Özgün Araştırma / Original Article

Jinekoloji - Obstetrik ve Neonatoloji Tıp Dergisi
The Journal of Gynecology - Obstetrics and Neonatology

Relationship Between First Trimester Low Pregnancy Associated Plasma Protein A Levels With Second Trimester Uterine Artery Doppler, Placental Size and Adverse Obstetric Outcomes

Birinci Trimester Gebelikle İlişkili Plasma Protein-A Düzeyinin, İkinci Trimester Uterin Arter Doppler, Plasental Boyut ve Kötü Obstetrik Sonuçlarla İlişkisi

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ABSTRACT

Aim: We aimed to demonstrate the relationship between pregnancy associated plasma protein-A (PAPP-A) levels below 3th percentile (≤0.30 Multiples of Median (MoM)) with second trimester placental size, mean Uterine Artery (UtA) doppler Pulsatility Index (PI) and adverse obstetric outcomes.

Material and Methods: We recruited 32 women with PAPP-A levels ≤ 0.30 corrected MoM (Group 1), and 50 women with PAPP-A levels > 0.30 corrected MoM (Group 2), attended to Dr. Lütfi Kırdar Kartal Education and Research Hospital perinatology outpatient clinic, between September 2010 and January 2011. Pregnant women were reevaluated at 18-24 weeks with placental size measurement and mean UtA doppler indices. Mean UtA doppler PI ≥1.45 considered to be abnormal as increased UtA resistance. We also grouped women as low PAPP-A and increased mean UtA PI (Group 1: n =7) and normal PAPP-A and normal mean UtA PI (Group 2: n = 75). All women are asked in postnatal period for pregnancy complications like preeclampsia (PE), intrauterine growth retardation (IUGR), preterm delivery, oligohydramniosis and stillbirth.

Results: When women were grouped according to the PAPP-A level adverse pregnancy outcomes were more prevalent in low PAPP-A group but statistically significant difference was seen only in preeclampsia (p=0.02). Second trimester placental size and UtA PI levels were not significantly different between groups. When grouped according to the PAPP-A and UtA PI levels, IUGR and oligohydramniosis was significantly higher (p= 0.03 and p=0.04 respectively) and birth weight was significantly lower (p=0.02) in low PAPP-A and high UtA PI group. There was no satistically significant difference in PE among groups (p=0.23).

Conclusion: Our results have shown that it is possible to predict unfavorable effects of placental insufficiency on mother and fetus, but it is obvious that there is no single screening method. Randomised clinical trials with larger sample sizes using combination of biochemical and ultrasonographic parameters is necessary for prediction of adverse pregnancy outcomes.

Key Words: Pregnancy associated plasma protein-A, uterine artery doppler, preeclampsia, intrauterine growth retardation.

ÖZET

Amaç: Birinci trimester Down Sendromu taramasında 3. persentilin altında (≤0.30 Multiples of Median (MoM)) olan pregnancy associated plasma protein-A (PAPP-A) düzeyinin, ikinci trimester ortalama uterin arter (UtA) pulsatilite indeksi (PI) ile plasental boyut ölçümü ve kötü obstetrik sonuçlarla ilişkisini araştırmayı amaçladık.

Gereç ve Yöntemler: Eylül 2010 ile Ocak 2011 tarihleri arasında Dr. Lütfi Kırdar Kartal Eğitim ve Araraştırma Hastanesi Perinatoloji polikliniğine başvuran birinci trimester tarama testinde PAPP-A düzeyi ≤ 0.30 düzeltilmiş MoM saptanan 32 (Grup 1), PAPP-A düzeyi >0.30 düzeltilmiş MoM saptanan 50 kadın (grup 2) çalışmaya dahil

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Geliş Tarihi/Received: 08.07. 2014
Kabul Tarihi/ Accepted: 19.07.2014

edildi. Gebeler 18-24 haftalarda plasenta boyut ölçümü ve UtA doppleri ile yeniden değerlendirildi. Artmış UtA direnç indeksi olarak ortalama UtA PI ≥1.45 anormal kabul edildi. Gebeler düşük PAPP-A ve artmış UtA PI (Grup 1:n=7) ve normal PAPP-A ve normal UtA PI (Grup 2:n=75) olarak tekrar gruplandı ve doğum sonrası preeklampsi, intrauterin gelişme geriliği (IUGG), oligohidramnios, erken doğum gibi gebelik komplikasyonları açısından sorgulandı.

