Low Second Trimester Estimated Fetal Weight as a Predictor of Small-for-Gestational Age Neonates in Patients with Low First Trimester Serum PAPP-A Levels

İlk Üç Ay Serum PAPP-A Değerleri Düşük Olan Hastalarda İkinci Üç Ay Tahmini Fetal Ağırlığın Düşük Doğum Ağırlıklı Bebekleri Tahmin Etmede Kullanılması

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ABSTRACT Objective: The aim of this study was to examine fetal growth in the second trimester and to detect its predictive value for delivering small-for-gestational age neonates in patients with low first trimester pregnancy associated plasma protein-A (PAPP-A) levels. **Material and Methods:** We searched the patient charts of our hospital for first trimester Down syndrome screening tests retrospectively (n=923), we identified patients with PAPP-A levels < 5th percentile (n=60) and then we searched their ultrasound records for second trimester estimated fetal weight (EFW) results (Hadlock) at 18-23 weeks. **Results:** The sensitivity of a low second trimester EFW for birth weights <5th percentile was 14.3%, specificity 90.7%, positive predictive value 33.3% and negative predictive value 76.4%. **Conclusion:** Combination of low second trimester EFW with low PAPP-A levels increase sensitivity and PPV of PAPP-A in detecting small-for-gestational age neonates.

Key Words: Infant, small for gestational age; pregnancy trimester, second; pregnancy-associated plasma protein-A

ÖZET Amaç: Bu çalışmanın amacı ilk üçay gebelik ilişkili plazma proteini A (PAPP-A) seviyeleri düşük bulunan hastalarda, ikinci üçay tahmini fetal ağırlık ölçümlerinin düşük doğum ağırlıklı fetüsleri tahmin etmede kullanılabilirliğini tespit etmektir. **Gereç ve Yöntemler:** Retrospektif olarak düzenlenen çalışmada hastanemizin gebe kayıtları incelendi ve ilk üçay Down sendromu tarama testlerinin sonuçları bulunarak (n=923), PAPP-A seviyeleri 5. persentilin altında kalan hastalar (n=60) tespit edildi. Bu hastaların ultrason kayıtlarından 18-23. haftalar arasında yapılmış ikinci üçay tahmini fetal ağırlık persentilleri (Hadlock) hesaplandı. **Bulgular:** İkinci üçay ultrasonunda düşük tahmini fetal ağırlık saptanmasının 5. persentilin altındaki yenidoğan doğum ağırlıklarını tespit etme duyarlılığı %14,3, özgüllüğü %90,7, pozitif kestirim değeri %33,3 ve negatif kestirim değeri %76,4 olarak bulundu. **Sonuç:** İkinci üçay tahmini fetal ağırlık ölçümü ile PAPP-A'nın birlikte kullanımı, PAPP-A'nın düşük doğum ağırlıklı yenidoğanları tespit edebilme duyarlılığını ve pozitif prediktif değerini arttırmaktadır.

Anahtar Kelimeler: Bebek, gestasyonel yaşa göre küçük; gebelik trimestırı, ikinci; gebelik ilişkili plazma proteini A

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Abnormalities of fetal growth begin in the first trimester of pregnancy with impaired trophoblastic invasion of uterine spiral arteries which can be demonstrated histologically.[1] Fetuses that are small for gestational age have an increased risk for perinatal morbidity and mortality.[2] Complications related to birth weight can be prevented with timely antenatal detection and closer surveillence of pregnancies with small-for-

gestational-age (SGA) fetuses.[3] With this knowledge in mind researchers aimed to find first trimester markers that can detect SGA fetuses.

Pregnancy associated plasma protein-A (PAPP-A) is a proteinase produced by the trophoblasts and it cleaves insulin like growth factor binding proteins (IGFBPs). Increased levels of IGFBPs or decreased levels of PAPP-A are detected in pregnancies with fetal growth restriction.[4] It is a marker of early placentation. PAPP-A is part of the first trimester screening for chromosomal abnormalities which is recommended to all of our patients. Patients with low serum PAPP-A levels in the absence of chromosomally abnormal fetuses are suggested to be at risk for delivering SGA fetuses.[5-7] Combined use of PAPP-A with many other parameters is suggested for early detection of fetuses with growth retardation.[8-10] All of the patients attending to our clinic undergo a second trimester ultrasound for the evaluation of fetal anatomy, during this procedure estimated fetal weight (EFW) is also calculated. Low second trimester EFW is suggested as a predictor of poor fetal outcome.[11-13] The aim of this study is to examine fetal growth in the second trimester and to detect its predictive value for SGA infants in patients with a low first trimester PAPP-A.

