Various Perspectives on Foreseeing Placental Failure

Plasental Yetersizliği Öngörmede Çeşitli Bakış Açıları

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Abstract

Objective: Low values of pregnancy-associated plasma protein-A (PAPP-A) routinely observed during the first trimester testing may be a preliminary indicator of developmental delay. Doppler flow measurements and fetal biometric measurements (FBMs) that would be performed in the second trimester together with low PAPP-A values may be useful in predicting poor pregnancy outcomes.

Methods: The pregnant women were followed until delivery. PAPP-A values measured during the first trimester test of pregnant women participating in the study were recorded. Later on, color pulsed Doppler ultrasound examination of umblical artery was performed on the 20th-24th and 28th-32th weeks of pregnancy.

Results: In the present study, we achieved a sensitivity of 70.6% and a specificity of 48.9% for poor pregnancy outcomes, when the cut-off value for umbilical artery pulsatility index (PI) was 1.135 during the 20th-24th weeks of pregnancy. On the 28th-32nd weeks of pregnancy; when the cut-off value of umbilical artery PI was taken as 0.85, a sensitivity of 82.4% and a specificity of 22.7% were achieved for poor pregnancy outcomes. In the present study, the pregnant women of whom estimated gestational age that was calculated based on ultrasonographic. FBMs performed on the 20th-24th and 28th-32nd weeks of pregnancy was more than 1 week behind the gestational age that was calculated according to the last menstrual period and the pregnant women with head circumference/abdominal circumference (HC/AC) ratio over 1.15 and 1.10 on the 20th-24th and 28th-32nd weeks of pregnancy, respectively were considered as risky group in terms of early-onset fetal growth retardation. The group of risky pregnant women was compared with the other group of pregnant women and significant difference was determined in terms of pregnancy outcomes.

Conclusion: We found that early prediction of unfavorable maternal and fetal outcomes of placental insufficiency might be possible using some test results, such as FBMs or assessment of HC/AC ratio, even though there is no method that can be used alone as a screening test.

Keywords: Fetal Doppler ultrasound, fetal biometric measurements, fetal growth retardation, placental insufficiency, umblical artery

Öz

Amaç: İlk trimester testi sırasında rutin olarak gözlemlenen düşük gebelikle ilişkili plazma protein-A (PAPP-A) değerleri, gelişimsel gecikmenin bir ön göstergesi olabilir. Düşük PAPP-A değerleri ile birlikte ikinci trimesterde yapılacak fetal Doppler akım ölçümleri ve fetal biyometrik ölçümler kötü gebelik sonuçlarını tahmin etmede faydalı olabilir.

Yöntem: Tüm gebeler doğuma kadar takip edildi. Çalışmaya katılan gebelerin ilk trimester testi sırasında ölçülen PAPP-A değerleri kaydedildi. Daha sonra gebeliğin 20.-24. ve 28.-32. haftalarında umblikal arterin renkli pulslu Doppler ultrason muayenesi yapıldı

Bulgular: Bu çalışmada, gebeliğin 20.-24. haftaları arasında umblikal arter pulsatilite indeksi (PI) için kesme değeri 1,135 iken, kötü gebelik sonuçları için %70,6 duyarlılık ve %48,9 özgüllük elde ettik. Gebeliğin 28.-32. haftalarında umblikal arter PI kesme değeri 0,85 olarak alındığında, kötü gebelik sonuçları için %82,4 duyarlılık ve %22,7 özgüllük elde edilmiştir. Çalışmamızda, gebeliğin 20.-24. ve 28.-32. haftalarında yapılan fetal biyometrik ölçümlerde son adet tarihine göre hesaplanan gestasyonel yaştan 1 haftadan fazla gerisinde kalan ve HC/AC oranı 20.-24. ve 28.-32. haftalar için sırasıyla 1,15 ve 1,10'un üzerinde

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Öz

olan gebeler erken başlangıçlı fetal büyüme geriliği açısından riskli grup olarak kabul edildi. Riskli gebeler grubu, diğer gebe grubu ile karşılaştırıldı ve gebelik sonuçları açısından anlamlı farklılık tespit edildi.