Bulgular: PAPP-A düzeyine göre gruplar karşılaştırıldığında kötü obsterik sonuçlar düşük PAPP-A grubunda fazla iken istatiksel olarak anlamlı fark yalnızca preeklampside izlendi (p=0.02). İkinci trimester plasenta boyutu ve UtA PI değerlerinde gruplar arasında anlamlı fark saptanmadı. Gebeler PAPP-A ve UtA PI değerine göre gruplandığında düşük PAPP-A ve yüksek UtA PI grubunda IUGG (p=0.03), oligohidramnios (p=0.04) daha fazla, doğum kilosu daha düşüktü p=(0.02) ve fark istatistiksel olarak anlamlıydı, preeklampsi açısından anlamlı fark saptanmadı (p=0.23).

Sonuç: Sonuçları iştir ki, plasental yetmezliğin anne ve fetus üzerindeki olumsuz etkilerini tahmin etmek mümkündür, ancak tek başına kullanılabilecek bir tarama metodu yoktur. Kötü obstetrik sonuçları tarama amaçlı, biyokimyasal ve ultrasonografik parametreleri bir arada kullanan daha geniş randomize klinik çalışmalara ihtiyaç vardır.

Anahtar Kelimeler: Pregnancy associated plasma protein-A, uterin arter doppler, preeklampsi, intrauterin gelişme geriliği.

Introduction

The insulin-like growth factor (IGF) system is involved in placental and fetal growth and development throughout pregnancy (1). When bound to IGF binding proteins (IGFBPs) in the circulation, their bioavailability is lost. PAPP-A is a marker used as part of the first trimester Down's syndrome screening test (2). It is synthesized primarily by the placenta and increases in maternal serum throughout pregnancy (3). PAPPA is responsible for IGFBP-4 protease activity in the placenta (4,5), which increases IGF bioavailability and may promote the invasion of the placenta into the maternal vasculature and normal placentation process. Independent of the presence of aneuploidy, women undergoing biochemical screening and found to have markedly reduced PAPP-A levels in the first trimester are increasingly being recognised as also at increased risk of other pregnancy complications such as miscarriage, growth restriction, hypertensive disorders, premature delivery and stillbirth due to placental insufficiency (6-9).

Second trimester UtA doppler analysis is used to evaluate uteroplacental circulation and to define pregnant women who are prone to complications due to uteroplacental insufficiency. PI ≥ 1.45, resistance index (RI) ≥ 0.58 or values of these indices greater than 90-95th percentile are determinants of increased uterine artery resistance (10,11). The other ultrasound based test of placental function is placental size.

In this study, we planned to demonstrate the relationship between the determinants of placental health such as PAPP-A, placental size and mean UtA doppler indices and obstetric outcomes.

Material and Methods

Blood samples for measurement of PAPP-A were drawn as a part of the first trimester Down's Syndrome screening test at 11-14 weeks. An abnormally low level was defined as ≤0.30 corrected MoM corresponding to values <3rd centile (12,13). We recruited 32 women with PAPP-A levels ≤ 0.30 corrected MoM (Group 1), and 50 women with PAPP-A levels > 0.30 corrected MoM (Group 2), attended to Dr. Lütfi Kırdar Kartal Education and Research Hospital, perinatology outpatient clinic, between September 2010 and January 2011. PAPP-A was measured via chemo-iluminescence method in Immulute 1000 analysator by using Immulite kits. Exclusion criteria were: systemic diseases such as diabetes mellitus, chronic hypertension, congestive heart failure, chronic renal failure, thrombophilia, autoimmune diseases, multiple pregnancies, abortus imminens history and assisted reproductive techniques.

