

Analysis of the relationship between maternal second trimester AFP, HCG, estriol levels and uterine artery Doppler findings in the prediction of pregnancy complications

Banu Dane¹, Gonca Batmaz¹, Kamuran Kılavuz², Yaprak Rüstemoğlu², Hande Güler², Cem Dane²

¹Department of Obstetrics and Gynecology, Faculty of Medicine, Bezmialem Vakıf University, Istanbul, Turkey

²Department of Obstetrics and Gynecology, Haseki Training and Research Hospital, Istanbul, Turkey

Abstract

Objective: The aim of this study was to evaluate the relationship between triple test markers, second trimester uterine artery Doppler findings, pregnancy-induced hypertension (PIH) and small for gestational age (SGA) babies.

Methods: Maternal serum alpha-fetoprotein (MSAFP), human chorionic gonadotropin (MSHCG) and Estriol were evaluated for Down syndrome screening in 829 pregnant women. Uterine artery Doppler studies were performed at 20th-26th weeks of gestation. Diastolic blood pressure >90 mmHg after the 20th week of gestation was defined as PIH. Birth weight <10th percentile was termed as SGA.

Results: PIH developed in 71(8.5%) women, and 136 (16.4%) of the babies were SGA. MSAFP level was higher in PIH (1.05 vs. 0.94 MoM; p=0.03) and SGA babies (1.12 vs. 0.92 MoM; p<0.0001). MSHCG level was higher in PIH group (1.32 vs. 1.15 MoM; p= 0.036). MSAFP level in cases with bilateral notching (BLN+) was higher than the cases with absent or unilateral notching (1.03 vs. 0.92 and 0.93 MoM; p=0.005). Using a cut off value >0.98 MoM for MSAFP, we could detect PIH cases in the group BLN+ (sensitivity 65%; specificity 63%), and using a cut off value >1.09 MoM, SGA babies of hypertensive mothers could be detected (sensitivity 75%; specificity 72.5%) in the study group.

Conclusion: High MSAFP, MSHCG levels, and abnormal uterine artery Doppler findings at second trimester are related with pregnancy complications. In cases with BLN+, high level MSAFP may contribute to the prediction of PIH. MSAFP level have a better predictive value for SGA birth weight associated with PIH.

Key words: Uterine artery, Doppler, triple test, hypertension, intrauterine growth restriction

Gebelik komplikasyonlarının öngörüsünde maternal ikinci trimester AFP, HCG, estriol değerleri ve uterin arter Doppler bulguları arasındaki ilişkinin değerlendirilmesi

Amaç: Bu çalışmanın amacı üçlü test belirteçleri, ikinci trimester uterin arter Doppler bulguları, gebeliğe bağlı hipertansiyon (PIH) ve gebelik haftasına göre küçük (SGA) bebekler arasındaki ilişkiyi değerlendirmektir.

Yöntem: Maternal serum alfa fetoprotein (MSAFP), maternal serum human koryonik gonadotropin (MSHCG) ve estriol değerleri Down sendromu taraması amacıyla 829 gebe kadında belirlendi. Uterin arter Doppler değerlendirmesi 20-26. gebelik haftaları arasında yapıldı. Diyastolik kan basıncı 20. gebelik haftasından sonra >90 mmHg olarak tespit edilenler PIH olarak kabul edildi. Doğum kilosu <10. persantilde olanlar SGA olarak tanımlandı.