MATERIAL AND METHODS

This was a retrospective study performed by searching the data of women attending to İstanbul Bilim University Avrupa Hospital for Down syndrome screening between January 2006 and August 2012. Ultrasound examinations were performed routinely at 11-13 weeks of gestation in the first trimester and at 18-23 weeks in the second trimester. All measurements were carried out by three obstetricians (NG,Hİ,ABY) using the 5-MHz curvilinear transabdominal transducer, GE Electric Voluson 730 Expert. Only women delivering at our institution were included. Exclusion criteria were the presence of incomplete information, smoking, known abnormal fetal karyotype, congenital malformations and pregnancies with more than one fetus. We did not exclude any case on the basis of abnormal fetal biometry or birth weight. Last menstrual period was recorded and the estimated date of delivery was corrected according to the crown-rump length (CRL) measurement obtained in the first visit (6-8 weeks of pregnancy). All serum analyses were performed at a single site and the values were corrected for maternal weight. The research project conforms to the ethical guidelines of the Declaration of Helsinki. Because of the retrospective nature of study we did not take ethical approval and informed patient consent.

Maternal serum samples for PAPP-A were assayed with the chemiluminescence UnicelDxl 800 Beckman coulter and the results were converted into multiples of median (MoM). For statistical analysis PAPP-A levels less than the 5th percentile (≤ 0.39 MoM) were considered as a risk factor for SGA infants. Second trimester fetal growth restriction was defined as an EFW< 25th percentile (Hadlock) as this was the previously reported cut-off associated with poor outcome in the second trimester of pregnancy.[14] SGA was defined as a birth weight less than the 10th percentile for the gestational age at delivery, but also statistical analysis for a birth weight less than the 5th and 25th percentiles were calculated.

For statistical analysis we used NCSS (Number Cruncher Statistical System) 2007 and PASS (Power Analysis and Sample Size) 2008 Statistical Software (Utah, USA). Data showing anthropometric parameters were presented as mean±standard deviation and median values. For categorical anaysis we used Mann Whitney U Test. The results were considered statistically significant when the p-value was calculated as less than 0.05 at a confidence interval of 95%.

RESULTS

We searched data of 923 pregnants and included 60 patients in our study. The demographic features of the patients were shown in Table 1. Mean maternal age was 31.8±4.2 years, mean maternal height was 161±1.6 cm (cm), mean maternal weight before pregnancy was 63± 11 kg (kg). Twenty-three percent of patients with a low first trimester PAPP-A level had a second trimester EFW <25%. The sensitivity of low second trimester EFW was

TABLE 1: Demographic features of patients.

		Second trimester ultrasound		
	Total (n=60)	<25% Percentile (n=14)	≥25% Percentile (n=46)	
	Mean±SD	Mean±SD (Median)	Mean±SD (Median)	p
Age (years)	31.8±4.2	33.7±4.7 (34)	31±3.9 (31.5)	0.073
Gravidity	1.6±0.9	1.8±0.9 (1.5)	1.6±0.9 (1)	0.405
Parity	0.4±0.7	0.6±0.9	0.4±0.6	0.466
Prepregnancy maternal weight (kg)	63±11	66.5±12.5 (62)	61.8±11 (58)	0.191
Weight gain in pregnany (kg)	16±6	13.3±4.8 (13)	17.5±6 (17)	0.078
Maternal weight at birth (kg)	81±11.9	80±11 (77.5)	81±12.4 (81)	0.843
Maternal height (cm)	161±1.6	159±3.6 (158)	166±5.1 (165)	0.002*
Delivery week	38±1.7	38.4±2 (38)	38±1.6 (38.5)	0.504
Birth weight (grams)	3214±571	3038±639 (3120)	3271±543 (3240)	0.235
EFW Percentile	43±32	33±22(37.5)	47±33 (37)	0.194
PAPP-A (MoM)	0.33±0.6	0.34±0.06 (0.36)	0.33±0.06 (0.33)	0.611

Mann Whitney U Test; *p<0.01.

