PERINATAL JOURNAL

Research Article

Perinatal Journal 2014;22(3):142-146

The association between low PAPP-A levels at first trimester and poor pregnancy outcomes

Atalay Ekin, Cenk Gezer, Cüneyt Eftal Taner, Mehmet Özeren

Department of Perinatology, İzmir Tepecik Training and Research Hospital, İzmir, Turkey

Abstract

Objective: Pregnancy-associated plasma protein A (PAPP-A) is one of the markers recommended to identify patients at early periods of pregnancy who are under risk in terms of poor pregnancy outcomes. Our aim in this study was to analyze the association between low PAPP-A levels at first trimester and pregnancy complications.

Methods: Serum PAPP-A results of pregnancies between 11 and 14 weeks of gestation who referred for first trimester chromosomal anomaly screening were analyzed retrospectively. While 0.35 MoM and higher values were considered as low PAPP-A level, the values between 0.35 and 2.07 MoM were considered as normal PAPP-A level. In order to evaluate poor pregnancy outcomes, the obstetric history of pregnant women including intrauterine growth retardation, gestational diabetes, preeclampsia, preterm labor diagnoses, delivery type, birth weight and fetal genders were recorded.

Results: The study was carried out on two groups, which are low PAPP-A group including 211 (47.6%) out of 443 pregnant women (PAPP-A ≤0.35 MoM) and normal PAPP-A group including 232 (52.4%) out of 443 pregnant women (2.07 MoM > PAPP-A > 0.35 MoM). The prevalence rates for intrauterine growth retardation (p=0.01), preeclampsia (p=0.019), early-onset preeclampsia (p=0.043), preterm labor (p=0.016), preterm premature rupture of membrane (p=0.038) and iatrogenic preterm labor (p=0.040) were significantly high in the low PAPP-A group compared to the control group. The birth weight was also low (p=0.01) and cesarean section rate was high (p=0.008) in the low PAPP-A group.

Conclusion: Our findings confirm that there is a significant association between poor pregnancy outcomes and low maternal serum PAPP-A levels. These observations indicate that the complications appearing at the late periods of pregnancy may be detected at the first trimester.

Keywords: Pregnancy-associated plasma protein A (PAPP-A), first trimester, poor pregnancy outcomes.

Özet: İlk trimester düşük PAPP-A seviyeleri ile kötü gebelik sonuçları arasındaki ilişki

Amaç: Gebeliğe özgü plazma proteini-A (PAPP-A) kötü gebelik sonuçları açısından riskli bulunan hastaları gebeliğin erken döneminde belirlemek için önerilen markerlardan biridir. Bu çalışmada amacımız ilk trimester düşük PAPP-A seviyelerinin gebelik komplikasyonları ile birlikteliğini incelemektir.

Yöntem: İlk trimester kromozomal anomali taraması için başvuran 11-14 hafta arasındaki gebeliklerin serum PAPP-A sonuçları retrospektif olarak incelendi. Düşük PAPP-A seviyesi olarak 0.35 MoM ve altındaki değerler ve normal PAPP-A seviyesi olarak ise 0.35 ile 2.07 MoM arasındaki değerler kabul edildi. Kötü gebelik sonuçlarının değerlendirilmesi için gebelerin obstetrik geçmişlerinde intrauterin gelişme geriliği, gestasyonel diyabet, preeklampsi ve preterm doğum tanısı alıp almadıkları, doğum şekli, doğum ağırlığı ve fetal cinsiyetleri kayıt edildi.

