First-Trimester Screening Tests and Perinatal Outcomes

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Abstract

Aim: Early diagnosis of trisomies occupies an important place in the working life of perinatologists and obstetricians. Early diagnosis of this condition is very important in raising a healthy generation. Early diagnosis informs decisions such as mental and physical preparation after birth or termination of pregnancy. Early detection of this risk is ensured by testing fetal nuchal translucency (NT), free human chorionic gonadotropin-β (free-βhCG) and pregnancy-related plasma protein-A (PAPP-A) levels at appropriate intervals. Also, with the help of these tests, perinatal risks such as chromosomal abnormalities, intrauterine growth retardation (IUGR) and preterm birth can be detected, and precautionary measures can be taken. In this study, we are trying to find out if it is possible to predict IUGR using these tests in the first trimester and evaluating the infants born here. Perhaps retrospective evaluation of these tests can be used to prevent poor pregnancy outcomes or, if necessary, to reduce the incidence of complications by delivering babies in more appropriate centers.

Method: One of the hospitals included in this study is a training and research hospital and the other is a state hospital with active birth management, where the number of births is higher than the regional average. This study was conducted using data obtained by pediatrics and obstetrics by scanning the records of patients who had gone to their centers for postnatal care and the babies who were born. The population that served as the control group was reached in the same way. The period for the study was limited to two years.

Results: 257 patients who had enrolled in centers for prenatal care over two years were included in the study. While 132 healthy pregnant women participated in the study as a control group, 125 pregnant women diagnosed with IUGR were included in the study. When the screening tests were compared in the first trimester, the mean PAPP-A level was higher in the control group than in the patient group (p=0.006). Free β-hCG was also higher in the control group (p=0.024). The result after performing the necessary statistical adjustments PAPP-A showed the statistical significance of its value in the analysis. However, the same tests

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did not show the same success in the IUGR group and were not statistically successful in predicting poor neonatal outcomes.

Conclusion: In this study, the use of PAPP-A level in the first trimester has been shown to provide successful results in estimating IUGR that may occur later in pregnancy. However, no parameter has shown the same predictive success in predicting poor neonatal outcomes.

Keywords: Intrauterine growth retardation, first-trimester screening, PAPP-A.

Birinci Trimester Tarama Testleri ve Perinatal Sonuçlar

Öz

Amaç: Trizomilerin erken teşhisi perinatolog ve kadın doğum uzmanlarının çalışma hayatında önemli bir yer tutmaktadır. Bu durumun erken teşhisi sağlıklı bir nesil yetiştirmek için çok önemlidir. Erken teşhis, doğumdan sonra veya hamileliğin sonlandırılmasından sonra zihinsel ve fiziksel hazırlık gibi kararlar hakkında bilgi verir. Bu riskin erken tespiti, fetal ense saydamlığı (NT), serbest insan koryonikgonadotropin-β (serbest-βhCG) ve gebelikle ilişkili plazma protein-A (PAPP-A) düzeylerinin uygun aralıklarla test edilmesiyle sağlanır. Ayrıca bu testler yardımıyla kromozom anomalileri, intrauterin gelişme geriliği (IUGR) ve erken doğum gibi perinatal riskler tespit edilerek önlem alınabilir. Bu çalışmada ilk trimesterde bu testleri kullanarak ve burada doğan bebekleri değerlendirerek IUGR'yi tahmin etmenin mümkün olup olmadığını bulmaya çalışılmıştır. Bu testlerin geriye dönük değerlendirilmesi, kötü gebelik sonuçlarını önlemek veya gerekirse bebekleri daha uygun merkezlerde doğumlarının sağlanması komplikasyon insidansını azaltmak için kullanılabilir.

Yöntem: Çalışmaya dahil edilen hastanelerden biri eğitim ve araştırma hastanesi diğeri ise aktif doğum yönetimine sahip bir devlet hastanesi olup, doğum sayısı bölge ortalamasının üzerindedir. Bu çalışma, gebelik takibi için merkezlere başvuran hasta ve onlardan doğan bebeklerin kayıtları taranarak pediatri ve kadın doğum hekimleri elde edilen verilerle yapılmıştır. Kontrol grubu olarak oluşturulan hasta grubuna da aynı şekilde ulaşılmıştır. Araştırma süresi iki yıl ile sınırlandırılmıştır.