Bulgular: PIH 71 (%8.5) kadında gelişirken, bebeklerin 136'sı (%16.4) SGA idi. MSAFP değerleri PIH (1.05'e karşılık 0.94 MoM; p=0.03) ve SGA bebeklerde (1.12'ye karşılık 0.92 MoM; p<0.0001) daha yüksekti. MSHCG değeri PIH grubunda daha yüksekti (1.32'ye karşılık 1.15 MoM; p= 0.036). MSAFP değeri bilateral çentiklenme (BLN+) bulunan olgularda çentiklenme bulunmayan veya tek taraflı olan olgulardan daha yüksekti (1.03, 0.92 ve 0.93 MoM; p=0.005). MSAFP değeri >0.98 MoM sınır olarak alındığında, BLN+ bulunan grupta PIH olgularını %65 duyarlılık, %63 özgüllük ile, MSAFP >1.09 MoM sınır olarak alındığında ise çalışılan grupta hipertansif annelerin SGA bebeklerini %75 duyarlılık, %72.5 özgüllük ile tespit edebildik.

Sonuç: İkinci trimester yüksek MSAFP, MSHCG değerleri ve anormal uterin arter Doppler bulguları gebelik komplikasyonları ile ilişkilidir. Bilateral çentiklenme bulunan olgularda yüksek MSAFP değeri PIH öngörüsünde katkı sağlayabilir. MSAFP değeri PIH ile ilişkili SGA doğum kilosunun öngörüsünde daha etkindir.

Anahtar sözcükler: Uterin arter, Doppler, üçlü test, hipertansiyon, intrauterin büyüme kısıtlılığı.

Correspondence: Banu Dane, MD. Emlak Bankası Konutları
B1D12 Fatih, Istanbul, Turkey.
e-mail: banudane@yahoo.com

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Introduction

Various serum markers of fetoplacental unit measurable in the maternal circulation have been evaluated in the prediction of preeclampsia. Abnormal elevations of serum markers, both alpha-fetoprotein (AFP) and human chorionic gonadotropin (HCG), have been reported to be associated adverse pregnancy outcomes.^[1-4] Uterine artery Doppler screening identifies women at high risk for pregnancy complications. Combining uterine artery waveform analysis with biochemical parameter of placental function is considered to be the key of improving the predictive value of Doppler velocimetry.^[5,6]

In women with extreme levels of feto-placental proteins used for Down syndrome screening, abnormal second trimester uterine artery Doppler findings were reported to be related with a high risk of adverse pregnancy outcome, small for gestational age birth weight in particular.^[7-10]

The aim of this study was to evaluate the relationship between triple test markers, uterine artery Doppler findings, pregnancy-induced hypertension (PIH) and small for gestational age (SGA) babies in our pregnant population.

Methods

Maternal serum alpha-fetoprotein (MSAFP), human chorionic gonadotropin (MSHCG) and Estriol (MSE3) were evaluated in the screening program (triple test) for Down syndrome in all of pregnant women at 16th-18th weeks unless they were screened at first trimester. Serum levels of the markers were assayed by chemiluminescent enzyme immunoassay methods (Immulite 2000, Siemens Healthcare Diagnostics Product LTD, Tarrytown, NY, US), absolute concentrations of the analyses were converted into multiples of the median (MoM) for gestational age. MoM values and adjusted risks were calculated by Prisca 4.0 package screening software (Typolog Software GmbH, Tornesch, Germany).

After the determination of aneuploidy risk, an ultrasound examination was offered at second trimester for measurement of fetal growth and examination of fetal anomalies. Uterine artery Doppler studies were performed at 20th-26th weeks of gestation by transabdominal ultrasound (Logiq 400 Pro, GE Healthcare, Buckinghamshire, UK). At the point where the uterine artery and external iliac artery appeared to have crossed

each other, as detected by color Doppler, pulsed wave Doppler was used to obtain three consecutive waveforms. Resistance index (RI), pulsatility index (PI) and the presence or absence of early diastolic notching were noted. The process was repeated for the contralateral uterine artery, the mean PI and RI values of the two vessels were calculated.

Data on pregnancy outcomes were obtained from examination of each patient's clinical history and labor ward records. Women with diastolic blood pressure >90 mmHg after the 20th week of gestation previously normotensive were defined as PIH.^[11] Birth weight <10th percentile was termed as SGA.