Bulgular: Çalışmaya dahil edilen 443 gebeliğin 211'i (%47.6) düşük PAPP-A grubunu (PAPP-A ≤0.35 MoM) ve 232'si (%52.4) de normal PAPP-A grubunu (2.07 MoM > PAPP-A > 0.35 MoM) oluşturdu. Düşük PAPP-A grubunda kontrol grubuna göre intrauterin gelişme geriliği (p=0.01), preeklampsi (p=0.019), erken başlangıçlı preeklampsi (p=0.043), preterm doğum (p=0.016), preterm erken membran rüptürü (p=0.038) ve iatrojenik preterm doğumun (p=0.040) görülme sıklığı anlamlı olarak daha fazlaydı. Aynı zamanda düşük PAPP-A grubundaki gebelerin doğum ağırlığı daha düşüktü (p=0.01) ve sezaryen oranları daha yüksekti (p=0.008).

Sonuç: Bulgularımız düşük maternal serum PAPP-A seviyeleri ile kötü gebelik sonuçları arasında anlamlı bir ilişkinin olduğunu doğrulamaktadır. Bu gözlemler gebeliğin geç dönemlerinde ortaya çıkan komplikasyonların ilk trimesterde belirlenebileceğine işaret etmektedir.

Anahtar sözcükler: Gebeliğe özgü plazma proteini-A (PAPP-A), ilk trimester, kötü gebelik sonuçları.

Correspondence: Atalay Ekin, MD. İzmir Tepecik Eğitim ve Araştırma Hastanesi, Perinatoloji, İzmir, Turkey.
e-mail: atalayekin@hotmail.com

Received: February 1, 2014; **Accepted:** May 31, 2014

Available online at:
www.perinataljournal.com/20140223007
doi:10.2399/prn.14.0223007
QR (Quick Response) Code:

Introduction

The screening tests during early periods of pregnancy are significant in order to provide preventive and therapeutic procedures. One of the markers recommended to identify patients at early periods of pregnancy who are under risk in terms of poor pregnancy outcomes is pregnancy associated plasma protein-A (PAPP-A). PAPP-A secreted by syncytiotrophoblasts appears in maternal serum just after the implantation and it increases its concentration during pregnancy until it reaches its maximum level at term. The most common purpose to use PAPP in clinics is chromosomal anomaly screening programs at first trimester. Besides, many studies were reported evaluating the relationship of fetal well-being at third trimester with PAPP-A.[1]

Although it is known that there is no association between high PAPP-A levels and poor pregnancy outcomes, low PAPP-A levels at early periods of pregnancy is closely associated with poor fetal and maternal prognosis even though karyotype is normal.[2-4] It has been shown that low PAPP-A levels between 10 and 14 weeks of gestation are accompanied by pregnancy complications such as IUGR, preterm labor and fetal death.[2] With these findings, it was claimed that low PAPP-A level at first trimester may be an early sign for placental defect on implantation process.[5] However, there are still uncertainties for using low serum PAPP-A levels as screening test to predict poor pregnancy outcomes and what *cut-off* value is required.

Our aim in this study is to analyze the association between low (≤5th percentile) PAPP-A levels at first trimester and pregnancy complications.

Methods

The serum PAPP-A results of pregnancies between 11 weeks and 0 day and 13 weeks and 6 days who admitted to İzmir Tepecik Training and Research Hospital for first trimester chromosomal anomaly screening between September 2012 and October 2013 were evaluated retrospectively. Serum PAPP-A was measured by using ELISA kit (Immulite One; BioDPC, Los Angeles, CA, USA) via sandwich ELISA method. In the study, PAPP-A median values calculated according to obstetric population between 11 and 14 weeks of gestation were used. Accordingly, 5th percentile of PAPP-A MoM values was determined as 0.35 MoM and 95th percentile was determined as 2.07 MoM. While 0.35 MoM and higher values were considered as low PAPP-A level, the values between 0.35 and 2.07 MoM were considered as normal PAPP-A level.

Maternal age, maternal weight, gestational age, parity, presence of pregestational diabetes mellitus (DM), smoking habit and conception type (spontaneous or in-vitro fertilization [IVF]) of pregnant women in both groups at the time of sampling were collected. In order to evaluate poor pregnancy outcomes, the obstetric history of pregnant women including intrauterine growth retardation, gestational diabetes, preeclampsia, preterm labor diagnoses, delivery type, birth weight and fetal genders were recorded. Pregnant women who could not be followed up until delivery for any reason, those who had multiple pregnancy, and those who had fetus with chromosomal or major structural anomaly were excluded from the study.