Bulgular: Çalışmaya iki yıl boyunca doğum öncesi bakım için merkezlerimize başvuran 257 hasta dahil edildi. Çalışmaya 132 sağlıklı gebe kontrol grubu olarak katılırken, IUGR tanısı almış 125 gebe çalışmaya dahil edildi. Birinci trimester tarama testleri karşılaştırıldığında, kontrol grubunda ortalama PAPP-A düzeyi hasta grubuna göre daha yüksekti (p=0,006). Serbest β-hCG de kontrol grubunda daha yüksekti (p=0,024). PAPP-A gerekli istatistiksel ayarlamaları yaptıktan sonra elde edilen sonuç, analizdeki değerinin istatistiksel olarak anlamlı olduğunu gösterdi. Ancak aynı testler IUGR grubunda aynı başarıyı göstermedi ve kötü yenidoğan sonuçlarını öngörmede istatistiksel olarak başarılı olmadı.

Sonuç: Çalışmada ilk trimesterde PAPP-A seviyesinin kullanılmasının, daha sonraki gebeliklerde ortaya çıkabilecek IUGR'yi tahmin etmede başarılı sonuçlar sağladığı gösterilmiştir. Bununla birlikte, hiçbir parametre, kötü yenidoğan sonuçlarını öngörmede aynı öngörücü başarıyı göstermedi.

Anahtar Sözcükler: İntrauterine gelişme geriliği, ilk trimester taraması, PAPP-A.

Introduction

Intrauterine growth and developmental delay (IUGR) describes conditions where the estimated fetal weight is below the expected and usually below the 10th percentile. In Utero growth of the fetus is influenced by many factors. Continuation of intrauterine development is possible with adequate oxygen and nutrient supply[1]. This occurs due to the constant change and development of the uteroplacental circulation during pregnancy. Fetal and perinatal deaths are common in fetuses with IUGR. It is important to identify IUGR that negatively affects perinatal mortality and morbidity and to treat it appropriately. Some of the screening tests used in prenatal follow-up are screening tests in the first trimester. This test is performed in the first 11-14 days of pregnancy for trisomy 18 and 21[2]. By testing fetal nuchal translucency (NT), free human chorionic gonadotropin-β (free-βhCG), and pregnancy-associated plasma protein A (PAPP-A) levels in the first trimester, early diagnosis of trisomy-21 and trisomy-18 can be detected more effectively and less by an invasive procedure. Perinatal risks such as other chromosomal abnormalities, IUGR, and preterm labor can also be detected with this test. Similarly, high HCG levels are associated with an increased incidence of gestational hypertension, preeclampsia, preterm delivery, and fetal loss[3]. High HCG and low PAPP-A levels may also be associated with some placental pathologies. In this study, we aim to investigate whether it is possible to predict IUGR in advance by comparing the postpartum outcomes of pregnant women diagnosed with IUGR and those who were able to achieve first-trimester screening test results. In addition, using these markers will demonstrate the success of predicting a poor neonatal outcome in pregnant women with IUGR.

Material and Methods

This study was conducted retrospectively after the decision of the ethics committee (Afyon Kocatepe University the Regional Ethical Review Board) approved the research protocol Date:10.11.21, Decision Number: 2021/113) by retrieving the information of pregnant women who had applied to a training and research hospital for 2 years from the hospital database and records. The study group consisted of those diagnosed with IUGR after the required examinations and who had delivered between 36-41 weeks of gestation, of whom we had access to first-trimester screening tests, and the control group consisted of those who had delivered a healthy baby between 36-41 weeks after a healthy pregnancy and of whom we had access to screening tests. The gestational week of the patients was calculated from their last menstrual period and confirmed by early