All women evaluated at 11-14 weeks, were reevaluated at 18-24 weeks. B-mode ultrasonography (USG) was used to determine placental size and doppler USG for bilateral UtA pulsatility indices. Placental size measurement and doppler USG was performed by Siemens Accuson Antares device which had 3,5-5 MHz convex transabdominal probe and colour doppler property.

Uterine artery pulsatility indices were measured as below

Ultrasound probe was placed on lower lateral abdominal quadrant and rotated to medial side. Doppler sample window was placed on 1 cm medial to the place where UtA emerges from internal iliac artery and crosses over external iliac artery. Three similar waveform obtained from this point was measured and recorded bilaterally via using 100 Hz wall filter and mean of PI values was taken (Figure 1). Increased UtA resistance was accepted as PI ≥1.45. We also grouped women as low PAPP-A and increased mean UtA PI (Group 1: n =7) and normal PAPP-A and normal mean UtA PI (Group 2: n = 75).

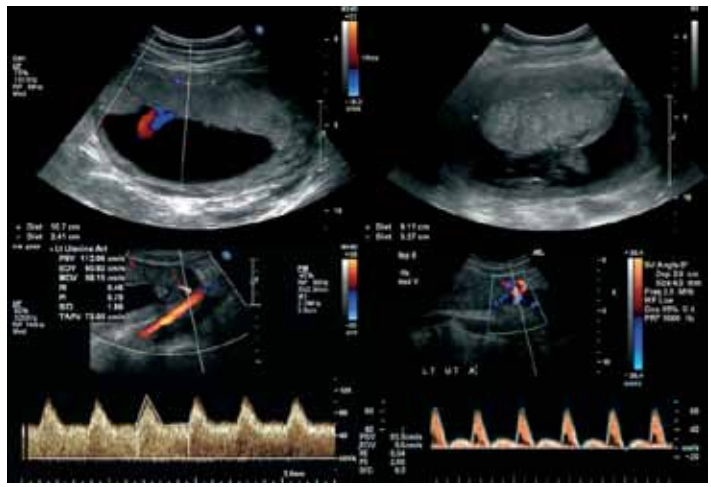

Figure 1: Ultrasonographic evaluation of UtA doppler and placental size. On the left a thin and long placenta and UtA Doppler waveform where PI<1,45 which is considered to be normal; on the right a thick and small placenta and UtA Doppler waveform had elevated PI which is considered to be abnormal.

Placental size was measured as below

Placenta was shown in longitudinal plane in the longest dimension via rotation of probe. Placental thickness was also measured on the same plane. If placenta was not lying in lineer fashion, ie. fundal placentation, the distance from the edge of placenta to the midpoint between chorionic and basal plate, than from this point to the opposite edge was measured and the sum of these measurements were taken. The lineer length was taken as placental size (Figure 1).

All pregnant women involved were asked for age, gravidity, parity, abortus, D&C, smoking habit and medicine taking status in antenatal period. Mode of delivery, if caesarean section its indication, birth week and weight of the fetus, presence of adverse obstetric outcomes like preterm delivery, IUGR or small for gestational age fetus, preeclampsia, gestational hypertension, oligohydramniosis and placental abruption was examined. IUGR was defined as pregnancies which are not successfully achieving normal fetal growth potential due to impairment of uteroplacental circulation (abnormal doppler measurements, alterations in fetal body proportions: significant retardation in abdominal circumference, amniotic fluid index<50 ml). Gestational hypertension and preeclampsia was defined according to the reports of the Working Group of the National High Blood Pressure Education Program modified in 2000.