Sonuç: Tarama testi olarak tek başına kullanılabilecek bir yöntem olmamasına rağmen, plasental yetmezliğin olumsuz maternal ve fetal sonuçlarının erken tahmin edilmesinin bazı fetal biyometrik ölçümler veya HC/AC oranının değerlendirilmesi kullanılarak mümkün olabileceğini bulduk.

Anahtar Kelimeler: Fetal Doppler ultrason, fetal biyometrik ölçümler, fetal büyüme geriliği, plasental yetmezlik, umblikal arter

Introduction

Hypertensive diseases due to pregnancy, preterm-premature labor and intrauterine growth retardation are the most significant poor results of placental insufficiency. A significant number of studies on risky pregnancies and poor pregnancy outcomes have focused on this possible placental insufficiency. For this, various biomarkers [such as alpha-fetoprotein, human chorionic gonadotropin (hCG), pregnancy-associated plasma protein-A (PAPP-A)] have been examined, various doppler currents have been measured during different gestational weeks by the help of advanced ultrasonic technologies, and attempts have been made to predict possible poor pregnancy outcomes[1,2].

PAPP-A (PAPP-A, pappalysin-1, EC 3.4.24.79), which is among the most prevalently studied biomarkers, is a specific protease of insulin-like growth factor (IGF) binding proteins (IGFBP). Thus, it has been shown to be one of the signs of placental insufficiency. IGFBPs bind to IGFs 1 and 2 and interrupt their association with cell surface receptors. For this reason, low PAPP-A values are associated with low bioactive IGF levels. IGFs that play an active role in cell division and differentiation are very important in regulating fetal and placental development and also in embryogenesis[1].

Low values of PAPP-A routinely observed during first trimester testing may be a preliminary indicator of developmental delay. Doppler flow measurements and fetal biometric measurements (FBMs) that would be performed in the second and third trimester together with low PAPP-A values may be useful in predicting poor pregnancy outcomes[3-5].

We aimed to determine the predictive value of maternal PAPP-A levels measured within the first trimester, umbilical artery Doppler velocimetry measured in the second and third trimesters and FBMs of the second and third trimester for poor pregnancy outcomes.

Materials and Methods

This prospective cohort study was designed at a single pregnancy clinic with an approval of the Dokuz Eylül University Ethics Committee. Singleton pregnant women were included, and their informed consent was acquired. A total of 175 patients were planned to participate in the study.

The pregnant women were followed until delivery. The PAPP-A values recorded during the first trimester tests of the pregnant women participating in the study were recorded (access PAPP-A© 2020 Beckman Coulter, Inc. Pregnancy-associated plasma protein A, A48571). Later on, color pulsed Doppler ultrasound examination of umbilical artery was performed at the 20th-24th and 28th-32nd weeks of pregnancy. Doppler flow indices [pulsatility index (PI) and resistance index] were measured, and their arithmetic means were calculated. Diastolic flow loss, absence or reverse current in the waveforms were recorded. During the same pregnancy weeks, fetal biparietal diameter, head circumference (HC), abdominal circumference (AC) and femur length were measured, and the HC/AC ratio was calculated. The pregnancies included in the study were followed up to birth; preterm birth, premature birth, threat of preterm labor, premature rupture of membranes, gestational hypertension or preeclampsia, ablatio placenta, fetal or neonatal death information was identified, and the birth weights were recorded. According to the outcomes, the women were divided into two groups as the group with poor pregnancy outcomes and the group without poor pregnancy outcomes. These groups were then compared by the results of the tests specified above to determine the predictive values of those analyses.

All measurements were performed by a single physician, using a Voluson 730 Expert Color Doppler ultrasonic device (General Electric Company, United States), and the records were evaluated by a single researcher.