ultrasound measurements. None of the pregnant women enrolled in the study had a poor obstetric history or maternal or fetal problems. Patients with multiple pregnancies, aneuploidy, neural tube defects, abdominal wall defects, severe anatomic defects, diabetes mellitus, pregnancy-related hypertension, preeclampsia, premature rupture of membranes, and chronic maternal disease during follow-up were excluded from the study. The diagnosis of intrauterine growth and development delay was made in pregnant women with a normally localized placenta if the estimated birth weight was below the 10th percentile corresponding to the gestational week calculated by early pregnancy ultrasound. Patients with serologically detected intrauterine infection by (T)oxoplasmosis, (O)ther Agents, (R)ubella, (C)ytomegalovirus, and (H)erpes Simplex (TORCH) antibody in maternal serum at prenatal visits were not included in the study. All pregnant women were required to have a 75-g oral glucose tolerance test (OGTT) at their prenatal visits at 24-28 weeks gestation. Those who were deficient in the tests were not included in the study. After birth, the babies' weights and appearance, pulse, grimace, activity, and respiration (APGAR)s were checked. Those whose general condition could not be transferred to the mother were admitted to the neonatal intensive care unit. As criteria for the poor neonatal outcome, cases with respiratory distress syndrome, necrotizing enterocolitis, intraventricular hemorrhage, polycythemia, hypoglycemia, perinatal death, and severe IUGR below the 3rd percentile corresponding to the week of birth weight were included. Among pregnant women enrolled in the study, nuchal translucency (NT), PAPP-A, and free β-hCG were measured as first-trimester screening tests in those whose gestational ages ranged from 11 weeks to 13 weeks and 6 days. In those whose NT measurement was between 11 weeks and 13 weeks and 6 days, nuchal translucency was measured in millimeters when the fetus was in the normal longitudinal Crown Rump Length (CRL) measurement position by ultrasound. The determined value was recorded as the MoM value (multiple of median), corrected for age, weight, and gestational week. PAPP-A, free β-hCG values were analyzed from maternal venous blood samples collected during the corresponding week. After ultrafiltration, hemolyzed and non-lipemic serum samples were collected. The Immulite 2000 kit was used to measure the markers. An enzyme-labeled chemiluminescent immunometric solid-phase assay technique was used for the measurement. The sensitivity of the kit is 0.025 mIU/ml for PAPP-A and 1 ng/ml for free β-hCG. The values found were recorded as MoM values corrected for age, weight, and week of gestation.

Statistical Analysis

Analyses were performed using SPSS 26 (Statistical Package for Social Sciences, SPSS Inc, Chicago, IL, United States). When analyzing the distribution of continuously measured variables, the Shapiro-Wilk test was preferred. Descriptive statistics were presented as mean ± standard deviation or median (minimum-maximum) and (%) for nominal variables for continuously measured variables and different conditions. Student's t-test was used for normal distributions and the Mann-Whitney U test for non-normally distributed analyses.

Results

Information was obtained on a total of 257 pregnant women who underwent first-trimester screening, 125 of whom were IUGR, while 132 healthy pregnant women were considered the control group. While the mean age in the control group was 25.12 years, it was 25.78 years in the pregnant women with IUGR. This difference was statistically significant (p<0.001). The weight of pregnant women with IUGR was lower than that of normal pregnant women (p<0.001). Cigarette consumption was higher in the IUGR group. Demographic characteristics are summarized in Table 1.

Table 1. Demographic characteristics

Variables	**IUGR mean ± SD**	**Control Group mean ± SD**	**p**
Age (years)	25.78±4.6	25.12±5.1	**<0.001**
Smoking Status	9(%8.2)	4(%3)	**<0.001**
Mom weight	56.33±8.9	61.92±10	**<0.001**
Gravida	1.88±1.1	1.89±0.9	0.271
Parity	0.59±0.8	0.64±0.7	0.344
Abortus	0.27±0.62	0.21±0.4	0.247

*Values are mean ± standard deviation (mean ± SD).

When comparing the parameters of the first-trimester screening test, the PAPP-A value was normal. The mean value was 0.83 MoM in the control group and 0.69 MoM in the patient group (p=0.011). The mean value of free β-hCG was 1.17 MoM in the control group and 0.89 MoM in the patient group (p=0.023). While PAPP-A and free β-hCG were lower in the IUGR group than in the control group, this was statistically significant, while NT did not cause a statistically significant difference in either group (p=0.8). When

an MoM value of 0.32, corresponding to the 5th percentile for PAPP-A, is used as a cut-off value, normal pregnant women can be distinguished from those with IUGR with a sensitivity of 17.9%, a specificity of 94%, and a positive predictive value of 75.7%. When the value of 0.35 MoM, which corresponds to the 5th percentile for free β-hCG, is used as the cut-off value, pregnant women with IUGR can be detected with a sensitivity of 11.2%, a specificity of 95.4%, and a positive predictive value of 65 %. There was a statistical difference between groups in the demographic characteristics of pregnant women included in the study in terms of age, smoking, and weight. When the effects of these characteristics on determinants are removed, the significant impact of PAPP-A below 0.34 MoM on the development of IUGR remains. After adjustment for the same demographic characteristics, free β-hCG was found to lose its significant effect on the development of IUGR (p=0.251). Among these three markers, PAPP-A was the one that most strongly influenced the probability of IUGR (W=6.20). The combination of PAPP-A, free β-hCG, and NT resulted in a sensitivity of 27.3%, specificity of 92.1%, and PPV of 74.4% for predicting IUGR (Table 2).