Gestational age was determined by calculating crown-rump length during nuchal translucency measurement. All measurements were done by specialists experienced in obstetric sonography. IUGR was defined as birth weight expected according to gestational age being <10p based on Hadlock formula.[6] Preterm labor was considered as the termination of pregnancy before 37 weeks 0 day. Preterm labor was divided into subgroups according to spontaneous preterm labor, preterm premature rupture of membrane (PPROM) and iatrogenic reasons. Preeclampsia was defined as gestational hypertension (GH) with 300 mg/24h. Preeclampsia was considered as early-onset if diagnosed before 34 weeks of gestation, and as late-onset if diagnosed after 34 weeks of gestation. Gestational DM diagnosis was established according to the evaluation of 50 g (and 100g, if necessary) glucose tolerance test results between 24 and 28 weeks of gestation.

Low and normal PAPP-A levels were evaluated in terms of clinical characteristics and gestational outcomes. Statistical analysis was done by SPSS software version 20.0 (Statistical Package for the Social Sciences; SPSS Inc., Chicago, IL, USA). Continuous variables were given as mean±standard deviation (SD). In the comparison of two groups, Mann-Whitney U test was used for continuous variables and chi-square test for categorical variables. $P<0.05$ was considered statistically significant.

Results

In our study, PAPP-A measurement was carried out on 9362 patients at our hospital during specified period. Of these patients, PAPP-A values were at and below 5th per-

centile in 471 cases (PAPP-A ≤0.35 MoM), between 5th-95th percentile in 8417 cases (2.07 MoM > PAPP-A >0.35 MoM) and at and above 95th percentile in 474 cases (PAPP-A ≥2.07 MoM). A total of 211 patients who were complying with study criteria and of whom we were able to access their data were evaluated in the low PAPP-A group. In order to compare the results of these patients, 232 patients were chosen randomly from the normal PAPP-A group. There was statistically no difference between two groups in terms of maternal age, maternal weight, gestational age during sampling date, pregestational DM, smoking habit, and IVF pregnancy (**Table 1**).

The prevalence rates for intrauterine growth retardation (p=0.01), preeclampsia (p=0.019), early-onset preeclampsia (p=0.043), preterm labor (p=0.016), preterm premature rupture of membrane (p=0.038) and iatrogenic preterm labor (p=0.040) were significantly high in the low PAPP-A group compared to the control group (**Table 2**). The birth weight was also low (p=0.01) which was statistically significant, and cesarean section rate was high (p=0.008) in the low PAPP-A group (**Table 2**). Statistically no significant difference was found in terms of late-onset preeclampsia (p=0.248), gestational DM (p=0.892), spontaneous preterm labor (p=0.914) and fetal genders (p=0.203) (**Table 2**).

Table 1. Clinical data of the study population according to PAPP-A values*.

	PAPP-A ≤0.35MoM n=211	0.35 MoM <PAPP-A <2.07 MoM n=232	p value
Maternal age (y)	28.7±6.4	27.7±6.5	0.108
Maternal weight (kg)	65.6±12.5	67.5±12.4	0.123
Gestational age (day)	87.1±4.9	86.6±4.9	0.204
Nullipara	82 (%38.9)	99 (%42.5)	0.437
Pregestational DM	4 (%1.9)	3 (%1.3)	0.607
Smoking habit	27 (%12.8)	32 (%13.7)	0.771
IVF	2 (%0.9)	4 (%1.7)	0.483

*Data was provided as n (%) or mean±standard deviation. **DM:** Diabetes mellitus, **IVF:** In-vitro fertilization; **PAPP-A:** Pregnancy-associated plasma protein A.

Table 2. The association of poor pregnancy outcomes with low and normal PAPP-A values.