Statistical analysis

SPSS 17th version for Windows was used for data analysis. In addition to descriptive statistical methods (mean and standart deviation), Mann Whitney-U test, which is non- parametric equivalent of Student-t test, was used to compare means of quantitative variables among groups. In the comparison of categoric variables chi-square and Fisher's exact tests were used. Results were evaluated in 95% confidence interval and p<0.05 was accepted as significant.

Results

There was no significant difference in demographic characteristics between groups when grouped according to the PAPP-A levels (Table 1). The mean longitudinal diameter of placenta was 120.8±19.5 mm in group 1 and 130.3±15 mm in group 2 and the difference between groups was not statistically significant (p= 0.30). There was no significant difference in second trimester UtA doppler PI values (Mean PIgrup1 =1.19 vs Mean PIgrup2 =1.16, p = 0.78). Obstetric outcomes were summarised in table 2. The mean gestational week at birth was 37.4±4.6 in group 1 and 38.6±2.6 in group 2 (p=0.23). The mean birth weight in group 1 was 2814±784 and 3136±672 in group 2 and the difference was statistically significant (p=0.03). PE was seen in 5 women in group 1 and 2 women in group 2 and difference was statistically significant (p=0.02). The difference in IUGR and oligohydramniosis was not statistically significant between groups (p=0.10 and p=0.08 respectively). In group 1, three women had preterm delivery and there was one stillbirth, and in group 2 there was one preterm delivery and one stillbirth.

When we grouped women as low PAPP-A and increased mean uterine UtA PI (Group 1: n =7) and normal PAPP-A and normal mean UtA PI (Group 2: n = 75), gestational hypertension and PE was found to be similar in both groups. The rates of IUGR and oligohydramniosis were 75% and 75% in group 1; 13% and 18,3% in group 2 respectively and the difference was statistically significant (p=0.03 and p=0.04 respectively). The mean birth weight in group1 was 2345±603 gr and 3118±613 gr in group 2 and the difference was significant (p=0.02) (Table 3).

Table 1: Demographic characteristics and second trimester USG results of low and normal PAPP-A

	Grup 1 (n= 32)	Grup 2 (n= 50)	P
Age	26,7±5,9	26,1±4,6	0,61
Gravidty	2±0,8	2,1±1,1	0,77
Parity	0,85±0,72	0,66±0,73	0,28
Abortus	0,28±0,46	0,30±0,58	0,85
Gestational week at second visit	21,44±1,96	21,18±1,65	0,59
Placental length (mm)	120,8±19,5	130,3±15	0,30
Placental thickness (mm)	33,8±5,3	31,8±6,2	0,30
Mean uterine artery PI	1,16±35	1,19±54	0,78

All results were defined as mean ±standard deviation

Table 2 : Relationship of low and normal PAPP-A levels with obstetric outcomes

	Grup 1 (n= 32)	Grup 1 (n= 32)	P
Gestational hypertension	0 / 32 (% 0)	2 / 50 (% 4)	0, 52
Preeclampsia	5 / 32 (% 16)	1 / 50 (% 2)	0, 02
IUGR	9 / 32 (% 29)	6 / 50 (% 12)	0, 10
Oligohydramniosis	8/32 (%25)	10/50 (%20)	0,08
Mode of delivery (caesarean)	20 / 32 (% 60)	23 / 50 (% 45)	0, 40
Stillbirth	1 / 32 (%3)	1 / 50 (% 2)	1
Birth week	37,4±4,6	38,6±2,6	0,23
Birth weight	2814±784	3136±672	0,03

All results were defined as mean ±standard deviation.