14.3%, specificity 90.7%, positive predictive value (PPV) 33.3% and negative predictive value (NPV) 76.4% for birth weights <5th percentile (Table 2). The sensitivity of second trimester EFW was 28.6%, specificity 76.7%, PPV 28.6% and NPV 76.7% for birth weights <10th percentile (Table 2). The sensitivity of second trimester EFW was 35.7%, specificity 67.4%, PPV 26.3% and NPV 76.3% for birth weights <25th percentile (Table 2).

DISCUSSION

First trimester pregnancy screening test for Down syndrome is commonly performed and pregnants with a low PAPP-A level but an euploid fetus can readily be identified. These patients mostly undergo a second trimester ultrasound examination, where the main purpose is the detection of fetal anomalies. Low PAPP-A levels are suggested as significant predictors of SGA fetuses in the absence of preeclampsia.[8,15] By using low PAPP-A levels only 3% of fetuses with growth restriction can be predicted, which makes it useless as a screening test.[16,17] In this study we found that combination of low second trimester EFW with low PAPP-A levels increase sensitivity and PPV of PAPP-A alone, but does not change the specificity. These results are similar to those of a previous report.[14] But the prevalence of fetuses with a low second trimester EFW among patients with low PAPP-A levels are higher in our study when compared to that of Fox et al.[14] In addition we found similar NPV for low second trimester EFW at different cut-off levels for birth weight, specificity was the highest for birth weights <5th centile.

Fetal growth restriction is the result of impaired trophoblastic invasion of uterine spiral arteries, the clinical manifestations of this cannot be detected until the second trimester.[1] PAPP-A increases the availability of IGF to accelerate fetal growth by enhancing trophoblast invasion to the decidua.[18] Low PAPP-A levels act as a marker of abnormal placentation and decrease delivery of nutrients to

TABLE 2: Sensitivity, specificity, positive (PPV) and negative (NPV) predictive values of second trimester sonographic signs of growth restriction in predicting small for gestational age newborns.

Fetal weight in second trimester ultrasound < 25th percentile	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Birth weight (<25th percentile)	35.7	67.4	26.3	76.3
Birth weight (<5th percentile)	14.3	90.7	33.3	76.5
Birth weight (<10th percentile)	28.6	76.7	28.6	76.7

chorionic villi, as a result small fetuses have smaller placentae. Abnormal placentation may decrease the genetically determined fetal growth rate.[19] Another consequence of abnormal first trimester placentation is pregnancy induced hypertension, which is also associated with a low second trimester EFW.[14,20] When PAPP-A is combined with second trimester uterine artery Doppler findings, predictive accuracy of first trimester PAPP-A for SGA fetuses and pregnancy induced hypertension increases.[14,21-23] After this week of pregnancy we cannot give medications to decrease morbidity and mortality, we can only provide effective monitorization of suspected cases and timely delivery when indicated.

Recent studies focusing on fetal growth in early pregnancy propose a CRL smaller than 7 days according to the expected dates as a risk factor for a birth weight below 2500 g.[24,25] These fetuses are also reported to have a higher mortality rate.[25] Placentation takes place in the first trimester of pregnancy and spiral arteries transform into low resistance arteries, therefore it is logical to expect fetal growth abnormalities at around 11-14 weeks of gestation. But studies on first trimester fetal growth abnormalities depend on the last menstrual period (LMP) and remembering LMP inaccurately or having irregular periods may create biases. Our study depends on first trimester CRL and this increases the strength of the study. The relatively small number of patients and the retrospective nature of the study are the limiting factors.

In conclusion combination of low second trimester EFW with low PAPP-A levels increase sensitivity and PPV of PAPP-A. Further research to find markers that can increase the positive predictive value of PAPP-A in the first trimester would be a better policy, but until then second trimester EFW can be used as an adjunct to PAPP-A to identify fetuses with growth restriction. We advise to make use of PAPP-A and second trimester EFW to detect SGA fetuses, when already performed for other purposes.

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