	PAPP-A ≤0.35MoM n (%)	0.35 MoM <PAPP-A <2.07 MoM n (%)	p value
IUGR	24 (%11.4)	8 (%3.4)	0.001*
Preeclampsia	17 (%8.1)	7 (%3)	0.019*
Early	11 (%5.2)	4 (%1.7)	0.043*
Late	6 (%2.8)	3 (%1.3)	0.248
Gestational DM	4 (%1.9)	4 (%1.7)	0.892
Preterm Labor	28 (%13.3)	15 (%6.5)	0.016*
Spontaneous	6 (%2.8)	7 (%3)	0.914
Preterm PROM	8 (%3.8)	2 (%0.9)	0.038*
Iatrogenic	14 (%6.6)	6 (%2.6)	0.040*
Delivery type			0.008*
Cesarean section	54 (%25.6)	36 (%74.4)	
Vaginal	157 (%15.5)	196 (%84.5)	
Fetal gender (F/M)	100/111: 0.9	124/108: 1.15	0.203*
Birth weight (gr, mean ± SD)	2832 ± 784	3076 ± 768	0.001*

*p<0.05. **DM:** Diabetes mellitus; **F:** Female; **IUGR:** Intrauterine growth retardation; **M:** Male; **PAPP-A:** Pregnancy-associated plasma protein A; **PROM:** Premature rupture of membrane; **SD:** Standard deviation

Discussion

In our study, it was shown that low maternal serum PAPP-A values between 11 and 14 weeks of gestation resulted with preeclampsia, IUGR, preterm labor, cesarean section delivery and pregnancies with low birth weight.

Low maternal serum PAPP-A levels accompanying with the development of gestational complications associated with insufficient placentation and/or placental dysfunction were reported in also previous studies.[2,5] Spencer et al. reported in the study screening more than 45,000 women that there was association between low PAPP-A levels at first trimester and low birth weight, fetal death and preeclampsia.[7-9] In a multi-centered study consisting of 34,271 pregnant women, a significant association was found between low PAPP-A levels at first trimester and preeclampsia, spontaneous fetal loss (≤24 weeks), birth weight below 5th percentile, gestational HT and preterm labor.[10] In another study including 5297 cases, it was reported that serum PAPP-A levels at between 10 and 14 weeks of gestation were lower in women whose pregnancies were complicated with abortion, IUGR and preeclampsia.[11] Smith et al. found that low PAPP-A levels increased fetal death risk associated with placental dysfunction for 46 times.[12]

PAPP-A concentration is the reflection of placental volume and probably the trophoblastic tissue amount. A series of maternal and gestational factors, particularly the gestational age, affect the serum concentrations of PAPP-A. However, in some of previous studies, clinical characteristics of case populations were disregarded.[10,11] Therefore, taking maternal factors into account such as body weight, smoking habit, IVF pregnancy and diabetes is the most significant advantage of this study.

The association between low PAPP-A level and increased preeclampsia risk has been shown in many studies.[7,13,14] Ong et al. found that the maternal serum PAPP-A levels in 23% of the preeclamptic cases were below 5th percentile.[11] Poon et al. reported that the low PAPP-A level is a marker with low sensitivity for particularly the development of early-onset preeclampsia.[14] In our study, although low PAPP-A levels were found in early-onset preeclampsia, no significant change was observed in first trimester PAPP-A levels when all preeclampsia cases were analyzed. We believe that this is because of the abundancy of late-onset preeclampsia case. Low PAPP-A level being significant in early-onset preeclampsia instead of late-onset preeclampsia can be attributed to the etiological difference. Accordingly, placental dysfunction that may affect PAPP-A concentration is the most significant etiological reason of early-onset preeclampsia.