Table 3 : Comparison of low PAPP-A and increased mean uterine artery PI with normal PAPP-A and normal mean uterine artery PI Discussion

	Grup 1 (n= 32)	Grup 1 (n= 32)	P
Gestational hypertension	0 / 7 (0 %)	2 / 75 (4 %)	0,3
Preeclampsia	2 / 7 (25 %)	5 / 75 (6,5 %)	0,27
IUGR	5 / 7 (75 %)	10 / 75 (13 %)	0,03
Oligohydramniosis	5 / 7 (75 %)	14 / 75 (18, 3 %)	0,04
Mode of delivery (caesarean)	4 / 7 (50 %)	37 / 75 (50 %)	1
Stillbirth	1/ 7 (14 %)	1 / 75 (1,3 %)	0,002
Birth week	37,2 ±2,2	38,6±2,8	0,13
Birth weight	2345±603	3118±613	0,02

Many studies have revealed significant associations between low serum PAPP-A and placenta-mediated complications of pregnancy including PE, IUGR, pre-

term delivery and stillbirth (12,14,15). The findings of this study have confirmed the results of Florio et al., who accepted cut off value for low PAPP-A as 0.40 MoM, that first-trimester low levels of maternal serum PAPP-A is significantly related with increased risk for subsequent development of preeclampsia, but not significantly related with other adverse pregnancy outcomes (16). On the other hand, Saruhan et al. found no statistically significant association between first trimester low PAPP-A level (low PAPP-A cut off accepted as $\leq$ 0.50 MoM) and obstetric outcomes (17). Many studies confirmed that predictive value of PAPP-A alone for preeclampsia and IUGR is low (8-23% and 11-24% respectively) and it is unacceptable to use it alone as a screening method for adverse obstetric outcomes (18,19). There are many first trimester serum markers such as free human chorionic gonadotropin, placental growth factor, and placental protein 13, endoglin, activin A and inhibin A, had been studied by many researchers were found to be related placenta related pathologies (20,21). Addition to these first trimester serum markers may increase the value of low PAPP-A in prediction of preeclampsia and IUGR.

The UtA doppler indices measured at various weeks of gestation is the other method to investigate pathologic placentation. In a retrospective study Spencer et al. (14) showed the relationship between pregnancy complications and first trimester maternal serum PAPP-A and second trimester UtA doppler. According to his findings, positive predictive values of PAPP-A was 14%, mean UtA PI was 55% and with the combination of uterine artery doppler and PAPP-A was 62% for detection of PE. Pilalis et al. showed that addition of first trimester UtA doppler indices to low PAPP-A improves screening characteristics for adverse perinatal outcomes compared with PAPP-A alone, but not to an acceptable threshold for recommendation in low-risk women (22). When we combined these in our study, IUGR was found to be higher in low PAPP-A and increased mean UtA PI group than controls and this was statistically significant (p=0.03), but there was no statistically significant difference in preeclampsia (p=0.27) among groups. This result may be due to limited sample size and small number of women with PI levels $\geq$1.45.

We know that reduced placental growth, reflected by weight and volume, generally precedes diminished fetal growth (23). There are many studies which accept lineer length as placental size. In a prospective cohort study recruited 90 women with PAPP-A $\leq$ 0.30 MoM, maximum lineer length $\leq$ 100 mm was defined as abnormally small placenta and small placenta was significantly associated with the development of severe IUGR, extreme preterm delivery (<32weeks'gestation) and stillbirth (24). Proctor et al. in this study emphasized that second trimester UtA doppler did nothing, but small placenta was very valuable for screening of adverse obstetric outcomes in patients with low PAPP-A (24). Although our study design is different from this cohort, we found that placental size was smaller in low PAPP-A group but the difference was not significant (p=0.30). Furthermore, there was only one placenta $\leq$ 100 mm in low PAPP-A group that is thought to be the result of small sample size.

Conclusion

In conclusion, our results have shown that it is possible to predict unfavorable effects of placental insufficiency on mother and fetus, but it is obvious that there is no single screening method. Randomised clinical trials with larger sample sizes using combination of biochemical and ultrasonographic parameters is necessary for prediction of adverse pregnancy outcomes.

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