The pregnant women, of whom estimated gestational age according to the ultrasonographic FBMs performed at the

20th-24th and 28th-32nd weeks of pregnancy was more than one week behind the gestational age calculated according to the last menstrual period, and the pregnant women with an HC/AC ratio over 1.15 and 1.10 at the 20th-24th and 28th-32nd weeks of pregnancy, respectively, were considered as the risky group in terms of early-onset growth retardation. These risky pregnant women and their measurements were compared to those of the pregnant women whose estimated gestational age according to the FBMs was consistent with the gestational age calculated according to the last menstrual period in terms of pregnancy outcomes and birth weight.

Gestational hypertension was diagnosed if the arterial blood pressure of the patient was 140/90 mmHg and higher, and preeclampsia was diagnosed if high blood pressure was accompanied by proteinuria (300 mg/dL and over in 24- hours urine sample)[6]. Births before the 37th week of pregnancy were considered as preterm birth, and births before the 32nd week of pregnancy were considered as premature birth.

Statistical Analysis

A prospective cohort study design was chosen to conduct the study to minimize a potential bias that could result from the nature of the trial. The obtained data were analyzed using chi-squared, Mann-Whitney U and Student's t-tests using the Statistical Package for Social Sciences, version 15.0 program. A value of $p < 0.05$ was considered as statistically significant. The parameters assumed to predict pregnancy outcomes were evaluated by receiver operating characteristic (ROC) curves.

Results

A total of 175 singleton pregnancies were included in the study. Among these pregnancies, 3 were terminated because of missed abortion, and 1 was terminated with the diagnosis of Trisomy 21. Thirteen patients were followed up in different parts of the study. The remaining 158 patients constituted the sample (Table 1). A total of 17 (10.75%) pregnant women, with at least one poor pregnancy outcome were observed in the follow-ups of the participants (Table 2).

The Doppler ultrasound of the umbilical artery was performed at the 20th-24th and 28th-32nd weeks of pregnancy. The umbilical artery PI (UAPI) values of these periods were calculated, and the ROC curve was drawn (Figures 1, 2). At the 20th-24th week of pregnancy, when the cutoff value for the UAPI was taken as 1.135, 70.6% sensitivity and 48.9% specificity were achieved for poor pregnancy outcomes. At

Table 1. The clinico-demographic characteristics of the study participants

Characteristics	Descriptive values	Additional explanation
Age	27.9±4.4 yr	Range: 17-41
Weight	62.8±10.1 kg	Range: 42-108
Smoking	8 women (5.06%)	2-8 pieces/day
First pregnancy	64 women (40.5%)	–
Previous poor pregnancy outcome	18 women (11.4%)	PIH, preeclampsia, GDM, preterm birth, EMR, IUGR, prematurity, Trisomy 21, fetal anomaly
Concomitant disease	13 women (8.2%)	Hypo-hyperthyroidism, FMF, psoriasis, cardiac valve diseases, chronic HT, asthma, thalassemia carrier
Medications	7 women (4.4%)	Levothyroxine, colchicine, alfa methyldopa

EMR: Early membrane rupture, FMF: Familial Mediterranean Fever, PIH: Pregnancy-induced hypertensive disease, GDM: Gestational diabetes mellitus, IUGR: Intrauterine growth retardation, HT: Hypertension, yr: Year

Table 2. Numeric and proportional distribution of poor pregnancy outcomes determined during follow-up

Outcomes	Number of patients (n=17)	Percentage (%)
PIH/preeclampsia	5 (3/2)	3.16
Threat of preterm labor	1	0.63
Premature membrane rupture	4	2.53
Preterm birth	14	8.86
Premature birth	–	–
Need for neonatal intensive care	7	4.43
Low birth weight	7	4.43
Placental abruption (ablatio placentae)	–	–

PIH: Pregnancy-Induced hypertensive disease

the 28th-32nd weeks of pregnancy, when the limit value of the UAPI was taken as 0.85, 82.4% sensitivity and 22.7% specificity were achieved for poor pregnancy outcomes.