The most of the early-onset preeclampsia cases was together with IUGR in a similar way with many other studies. In one of two studies where there is no significant difference between IUGR and low PAPP-A level, Johnson et al. analyzed only the patients who had fertility treatment.[15] In another study carried out by Morssink et al., the number of patients participated in the study group was quite lower than studies reported.[16]

A significant association was observed in terms of low PAPP-A levels and preterm labor, together with the impact of maternal and fetal indications secondary to preeclampsia and IUGR. Johnson et al.[15] and Pedersen et al.[17] showed that there is association between low PAPP-A levels and spontaneous preterm labor, even it is weaker. It is known that intraamniotic infection is the most important factor of the process leading to preterm labor. However, it was also asserted that vascular developmental defects during placentation may also have a role in the pathogenesis of preterm labor.[18] She at al. suggested that first trimester PAPP-A levels in preterm labor with both PPROM and intact membranes were lower than term pregnancies.[19] Although this association was shown in PPROM group in our study, no significant difference was observed in the first trimester PAPP-A levels of the cases with spontaneous preterm labor. The possible reason of this difference may be that the placental vasculopathy may progress more severely in PPROM group compared to spontaneous preterm labor group.

In our study, the low PAPP-A levels are seen together with the increased cesarean section rates and low birth weights. These findings arise from the expected early termination of pregnancies complicated with IUGR, preeclampsia and PPROM. Pederson et al. measured PAPP-A values of 93 pregnant women through their maternal serum between 8 and 14 weeks of gestation and found that there was an inverse proportion between these values and the gestational period but a direct proportion with birth weight.[17] However, Morssink et al. compared newborns with birth weight below 5th percentile and those with normal birth weight, and found no significant difference between two groups in terms of PAPP-A levels.[16]

The measurement of all proteins flowing in maternal blood at first trimester cannot determine poor pregnancy prognosis. Although free beta-HCG is another protein synthesized by syncytiotrophoblasts, its low levels are insufficient to predict poor obstetric outcomes such as PAPP-A.[2] Kavak et al. showed that first trimester maternal free beta-HCG values could not be used to predict low birth weight that may develop later, gestational DM and hypertensive disorders.[20] PAPP-A is not only a marker showing the volume or the health of syncytiotrophoblasts, but also a regulator helping trophoblast to function. PAPP-A is a protease having affinity for insulin-like growth factor binding protein-4 (IGFBP-4).[21] Decrease of PAPP-A level in blood increases IGFBP concentration and decreases free IGF amount. IGFs controls glucose and amino acid transportation to trophoblasts and have a role in fetal and placental growth. It is believed that IGFs are included in the autocrine and paracrine controls required during the decidual invasions of trophoblasts.[22]

Some authors consider that PAPP-A does not have sensitivity and specificity sufficient enough to be used as a screening test alone for determining the perinatal complications of pregnancy.[10,14,20,23] Retrospective planning of our study makes it difficult to interpret the predictivity of low PAPP-A. Smith et al. reported that PAPP-A values below 1st percentile have high positive predictive value to determine IUGR.[12] Therefore, a lower threshold value for PAPP-A would have higher prediction capacity.

Conclusion

In conclusion, our findings confirm that there is a significant association between poor pregnancy outcomes and low maternal serum PAPP-A levels. These obser-

vations indicate that complications appearing at the late periods of pregnancy may be determined at first trimester and the early check of IGF system during early pregnancy has a critical role for the normal placental development. However, PAPP-A does not have sufficient reliability to use as an isolated marker for screening the whole population. Therefore, it will be helpful for increasing the clinical benefit to use PAPP-A together with other biochemical and sonographic markers in the patient population with high risks in whom gestational problems may recur.

Conflicts of Interest: No conflicts declared.

