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RESEARCH ARTICLE

First trimester serum PAPP-A levels and the prediction of small-for-gestational age infants

İlk trimester serum PAPP-A düzeyleri ve gebelik yaşına göre küçük bebeklerin tahmin edilmesi

Nilgün Güdücü, Gökçenur Gönenç, Herman İşçi, Alin Başgül Yiğiter, İlkkan Dünder

İstanbul Bilim University, Europe Hospital, Department of Obstetrics and Gynecology, İstanbul, Turkey

ABSTRACT

Objectives: The aim of this study was to detect the predictive value of PAPP-A in small-for-gestational age (SGA) infants.

Materials and methods: We retrospectively searched the patient charts of our hospital for first trimester Down syndrome screening test results. PAPP-A levels less than 5th percentile were considered as predictive of SGA infants.

Results: Low PAPP-A levels were associated with SGA infants, sensitivity was 3,5%, specificity 90%, positive predictive value 1,6% and negative predictive value 95%.

Conclusions: The low positive predictive value of PAPP-A prevents it from being used as a screening test for the detection of SGA infants. *J Clin Exp Invest 2012; 3(2): 185-188*

Key words: Small for gestational age, PAPP-A, pregnancy

ÖZET

Amaç: Bu çalışmanın amacı ilk trimester serum PAPP-A (pregnancy aasociated plasma protein A) seviyelerinin gebelik yaşına göre küçük (GYK) bebekleri tahmin etmede kullanılabilirliğini tespit etmektir.

Gereç ve yöntem: Geriye dönük olarak hastanemizin gebe kayıtları incelendi ve ilk trimester Down sendromu tarama testlerinin sonuçları bulundu. PAPP-A seviyeleri 5. persentilin altında kalanlar GYK bebek olarak kabul edildi.

Bulgular: Düşük PAPP-A seviyeleri ile GYK bebekler arasında bir ilişki mevcuttur, testin duyarlılığı %3,5, özgüllüğü %90, pozitif kestirim değeri %1,6 ve negatif kestirim değeri %95tir.

Sonuç: Testin pozitif kestirim değerinin düşük olması nedeniyle GYK bebekleri tahmin etmek için kullanılması uygun değildir.

Anahtar kelimeler: gebelik yaşına göre küçük bebek, PAPP-A, gebelik

INTRODUCTION

Early antenatal detection of pregnancies with small-for-gestational-age fetuses is important to provide monitoring for the prevention of complications.[1,2] Pregnancies at increased risk of developing small for gestational age (SGA) fetuses can be diagnosed by making additional use of tests formerly obtained for Down syndrome screening. First trimester serum screening for Down's syndrome uses fetal nuchal translucency (NT) with free beta-human chorionic gonadotropin (free β-hCG) and pregnancy associated plasma protein A (PAPP-A). PAPP-A is a trophoblast-derived metalloproteinase breaking down IGFBPs, degraded particles of IGFBPs bind IGFs and inhibits their interaction with cell surface receptors.[3] It is released into the fetal blood and then it passes from placenta to maternal blood, concentrations increase as the gestation progresses from 10 to 13 weeks due to enlargement of the placenta.[4] The aim of our study was to search the role of PAPP-A as a screening test for the detection of SGA fetuses, previously some studies suggested a connection and others claimed no significant association.[5,6,7,8]

MATERIALS AND METHODS

This was a retrospective study performed by searching the data of women attending to İstanbul Bilim University Europe Hospital for Down syndrome screening between January 2006 and December 2010. Ultrasound examinations were performed routinely at 11-13 weeks of gestation. All measurements were carried out by two obstetricians (NG, Hİ) using the 5-MHz curvilinear transabdominal transducer, GE Electric Voluson 730 Expert. Only

Correspondence: Dr. Nilgün Güdücü
İstanbul Bilim University, Department of Obstetrics and Gynecology İstanbul, Turkey, E-mail: nilgun.kutay@gmail.com
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women delivering at our institution were included. Exclusion criteria were the presence of incomplete information, smoking, known abnormal fetal karyotype, congenital malformations, pregnancies with more than one fetus and pregnancies with missing information. 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 first trimester crown-rump length (CRL) measurement. All serum analyses were performed at a single site and the values were corrected for maternal weight. The research project has been approved by the Ethics Committee of our University and it conforms to the ethical guidelines of the Declaration of Helsinki.

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. Small for gestational age was defined as a birth weight less than the 10th percentile for the gestational age at delivery. .

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. For categorical anaysis we used McNemar test. The results were considered statistically significant when the p-value was calculated less than 0.05 at a confidence interval of 95%.