Statistical analysis

The collected data were analyzed by MedCalc for Windows. Data were presented as means $\pm$ standard deviations or numbers of subjects and percent. Student's t-test was used for continuous variables, while one-way ANOVA was used to compare the variables of three groups. The efficiency of serum markers in predicting PIH was determined by establishing the receiver operator characteristic (ROC) curves. A P value of <0.05 was regarded as significant.

Results

During the study period (January 2008-March 2011), 1064 women underwent both triple test and second trimester sonographic examination. The pregnancy outcome was determined in 845 cases. Sixteen cases were excluded from the study (Down syndrome in 3, neural tube defect 3, fetal cardiac anomaly 1, idiopathic thrombocytopenic purpura 1, placenta previa 1, chronic renal disease 1, type 1 diabetes 6 cases). The study group consisted of 829 cases with a median age of 27 (range 17-42 years), 352 women (42%) were nulliparous. In 212 (25%) of the cases bilateral early diastolic notching (BLN+) was present. Mean MSAFP level in cases with BLN+ was significantly higher than the cases with absent or unilateral notching (1.03 vs. 0.92 and 0.93 MoM; $p=0.005$) (**Table 1**).

PIH developed in 71(8.5%) women. Mean levels of MSAFP (1.05 vs 0.94 MoM; $p=0.03$) and MSHCG (1.32 vs. 1.15 MoM; $p=0.036$), pI, RI and the prevalence of cases with BLN+ were significantly higher in cases in the group of PIH (Table 2). In the study group 136 (16.4%) of the babies were SGA. Mean level of MSAFP (1.12 vs. 0.92 MoM; $p<0.0001$), PI, RI and the

Table 1. Comparison of mean levels of the markers in the presence of early diastolic notching.

	AN (n:468)	ULN (n:149)	BLN (n:212)	P value
AFP MoM (mean)	0.92	0.93	1.03	0.005
HCG MoM (mean)	1.15	1.13	1.23	0.26
E3 MoM (mean)	1.47	1.47	1.45	0.93

AN: Absent notch, ULN: Unilateral notch, BLN: Bilateral notch

Table 2. Demographic characteristics, maternal serum markers and Doppler findings.

	Normotensive (n=758)	PIH (n=71)	P value
Maternal age (years, mean $\pm$ SD)	27.6 $\pm$ 5.3	29.45 $\pm$ 6	0.005
GA at scan (weeks, mean $\pm$ SD)	22.06 $\pm$ 1.16	22.3 $\pm$ 1.25	0.09
Nulliparity	316(41.6%)	36(50.7%)	0.17
AFP MoM (mean $\pm$ SD)	0.94 $\pm$ 0.4	1.05 $\pm$ 0.49	0.03
HCG MoM (mean $\pm$ SD)	1.15 $\pm$ 0.63	1.32 $\pm$ 0.88	0.036
E3 MoM (mean $\pm$ SD)	1.47 $\pm$ 0.66	1.45 $\pm$ 0.79	0.81
PI (mean $\pm$ SD)	0.88 $\pm$ 0.28	1.2 $\pm$ 0.44	<0.0001
RI (mean $\pm$ SD)	0.53 $\pm$ 0.08	0.62 $\pm$ 0.11	<0.0001
Bilateral notch	168 (22.1%)	44 (61.9%)	<0.0001

PIH: Pregnancy-induced hypertension

prevalence of cases with BLN+ were significantly higher in the group of SGA babies (**Table 3**).

MSAFP (AUC=0.56; p=0.08), MSHCG (AUC=0.53; p=0.39) and MSE3 (AUC=0.52; p=0.47) were not effective in the prediction of PIH. In the cases with bilateral notching MSAFP level (AUC 0.63;

p=0.0055) was effective in the prediction of PIH, while MSHCG level (AUC 0.54; p=0.45) and MSE3 (AUC 0.5; p=0.97) were not effective (**Fig. 1**). In the group with BLN+ using a cut off value > 0.98 MoM for AFP, we could detect the cases with PIH with a sensitivity of 65% and specificity 63%.