References

1. Klopper A. Fetal monitoring. Biochemical methods. Baillieres Clin Obstet Gynaecol 1987;1:1-16.
2. 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.
3. Hurley PA, Ward RH, Teisner B, Iles RK, Lucas M, Grudzinskas JG. Serum PAPP-A measurements in first-trimester screening for Down syndrome. Prenat Diagn 1993; 13:903-8.
4. Kulaksizoglu S, Kulaksizoglu M, Kebapcilar AG, Torun AN, Ozcimen E, Turkoglu S. Can first trimester screening program detect women at high risk for gestational diabetes mellitus? Gynecol Endocrinol 2013;29:137-40.
5. Dugoff L; Society for Maternal-Fetal Medicine. First and second trimester maternal serum markers for aneuploidy and adverse obstetric outcomes. Obstet Gynecol 2010;115:1052-61.
6. Hadlock FP, Harrist RB, Sharman RS, Deter RL, Park SK. Estimation of fetal weight with the use of head, body and femur measurements - a prospective study. Am J Obstet Gynecol 1985;151:333-7.
7. Spencer K, Cowans NJ, Nicolaides KH. Low levels of maternal serum PAPP-A in the first trimester and the risk of pre-eclampsia. Prenat Diagn 2008;28:7-10.
8. Spencer K, Cowans NJ, Molina F, Kagan KO, Nicolaides KH. First-trimester ultrasound and biochemical markers of aneuploidy and the prediction of preterm or early preterm delivery. Ultrasound Obstet Gynecol 2008;31:147-52.
9. Spencer K, Cowans NJ, Avgidou K, Molina F, Nicolaides KH. First-trimester biochemical markers of aneuploidy and the prediction of small-for-gestational age fetuses. Ultrasound Obstet Gynecol 2008;31:15-9.
10. 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 gonadotrophin concentrations and nuchal transluceny are associated with obstetric complications: a population-based screening study (the FASTER Trial). Am J Obstet Gynecol 2004;191:1446-51.
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. Smith GC, Crossley JA, Aitken DA, Pell JP, Cameron AD, Connor JM, et al. First-trimester placentation and the risk of antepartum stillbirth. JAMA 2004;292:2249-54.
13. 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.
14. Poon LC, Maiz N, Valencia C, Plasencia W, Nicolaides KH. First-trimester maternal serum pregnancy-associated plasma protein-A and pre-eclampsia. Ultrasound Obstet Gynecol 2009;33:23-33.
15. Johnson MR, Riddle AF, Grudzinskas JG, Sharma V, Collins WP, Nicolaides KH. Reduced circulating placental protein concentrations during the first trimester are associated with preterm labor and low birthweight. Hum Reprod 1993;8: 1942-7.
16. 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.
17. Pedersen JF, Sorensen S, Ruge S. Human placental lactogen and pregnancy-associated plasma protein A in first trimester and subsequent fetal growth. Acta Obstet Gynecol Scand 1995;74:505-8.
18. Kim YM, Chaiworapongsa T, Gomez R, Bujold E, Yoon BH, Rotmensch S, et al. Failure of physiologic transformation of the spiral arteries in the placental bed in preterm premature rupture of membranes. Am J Obstet Gynecol 2002; 187:1137-42.
19. She BQ, Chen SC, Lee FK, Cheong ML, Tsai MS. Low maternal serum levels of pregnancy-associated plasma protein-A during the first trimester are associated with subsequent preterm delivery with preterm premature rupture of membranes. Taiwan J Obstet Gynecol 2007;46:242-7.
20. Kavak ZN, Basgul A, Elter K, Uygur M, Gokaslan H. The efficacy of first-trimester PAPP-A and free beta hCG levels for predicting adverse pregnancy outcome. J Perinat Med 2006;34:145-8.
21. 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.
22. Kniss DA, Shubert PJ, Zimmerman PD, Landon MB, Gabbe SG. Insulinlike growth factors. Their regulation of glucose and aminoacid transport in placental trophoblasts isolated from first-trimester chorionic villi. J Reprod Med 1994;39: 249-56.
23. Saruhan Z, Ozekinci M, Simsek M, Mendilcioglu I. Association of first trimester low PAPP-A levels with adverse pregnancy outcomes. Clin Exp Obstet Gynecol 2012;39: 225-8.