RESULTS

We included 642 patients in our study. The demographic features of the patients were shown in Table 1. Mean maternal age was 30±4 years (18-42 years), mean maternal height was 164±6cm (149-180cm), mean maternal weight before pregnancy was 62±10 kg (40-104 kg), mean maternal weight at delivery was 77±10kg (54-115 kg), mean maternal weight gain during pregnancy was 15±5 kg (-2 to +45 kg), mean gestational age at the time of first trimester screening test was 12+1 weeks. The sensitivity of PAPP-A was 3,5%, specificity 90%, positive predictive value 1,6% and negative predictive value 95% (Table 2). There was a statistically significant correlation between PAPP-A and SGA infants (p<0,001). Odds Ratio was 0,32 (0,042-2,37).

Table 1. Demographic characteristics of the patients

(n=642)	Min-Max	Mean ±SD
Age (years)	18-43	30±4
Gravidity (n)	0-7	1,6±1
Parity (n)	0-3	0,3±0,5
Abortus (n)	0-4	0,1±0,4
Maternal weight before pregnancy (kg)	40-104	62±10
Maternal weight at delivery (kg)	54-115	77±10
Maternal weight gain in pregnancy (kg)	-2 to 45	15±5
First trimester screening test (weeks)	11+4 to 13+6	12+2
Gestational age at delivery (weeks)	34-42	39±1,2

Table 2. The relationship between serum PAPP-A levels and birth weight percentile

Birth weight percentile	PAPP-A*		
	< %5	≥ %5	Total
SGA*	1 (%3,4)	62 (%10,1)	63 (%9,8)
Non-SGA	28 (%96,6)	551 (%89,9)	579 (%90,2)
Total	29 (%4,5)	613 (%95,5)	642 (%100)
p	*0,001***		
Sensitivity (%)	3,5		
Specificity (%)	90		
Positive predictive value	1,6		
Negative predictive value	95		

McNemar Test **p<0,01

PAPP-A: pregnancy associated plasma protein A

SGA: small for gestational age

DISCUSSION

The mechanisms underlying the development of a SGA infant are initiated in the first trimester of pregnancy,[9] but the manifestations cannot be detected until the second trimester. The trophoblast-derived PAPP-A increases the availability of IGF, which is known to regulate fetal growth by enhancing trophoblast invasion to the decidua[10] and low levels

of PAPP-A show impaired placental function. Low PAPP-A levels were suggested to result in SGA infants by decreasing the availability of nutrients to chorionic villi.[11] The resulting early-onset abnormal placentation leads to a late-onset pregnancy complication.

When we use PAPP-A as a marker for the detection of SGA infants, only 3% of them could be predicted. A previous study where ≤ 0,3 MoM was used as a cut-off level, sensitivity was given as 5,1%,[12] similar to our study. This prevents its use as a screening test without an adjunctive test. The search for finding a marker that could detect growth restriction earlier has not been successful yet.[13] Detection of such a marker may give us the advantage of intervention with aspirin to decrease the effects of abnormal placentation.[14] Combination of PAPP-A with second trimester uterine artery Doppler findings were shown to increase the predictive accuracy of first trimester PAPP-A[15] when is too late for intervention. This can at least provide effective monitorization of suspected cases and delivery when indicated, such a policy was shown to decrease the mortality and morbidity.[1]

Previously low and high levels of PAPP-A were shown to be associated with SGA and LGA infants respectively.16 PAPP-A levels below the 5th percentile were shown to be associated with higher rates of low birth weight infants.[5,17,18] Yet another study found no association between decreased PAPP-A levels and low birth weight infants.[8] The association between serum PAPP-A levels and delivery of SGA infants was relatively weak in our study. Due its low predictive value the use of serum PAPP-A level as a primary screening test is limited.

The association between decreased PAPP-A levels and smoking has been demonstrated before[19] and chronic maternal diseases have been associated with an increased risk of delivering SGA infants,[20] therefore we excluded women with chronic maternal diseases and smokers instead of making an adjustment.

Our study had the disadvantage of using traditional growth centiles, it has been shown that customized growth centiles based on physiologic determinants of birth weight discriminated constitutionally small babies better from growth-restricted babies.[21] We also did not take the gender of the infants into consideration.

In conclusion serum PAPP-A level cannot be used as a screening test for the determination of SGA infants, but it can be taken into consideration when a first trimester Down syndrome screening test is already presented. Further research to find markers that can increase the predictive value of PAPP-A are warranted.

Conflicts of Interest: The authors declare no conflicts of interest

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