Table 3. Demographic characteristics, maternal serum markers and Doppler findings.

	AGA and LGA (n=693)	SGA (n=136)	P value
Maternal age (years, mean $\pm$ SD)	27.83 $\pm$ 5.3	27.6 $\pm$ 5.5	0.64
GA at delivery (weeks, mean $\pm$ SD)	39.2 $\pm$ 1.4	38 $\pm$ 3.1	<0.0001
Nulliparity	282(40.6%)	70(51.4%)	0.025
AFP MoM (mean $\pm$ SD)	0.92 $\pm$ 0.35	1.12 $\pm$ 0.6	<0.0001
HCG MoM (mean $\pm$ SD)	1.15 $\pm$ 0.64	1.23 $\pm$ 0.71	0.19
E3 MoM (mean $\pm$ SD)	1.47 $\pm$ 0.66	1.46 $\pm$ 0.75	0.87
PI (mean $\pm$ SD)	0.87 $\pm$ 0.26	1.14 $\pm$ 0.41	<0.0001
RI (mean $\pm$ SD)	0.53 $\pm$ 0.08	0.6 $\pm$ 0.1	<0.0001
Bilateral notch	135(19.4%)	77(56.6%)	<0.0001

AGA: Average for gestational age, LGA: Large for gestational age, SGA: Small for gestational age

MSAFP level was effective in the prediction of SGA babies (AUC: 0.59; $p=0.0014$, SE 0.028). MSHCG

(AUC 0.52; $p=0.48$) and estriol (AUC 0.51; $p=0.49$) did not have any predictive value (**Fig. 2**). Using a cut off

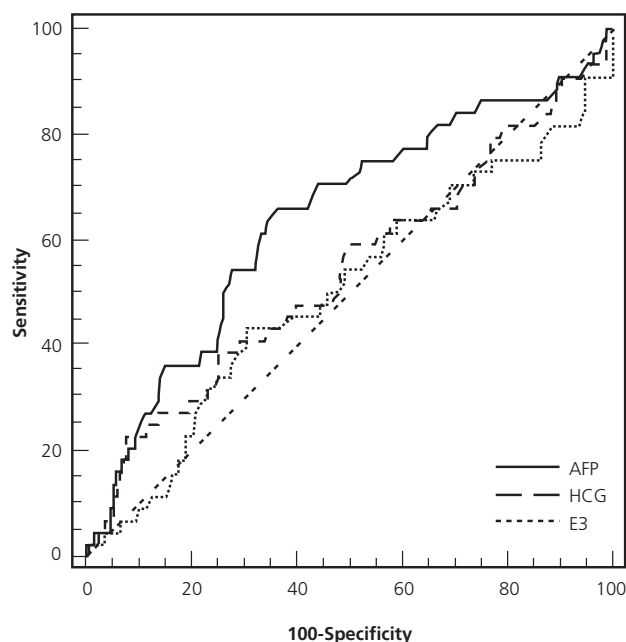


Fig. 1. Roc curves of the markers for the prediction of PIH in cases with BLN+.