The mean values of (UAPImean) obtained during the 20th-24th and 28th-32nd weeks of pregnancy were calculated, and two groups were formed according to these values (Tables 3, 4). The pregnancy outcomes and infant birth weights of these two
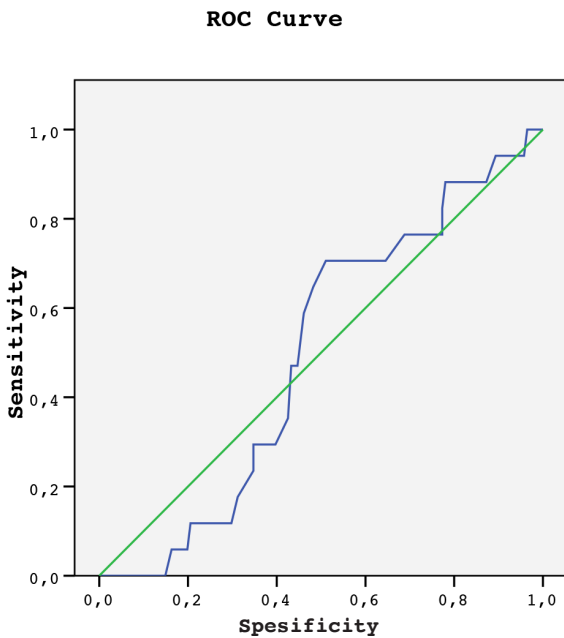
ROC Curve

Figure 1. Receiver operating characteristic curve for umbilical artery pulsatility index values at the 20th-24th weeks of pregnancy

ROC Curve

Figure 2. Receiver operating characteristic curve for umbilical artery pulsatility index values at the 28th-32nd weeks of pregnancy

groups were compared. At the 20th-24th weeks of pregnancy, there was no significant difference between the pregnancy outcomes in the two groups according to the mean value of 1.17±0.25 (p value=0.852). There was a weight difference of 126 g in favor of the group below the UAPImean, but this difference was not statistically significant (p value=0.069). At the 28th-32nd weeks of pregnancy, two groups were formed according to the mean value of 0.97±0.15, and the mean fetal weight was higher in the group below the UAPImean (about 104 gr), but this difference was not statistically significant (p value=0.133). There was no significant difference according to the pregnancy outcomes between the two groups (p value=0.783).

ROC curves were generated for the HC/AC ratios observed during 20th-24th and 28th-32nd weeks of pregnancy (Figures 3, 4).
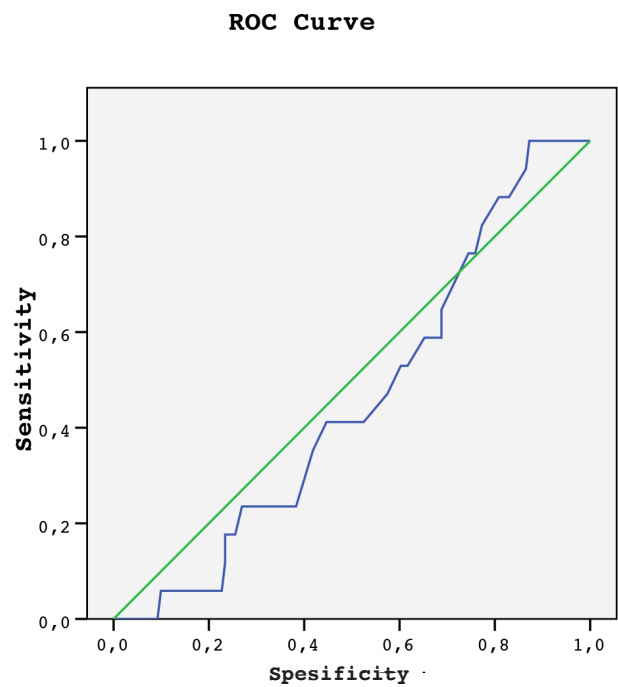
When the limit value of 1.135 was taken for the 20th-24th weeks of gestation [standard error, (SE): 0.039] [95% confidence interval (CI): 0.646-0.798], the sensitivity, specificity, PPV and NPV for poor pregnancy outcomes were 58.8%, 49.6%, 56% and 49%, respectively. When the cutoff value of the HC/AC ratio for the 28th-32nd weeks of pregnancy was taken as 1.075 (SE: 0.039) (95% CI: 0.646-0.798), the resulting values were as 52.9% sensitivity, 41.1% specificity, 59% PPV and 67% NPV.

