Prediction of small for gestational age neonates in twin pregnancies by first trimester maternal serum PAPP-A and free β-hCG

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Abstract

Objective: To determine the association between first trimester serum markers and pregnancy complications such as SGA and preterm delivery in twin pregnancies.

Methods: The study included 86 multiple pregnancies. Total study population divided into three study groups as follows: very preterm pregnancies (<32 weeks), preterm pregnancies (≥32 and <37 weeks) and term pregnancies (≥37 weeks). PAPP-A, free β-hCG and birth weight percentile differences between study groups were tested for statistical significance.

Results: According to birth weight percentiles, there was statistically significant difference between very preterm-preterm and very preterm-term groups (p<0.05). PAPP-A and free β-hCG medians for each group were not significantly different (p>0.05). PAPP-A levels below 5th percentile were associated with low birth weight percentiles in twin pregnancies (OR=0.968, 95% CI for OR 0.945-0.992, p=0.008). However, significant association with free β-hCG was not found regarding SGA.

Conclusion: First trimester maternal serum PAPP-A can be used to predict pregnancy complications like SGA in twin pregnancies.

Keywords: Preterm, twin pregnancies, SGA, PAPP-A, free β-hCG.

Özet: **İkiz gebeliklerde ilk trimester maternal serum PAPP-A ve serbest β-hCG ile SGA ilişkisi**

Amaç: İkiz gebeliklerde preterm doğum ve SGA gibi komplikasyonlar ile birinci trimester serum belirteçleri arasındaki ilişkinin belirlenmesi.

Yöntem: Bu çalışmada 86 ikiz gebelik yer almıştır. Tüm çalışma popülasyonu üç alt gruba ayrılmıştır; ileri derece preterm gebelikler (<32 hafta), preterm gebelikler (≥32 ve <37 hafta) ve term gebelikler (≥37 hafta). Çalışma grupları arasında PAPP-A, serbest β-hCG ve doğum kilosu persentili farklılıkları istatistiksel anlamlılık yönünden test edilmiştir.

Bulgular: Doğum kilosu persentillerine göre ileri derece preterm-preterm ve ileri derece preterm-term grupları arasında istatistiksel olarak anlamlı fark bulunmuştur (p<0.05). Her bir grup için PAPP-A ve serbest β-hCG medyanları arasında istatistiksel olarak anlamlı fark bulunmamıştır (p>0.05). Beşinci persentilin altındaki PAPP-A düzeyleri ikiz gebeliklerde düşük doğum kilosu persentilleri ile ilişkili bulunmuştur (OR=0.968, %95 CI 0.945-0.992, p=0.008). Fakat SGA bakımından serbest β-hCG ile anlamlı bir ilişki bulunamamıştır.

Sonuç: İkiz gebeliklerde birinci trimester maternal serum PAPP-A düzeyleri SGA gibi gebelik komplikasyonlarının önceden belirlenmesinde kullanılabilir.

Anahtar sözcükler: Preterm, ikiz gebelik, SGA, PAPP-A, serbest β-hCG.

Introduction

The incidence of twin pregnancy is increasing secondary to delayed childbearing and increased use of assisted reproductive techniques.[1] Perinatal complication risk is appreciably increased in multifetal gestations compared with singletons.[2] Maternal levels of pregnancy associated plasma protein A (PAPP-A) and free beta-human chorionic gonadotropin (free β-hCG) measured in first

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trimester screening have been shown to be associated with development of pregnancy complications such as fetal loss, small for gestational age neonate (SGA), preterm birth or preeclampsia.[3]

Preterm delivery is the most important cause of neonatal mortality and morbidity. Respiratory distress syndrome (RDS) and low birth weight (<2500 g) are very common in infants born before 37 weeks of gestation. Very low birth weight (<1500 g) is also observed in some preterm infants. According to data of National Center for Health Statistics in U.S., 7.2% of all live-births were low birth weight and 1.3% of all live-births were very low birth weight.[4]