Table 2. Performance measures for dual test components in predicting IUGR as a result of univariate analyses and combined tests (with 5% false positivity)

Dual test components	**Sensitivity**	**Selectivity**	**P.P. Val****	**N.P.Val*****
PAPP-A (<0.34)	%17.9	%94	%75.7	%57.3
free β-hCG (<0.38)	%11.2	%95.4	%65.0	%52.7
NT (<0.58)	%6	%96	%55.2	%54.7
DST*	%27.3	%92.1	%74.4	% 59

The values in *( ) are given as MoM values.

* PAPP-A+ free β-hCG + NT (Double Screening Test)

** Positive Estimated Value

*** Negative Estimated Value

The first-trimester screening test was performed on 125 patients from the group of pregnant women with IUGR. Of these, 78 had a good neonatal outcome and 47 had a poor neonatal outcome (11 respiratory distress syndrome, 2 necrotizing enterocolitis, 2 intraventricular hemorrhages, 10 polycythemia, 8 hypoglycemia, 3 meconium aspiration syndrome, 2 perinatal death, and 9 other causes). In these groups, the values for PAPP-

A and free β-hCG were the same in both groups. The NT value was significantly higher in the good neonatal outcome group than in the poor neonatal outcome group (p=0.02) (Table 3).

Table 3. The effect of first-trimester screening test on poor perinatal outcome in the group with IUGR

First-trimester screening test	GNO Median (min-max)	BNO Median (min-max)	p
PAPP-A (MoM)	0.57 (0.11-3.19)	0.65 (0.14-1.34)	0.672
free β-hCG (MoM)	0.87 (0.15-2.38)	0.71 (0.21-2.53)	0.154
NT (MoM)	0.91 (0.14-1.35)	1.01 (0.54-1.62)	0.010

GNO-Good neonatal outcome BNO-Bad neonatal outcome Median values and values in parentheses are expressed as minimum-maximum.

After adjustment for age, weight, and smoking, the difference in NT values, significant in itself, loses its value completely. None of the markers of the first-trimester screening test were successful in predicting low false positivity and poor perinatal outcomes. The sensitivity of the combined test was also 3% (Table 4).

Table 4. The performance criteria for predicting adverse perinatal outcomes in the IUGR group were assessed using single-variable analyses and combined test results.

Dual test components	Sensitivity	Selectivity	P.P. Val **	N.P.Val***
PAPP-A (<0.34)	%17.9	%81.2	%38.1	%61.1
free β-hCG (<0.38)	%14.8	%91.1	%51.2	%61.8
NT (<0.58)	-	%90.8	-	%59.3
DST *	%3.1	%95.5	%32.6	% 62.0

The values in *( ) are given as MoM values.

* PAPP-A+ free β-hCG + NT (Double Secreening Test)

** Positive Estimated Value

*** Negative Estimated Value

Discussion

When demographic characteristics were considered, there were no major differences between participants, except for variables such as smoking, age, and weight. In the group diagnosed with IUGR, the frequency of cigarette smoking was strikingly high[4]. Regarding maternal weight, it was found that the patient group, except for the control group, had a lower weight. To increase statistical certainty, adjustments were made for the variables of age, smoking, and weight. As mentioned in the introduction, the focus of this study was to determine whether certain fetoplacental steroids and/or proteins, such as PAPP-A and hCG, could be associated with poor perinatal outcomes in late pregnancy. Using the first-trimester screening test markers PAPP-A, free β-hCG, and NT, we found significant differences using MoM adjusted for age, smoking, and weight and correcting for gestational age[5]. There is a publication in the literature examining the ability of these markers to predict pregnant women with IUGR[6].