The risky pregnant women in terms of early-onset growth retardation specified in the material and methods section and their measurements (inconsistent FBMs subgroup) were compared to those of the pregnant women of whom estimated gestational age according to the FBM was consistent with the gestational age calculated according to the last menstrual

Table 3. Comparisons of two groups formed by UAPImean value on the 20th-24th weeks of pregnancy with pregnancy outcomes and mean fetal birth weight

| UAPImean	Pregnancy outcome* (n=158)		Fetal birth weight (n=158)
	Poor (n=17)	Not poor (n=141)	Mean (g)**
≤1.16 (n=87)	9 (10.3%)	78 (89.7%)	3310.1 (±428.7)
≥1.17 (n=71)	8 (11.3%)	63 (88.7%)	3184.7 (±428.6)
*Chi-square test: p=0.852 for comparison between pregnancy outcomes and UAPImean.			
**T-test: p=0.069 for comparison between mean fetal birth weight and UAPImean.			
UAPImean: Mean values of umbilical artery pulsatility index			

period (consistent FBMs subgroup) in terms of pregnancy outcomes and birth weight. A statistically significant difference was determined between the two subgroups in terms of the pregnancy outcomes (p=0.045). There was 217 g. of difference between the subgroups in terms of birth weight, which was statistically significant (p=0.011) (Table 5). Additionally, the inconsistent FBMs subgroup was compared to the consistent FBMs subgroup according to the PAPP-A
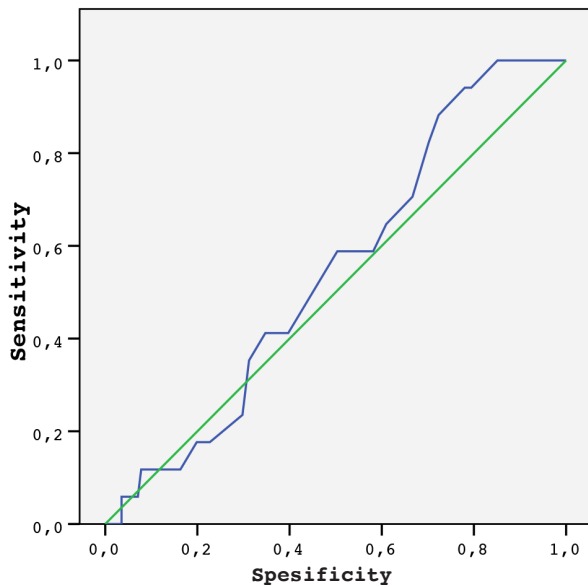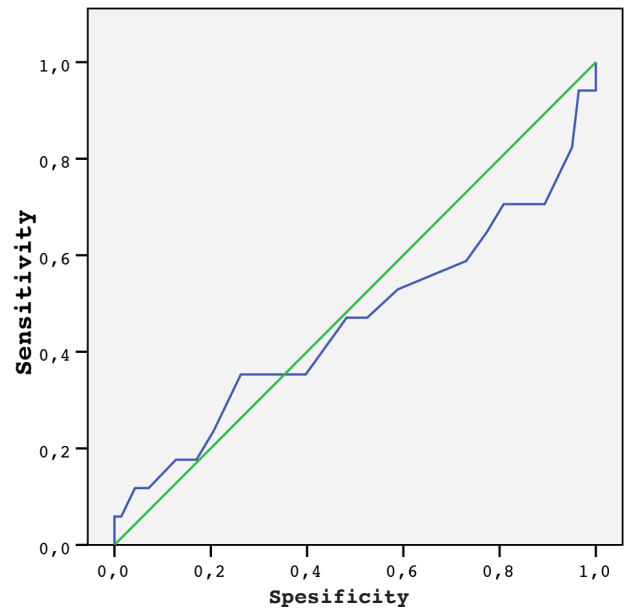
ROC Curve