Similar to second- trimester serum markers, first trimester free β-hCG and PAPP-A levels are about twice as high in twins compared with singleton pregnancies. In studies of normal twin pregnancies, average first- trimester free β-hCG levels were 1.86 multiple of the median (MoM) and PAPP-A levels were 2.10 MoM.[5] Many studies in literature suggest that the concentrations of first trimester serum markers were lower in pregnancy complications such as premature delivery, SGA, and preeclampsia.[6-8]

The adverse outcomes resulting from premature delivery and SGA impose a considerable burden on healthcare resources.[9] Therefore, the ability to predict factors which target patients, at higher risk of developing an adverse pregnancy outcome, early in pregnancy would be helpful in the planning of prenatal care.[10]

In this study, our purpose was to determine the relationship between first trimester serum markers and pregnancy complications such as SGA and preterm delivery in twin pregnancies.

Methods

In our study we retrospectively evaluated the data of 86 multiple pregnancies who admitted to the Biochemistry Laboratory of Eskişehir State Hospital to have a first trimester screening test between 2010 and 2012. We determined serum levels of free β-hCG and PAPP-A by IMMULITE 2000 device (Diagnostic Product Corporation, Los Angeles, CA, USA) of BIO-DPC company which runs with chemiluminescence method. Gestational ages of pregnants were between 11 and 13 weeks (11w+0d and 13w+6d). Total study population was divided into 3 study groups as follows: very preterm

pregnancies (<32 weeks) which includes 14 cases, preterm pregnancies (≥32 and <37 weeks) which includes 54 cases, and term pregnancies (≥37 weeks) which includes 18 cases.

Birth weight percentiles of twins were evaluated according to Fenton TR generated from Babson and Benda's growth chart by updating with recent data and a new format.[11] PAPP-A, free β-hCG and birth weight percentile differences between study groups were tested for statistical significance. This study was approved by Ethical Committee of Eskişehir State Hospital.

SPSS IBM 20.0 software (SPSS Inc., Chicago, IL, USA) was used for statistical analysis. Since birth weight percentile, PAPP-A, and free β-hCG parameters not normally distributed, Kruskal-Wallis one-way analysis of variance by ranks was used. Median (quartiles) values used as defining statistics. In order to assess the relationship between PAPP-A, free β-hCG and SGA, binary logistic regression analysis was used. A p value less than 0.05 (p<0.05) was considered as statistically significant.

Results

We found statistically significant difference between study groups according to birth weight percentiles (p=0.015). **Table 1** shows the comparison of the three study groups according to birth weight percentiles. There was statistically significant difference between very preterm-preterm group and very preterm-term group (p=0.015, p=0.035). But there was no statistical difference between preterm-term groups (p=1.000).

We found that PAPP-A medians and free β-hCG medians for each group was not significantly different (p=0.375, p=0.772). PAPP-A and free β-hCG medians of study groups are presented in **Table 2**.

The proportion of SGA events was compared among percentiles of PAPP-A and free β-hCG by binary logistic regression analysis. PAPP-A levels below 5th

Table 1. Comparison of birth weight percentiles between study groups.

Groups	N	Medians (Quartiles)	Comparisons	p value
1. Very preterm	14	43 (35-65)	1-2	0.015
2. Preterm	54	24.5 (11.5-40)	1-3	0.035
3. Term	18	24.0 (2.5-42.5)	2-3	1.000

percentile were associated with low birth weight percentiles and PAPP-A levels below 5th percentile caused 1.033 times decrease in birth weight percentiles. Low first trimester PAPP-A levels were a strong predictor for SGA in twin gestations (Odds Ratio [OR]=0.968, 95% CI for OR 0.945-0.992, p=0.008).

On the other hand, free β-hCG association with birth weight percentiles did not reach a statistically significant level at different percentile cut-offs. Free β-hCG levels below 25th percentile caused 1.017 times increase in birth weight percentiles (OR=1.017, 0.975-1.061 p=0.425) and free β-hCG levels above 95th percentile caused 1.028 times decrease in birth weight percentiles (OR=0.973, 0.942-1.005, p=0.103).