These have contradictory results. For example, one study says that first-trimester PAPP-A levels of babies born weighing less than the 5th percentile of gestational age and babies born weighing normal were compared, and no statistically significant difference was found[7]. However, another study revealed a positive correlation between birth weight and PAPP-A levels in early pregnancy[8]. In these studies, no adjustments were made for smoking and maternal weight[9]. In another study 1622 pregnant women who were in IUGR and examined the levels of PAPP-A, free β-hCG, and fetal NT between the groups, and they found that only the PAPP-A level was 3.3 times significant in detecting IUGR below 0.50 MoM[10]. In the group with IUGR, PAPP-A was successful in predicting IUGR with an odds ratio (OR) value of 5.4, a sensitivity of 3.3%, specificity of 99.3%, and a positive predictive value (PPV) of 24.1%, below 0.29 MoM, which is the 1st MoM. Free β-hCG, on the other hand, showed a sensitivity of 2% with a OR value of 2.7, a specificity of 99.2%, and a PPV of 14.3%, under the condition of being below the 0.21 MoM value, which is also the 1st percentile. In this study, similar to the literature, low levels of PAPP-A and free β-hCG in the first trimester were found to have a high predictive value for IUGR. We found that the value of NT was not significant in this regard. Although in many studies there was no association between free β-hCG level and IUGR[11]. These reflect different pathophysiological mechanisms and trophoblast function in the first trimester and poor perinatal outcomes in the late period. PAPP-A occupies a special position in the regulation of trophoblast function. PAPP-A is a protease for insulin-like growth factor binding protein (IGFBP)[12]. Because IGFBP cannot be destroyed by PAPP-A deficiency,

its level increases. The increase in IGFBP level binds more IGF-1 and IGF-2, and as free IGF decreases, this negatively affects fetal growth[3,11,12]. IGF controls the uptake of glucose and amino acids by trophoblasts and controls trophoblast invasion of the decidua in an autocrine and paracrine manner[13].

In a similar study, combining first-trimester screening markers for IUGR revealed that sensitivity below 0.45 (5th percentile) MoM value for PAPP-A and below 0.21 (1st percentile) MoM value has the highest sensitivity for free β-hCG when combined with NT 11.2% sensitivity, 95.3% specificity, and 13.8%. This study with PPV showed similar results. In this study, it was parallel to other studies[13]. Despite the variety of biochemical markers and different combinations with ultrasound markers, to date, we have not been able to find the combination that covers the following two criteria. 1. high PPV and NPV with high sensitivity and specificity at 5% false positivity 2. a screening test to predict IUGR in an unselected pregnant population. Since the studies in the literature were generally conducted between 1-15 centers over 2-7 years and generally investigated all poor pregnancy outcomes such as preeclampsia, IUGR, preterm labor, preterm rupture of membranes, etc., this study seems to be outnumbered[14]. This study seems to be outnumbered because it included all births at all weeks in the study. Some studies did not include changes in smoking, maternal weight, and age. In this study, only IUGR and the resulting poor perinatal outcomes were considered. In addition, only those who had delivered at 36 weeks or more were included in the study to avoid confounding the effects of preterm birth. The second aim of this study was to determine the success of predicting poor perinatal outcomes in patients with IUGR using screening tests in the first trimester. We compared fetuses with IUGR with poor perinatal outcomes to fetuses with IUGR with good perinatal outcomes we found that the levels of PAPP-A, free β-hCG, and NT were not significantly different between the two groups, and the combined test did not predict poor perinatal outcomes. We could not find any other study in the literature that investigated the success of predicting poor perinatal outcomes in pregnant women with IUGR using the levels of PAPP-A, free β-hCG, and NT, which are markers of first-trimester screening tests. Therefore, this study is important in that it is the only study on this topic.

Conclusion

A low serum PAPP-A level in the first trimester may be useful to assess poor pregnancy outcomes and the diagnosis of IUGR, which may develop in the later stages of pregnancy. We found that the sensitivity of PAPP-A, free β-hCG, and NT for IUGR was 27.3%,

specificity was 92.1%, and positive predictive value was 74.4%. In the next part of the personnel, we compared babies with IUGR with those with good and poor perinatal outcomes. In the results obtained here, we found that no marker was associated with poor perinatal outcomes. In this literature search, we concluded that there are few similar studies and that larger studies will contribute to the literature.

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