Figure 3. Receiver operating characteristic curve for head circumference/abdominal circumference ratio measured at the 20th-24th weeks of pregnancy

ROC Curve

Figure 4. Receiver operating characteristic curve for head circumference/abdominal circumference ratio measured at the 28th-32nd weeks of pregnancy

Table 4. Comparisons of two groups formed by UAPImean value on the 28th-32nd weeks of pregnancy with pregnancy outcomes and mean fetal birth weight

UAPImean	Pregnancy outcome* (n=158)		Fetal birth weight (n=158)
	Poor (n=17)	Not poor (n=141)	Mean (g)**
≤0.96 (n=88)	10 (11.4%)	78 (88.6%)	3299.1 (±455.7)
≥0.97 (n=70)	7 (10%)	63 (90%)	3196.6 (±395.7)
*Chi-square test: p=0.783 for comparison between pregnancy outcomes and UAPImean.			
**T-test: p=0.133 for comparison between mean fetal birth weight and UAPImean.			
UAPImean: Mean values of umbilical artery pulsatility index			

Table 5. Comparisons of two subgroups formed by fetal biometric measurements with pregnancy outcomes and mean fetal birth weight

Fetal biometric measurements	Pregnancy outcome* (n=158)		Fetal birth weight (n=158)		
	Poor (n=17)	Not poor (n=141)	Mean (g)**	Median	Range
Consistent (n=130)	11 (8.5%)	119 (91.5%)	3292.1 (±440.7)	3313.5	1860-4600
Inconsistent (n=28)	6 (21.4%)	22 (78.6%)	3075.7 (±341.1)	3110	2500-3740
*Chi-square test: p=0.045 for comparison between pregnancy outcomes and fetal biometric measurements.					
**Mann-Whitney U test: p=0.011 for comparison between mean fetal birth weight and fetal biometric measurements					

Table 6. Comparisons of two groups formed by fetal biometric measurements on the 20th-24th and 28th-32nd weeks of pregnancy and maternal PAPP-A values on the 10th-14th weeks of pregnancy			
Fetal biometric measurements	PAPP-A<0.55	PAPP-A≥0.55	Total
Consistent	18 (13.8%)	112 (86.2%)	130 (100%)
Inconsistent	5 (17.9%)	23 (82.1%)	28 (100%)
Total	23 (14.6%)	135 (85.4%)	158 (100%)
*Chi-square test: p=0.585 for comparison between maternal PAPP-A values and fetal biometric measurements. PAPP-A: Pregnancy-associated plasma protein-A			

values which were measured during the first trimester tests of pregnancy (Table 6). In terms of the PAPP-A values, no significant difference was found between the two groups (p=0.585).

Discussion

Insufficient placentation is the most significant cause for poor pregnancy outcomes. Lots of studies on the etiology of risky pregnancies, such as IUGR, preeclampsia, preterm and premature birth, underline the importance of normal placental development. Markers that could indicate these changes prior to the onset of a disorder will provide us with a chance to take early preventive measures and even prevent these in the future. For this reason, particularly in recent years, many studies on numerous placental biochemical markers, various Doppler ultrasound techniques and parameters and various ultrasonographic methods that evaluate fetal and placental development in order to determine placental defects have been carried out.

The association between low hCG (<0.5 MoM) and PAPP-A (<0.4 MoM) levels, which are measured at the 10th-14th weeks of pregnancy, and the complications of pregnancy has been demonstrated previously[7,8]. In this study, as well, poor pregnancy outcomes could be predicted with 82.4% sensitivity and 29.8% specificity when the cutoff value was taken as 0.72 MoM in the ROC curve drawn for PAPP-A, which was measured at the 11th-14th weeks of pregnancy.