Discussion

Fetuses at risk for neural tube defects or fetal chromosomal abnormalities as well as women at risk for third trimester obstetric complications can be defined by prenatal screening tests. Maternal serum screening decreases fetal mortality and morbidity by early diagnosis and also helps couples to decide about appropriate delivery strategies.[12] The week of gestation (i.e. 10-14) used for first trimester screening is also the optimal time for early definition of complication risk.[10]

Abnormal fetal growth patterns SGA, and large-for-gestational age neonate (LGA) are important causes of perinatal morbidity and mortality. By the use of new growth charts that include maternal demographic characteristics, the detection rate for SGA is increased. First trimester PAPP-A and free β-hCG were studied previously in singleton pregnancies to predict SGA and other third trimester complications, and results of many studies demonstrated a positive correlation of PAPP-A and birth weight.[6-8] However, the association between free β-hCG and birth weight is not clear.[13] In our study we found statistically significant difference in study groups (very preterm- preterm and very preterm-term) according to birth weight percentiles (p<0.05).

Brameld et al. have documented that when PAPP-A is below the 5th percentile, the risk of preterm birth increased significantly.[14] Laughon demonstrated that free β-hCG levels below 25th percentile were associated with very preterm birth before 32 weeks of gestation but not with preterm birth between ≤32 and <37 weeks of gestation. PAPP-A was associated with a trend in increased risk of very preterm birth in twin gestations.[15] In our study we found that PAPP- A and free β-hCG medians were not significantly different for each group (very preterm, preterm, term) in twin pregnancies. When the rates of complications were compared between different PAPP-A levels, severity of growth restriction was found highest at the lowest PAPP-A concentrations.[16] PAPP-A is a trophoblast-specific protein regulating release of free IGFs. Control of the IGF function in early pregnancy may be essential for normal placental perfusion. Many pregnancy complications such as premature delivery, SGA, and preeclampsia may be associated with protease activity of PAPP-A affecting free IGF concentrations and poor placental perfusion.[6]

Our findings, like previous reports on singleton pregnancies demonstrate that risk of pregnancy complications such as SGA and premature delivery can be identified in the first trimester in twin gestations and recommended for further testing and closer surveillance throughout the rest of their pregnancy. The objective of this study was to explain the association between first trimester serum markers and the incidence of pregnancy complications by comparing the relative incidence at different percentiles of PAPP-A and free β-hCG to define the likelihood ratio for SGA and preterm delivery at different marker levels. We found that PAPP-A levels below 5th percentile were associated with 1.033 times decrease in birth weight percentiles. Low first trimester PAPP-A levels were a strong predictor for SGA in twin gestations (OR=0.968, 95% CI for OR 0.945-0.992, p=0.008). However, free β-hCG association with birth weight percentiles at different percentile cut-offs did not reach a statistically significant level.

Conclusion

Since perinatal mortality risk for twins is much higher than for singleton pregnancies and the great economic burden associated with mortality and morbidity is caused by pregnancy complications, defining the real need for targeting and directing patients in terms of intensive monitoring and interventions is extremely

Table 2. PAPP-A and free β-hCG results of very preterm, preterm and term groups.

Groups	Very preterm medians (Quartiles)	Preterm medians (Quartiles)	Term medians (Quartiles)	p value
PAPP-A	5.2 (3.7-7.7)	6.7 (4.4-9.9)	5.62 (4.03-8.7)	0.375
β-hCG	53.4 (37-84.8)	57.1 (43.3-89)	64.6 (48.1-85.1)	0.772

important. The results of our study demonstrate that low first trimester maternal serum PAPP-A was a strong predictor for SGA in twin gestations and it may be used as a screening marker for pregnancy complications like SGA in twin pregnancies.

Conflicts of Interest: No conflicts declared.

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