR in patients with low maternal serum levels of PAPP-A and β-hCG measured between 10-14 weeks, the authors determined a significant relation between PAPP-A MoM values and gestational hypertension, spontaneous abortus, SGA < 10th, < 5th, < 3rd percentile, preeclampsia and gestational diabetes mellitus, while no significant relation was detected with preterm labor [22]. They concluded that first trimester low PAPP-A and free β-hCG had a weak sensitivity for pregnancy complications and this was similar to findings with abnormal serum biochemistry in the second trimester. Low levels of PAPP-A at 10-14 weeks may be a marker of impaired placentation and a smaller placental mass [22]. The paracrine effects of insulin-like growth factors (IGF) are thought to control the invasion of trophoblasts into the decidua. As PAPP-A is

a protease for IGF-binding proteins (IGFBP), low PAPP-A is associated with high levels of IGFBP, which consequently causes lowering of free IGF, leading to impaired invasion of the trophoblasts into the maternal decidua. This process may lead to adverse pregnancy outcomes. In another retrospective study, first trimester low PAPP-A level (≤ 0.25 MoM) was found to be a risk factor for IUGR, preeclampsia and spontaneous abortus but this study could not demonstrate any single cutoff value below [23].

In a prospective multicenter study a significant relation was found between PAPP-A and β-hCG levels measured at 8-14 weeks and pregnancy complications [20]. A significant relation was revealed between PAPP-A < 5th percentile and SGA < 5th percentile, preterm birth 33-36 weeks, preterm birth 24-32 weeks, preeclampsia and the death of placental origin, while β-hCG < 5th percentile was related significantly only with SGA < 5th percentile.

In another prospective multicenter study, low PAPP-A levels were determined as the most relative marker with pregnancy complications [10]. However, no relation was detected between high PAPP-A levels and adverse pregnancy results. A significant relation was determined in patients with PAPP-A level ≤ 5th percentile between SGA < 10th percentile, SGA ≤ 5th percentile, preterm birth < 37 weeks, preterm birth ≤ 32 weeks, preeclampsia, gestational hypertension, and < 24 weeks spontaneous abortus.

As stated by the authors of the aforementioned study, if PAPP-A is an important factor in fetal development, a relation could be expected between its high levels and macrosomia. The fact that it could not be demonstrated with such a large patient population indicates that PAPP-A is not the only factor that controls fetal growth and there should be other factors with important roles.

A new model for early prediction of SGA has recently been published [24]. The authors used maternal characteristics, NT thickness, PAPP-A, free β-hCG, mean arterial pressure, uterine artery pulsatility index, placental growth factor, placental protein 13, and A disintegrin and metalalloprotease to predict SGA. They concluded that combinating maternal factors and biophysical and biochemical markers at 11-13 weeks could detect half of pregnancies with SGA neonates in the absence of preeclampsia.

In our study, calculated 5th and 10th percentile PAPP-A MoM values were lower than most previous studies reported, but similar to the one of the study reported by Marttala *et al*. [25]. They also could not find any explanation for this situation and suspected the genetic background of the region was a factor.

As a result of our study, we could not find any significant relation between PAPP-A ≤ 10th percentile values and such pregnancy complications as SGA, preterm birth, preeclampsia, gestational hypertension, and gestational diabetes. Our study has several limitations, including its retrospective design and small sample size which could affect the inconsistency between previous results. Therefore, further prospective studies should be implemented, especially on larger populations.

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