Doppler ultrasonography of the umbilical arteries is the other method used for early prediction of pathological placentation and can be performed in various weeks of pregnancy[9-12]. In this study, the Doppler ultrasound of umbilical arteries was performed at the 20th-24th and 28th-32nd weeks of pregnancy, the mean values were calculated, and then, ROC curves were drawn. We achieved a sensitivity of 70.6% and a specificity of 48.9% for poor pregnancy outcomes, when the cutoff value for UAPI was 1.135 during the 20th-24th weeks of pregnancy. At the 28th-32nd weeks of pregnancy, when the cutoff value of the UAPI was taken as 0.85, a sensitivity of 82.4% and

a specificity of 22.7% were achieved for poor pregnancy outcomes.

In a study conducted by Ghosh and Gudmundsson[13], in 353 pregnancies, pathological Doppler findings of the uterine artery and/or umbilical artery were found to be significant in terms of fetal growth retardation. Furthermore, Romero Arauz et al.[14] examined the umbilical artery Doppler flows of 43 severe preeclamptic pregnancies, who were in their 27 to 33 weeks of gestation, and found that perinatal outcomes were worse in patients with a PI index greater than 95% or a pathological wave form. Conversely, Stampalija et al.[15] suggested that uterine artery and umbilical artery Doppler ultrasound examination did not benefit the mother or the baby in low-risk pregnancies, according to the Cochrane study involving 14,185 pregnancies.

Other important ultrasonographic indicators of placental insufficiency are FBMs and their ratio to each other. In this study, the pregnant women in whom estimated gestational age that was calculated based on ultrasonographic FBMs performed at the 20th-24th and 28th-32nd weeks of pregnancy was more than 1 week behind the gestational age that was calculated according to the last menstrual period and the pregnant women with an HC/AC ratio over 1.15 and 1.10 at the 20th-24th and 28th-32nd weeks of pregnancy, respectively, were considered as the risky group in terms of early-onset fetal growth retardation. The group of risky pregnant women was compared to the other group of pregnant women, and a statistically significant difference was determined in terms of the pregnancy outcomes (p=0.045). There was a 217-g difference, which was statistically significant (p=0.011), between the mean fetal birth weights of the groups. In the literature, studies on this topic are not many, excluding two separate studies conducted by Fox et al.[16,17] suggesting an association between a HC/AC ratio >90th percentile and poor pregnancy outcomes and the study conducted by Colley et al.[18] determining a weak correlation between the HC/AC ratio and the ponderal index. In addition to the information in the literature, the results of this study indicated that it is

possible to obtain significant results in terms of pregnancy outcomes and fetal birth weight in the light of precise FBMs and assessment of the HC/AC ratio[19].

Study Limitations

It can be listed as the small number of patients and the fact that the study was conducted only in one center.

Conclusion

We aimed to determine the predictive value of the maternal PAPP-A level of the first trimester, umbilical artery Doppler velocimetry of the second and third trimesters and FBMs of the second and third trimesters for poor pregnancy outcomes which would probably occur due to placentation defect in pregnant women and found that early prediction of unfavorable maternal and fetal outcomes of placental insufficiency might be possible using some test results, such as FBMs or assessment of the HC/AC ratio, even though there is no method that can be used alone as a screening test. Therefore, different combinations of current biochemical and ultrasonographic methods may be necessary. In order to predict obstetric complications due to placental insufficiency, a screening test with a specific combination and definite limit values for biochemical and ultrasonographic markers, which will be created in the light of multicenter studies with a broader patient population, should be established in the future.

Ethics

Ethics Committee Approval: The study were approved by the Dokuz Eylül University Ethics Committee.

Informed Consent: Consent form was filled out by all participants.

Peer-review: Externally peer-reviewed.

Financial Disclosure: The author declared that this study received no financial support.

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