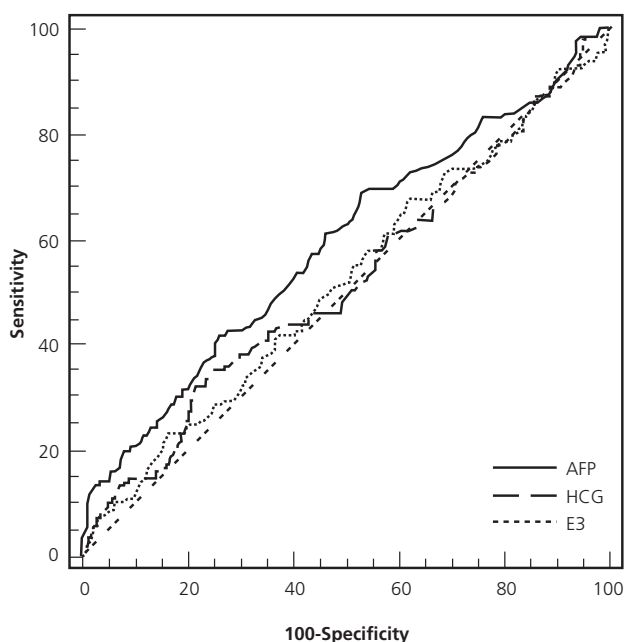


Fig. 2. Roc curve analysis of the markers for the prediction of SGA babies.

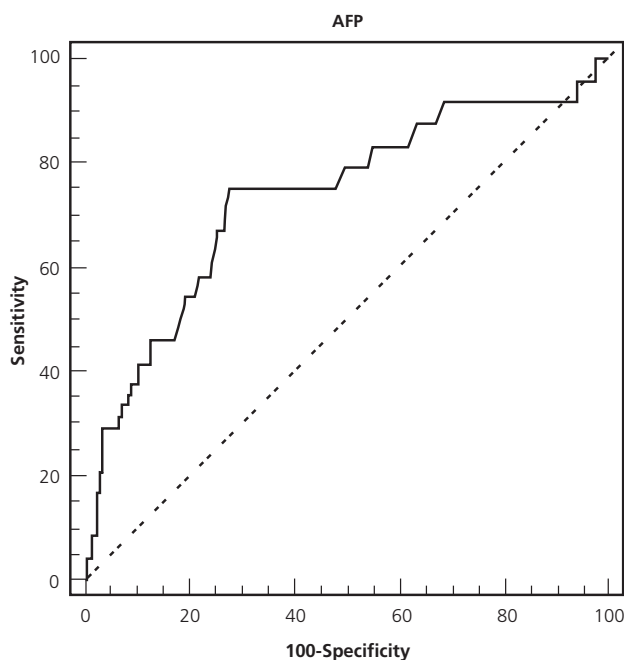


Fig. 3. Roc curve analysis of MSAFP level for the prediction of SGA birth weight in PIH cases.

value > 0.82 MoM for MSAFP, we could detect SGA babies with a sensitivity of 69% and specificity 47%. In this group 24 (2.89%) of the cases developed PIH and had a SGA baby. MSAFP level showed a higher predictive value for the cases of SGA associated with PIH (AUC 0.736; $p=0.0001$, SE 0.06) ($p=0.034$). Using a cut off value >1.09 MoM, we could detect SGA babies of hypertensive mothers with a sensitivity of 75% and specificity of 72.5% (**Fig. 3**).

A power analysis indicated that this study had adequate power ($>90\%$) in determining the role of MSAFP level in the prediction of PIH or SGA babies.

Discussion

Second trimester maternal serum screening is widely performed for the detection of fetal aneuploidy and/or neural tube defect. Abnormal results of the markers were suggested to be utilized for the identification of pregnancies at risk of adverse outcome. The plan for the clinical management of the cases with high risk includes patient education on signs and symptoms of

the complications and increases the frequency of antenatal visits.^[12] In this study we evaluated the relationship between triple test markers and second trimester uterine artery Doppler findings in the prediction of adverse outcome for a more effective utilization these markers.

Costa et al. found a significant association between abnormal placental morphology, elevated HCG and/or AFP levels at second trimester and adverse outcome (intrauterine growth restriction (IUGR), abruption, severe preeclampsia/HELLP syndrome, delivery <32 weeks, or stillbirth) in pregnancies at high risk.^[13] In our study group mean level of MSAFP and MSHCG was significantly higher in cases PIH. MSAFP was also found to be higher in cases with SGA birth weight.

Odibo et al. termed birth weight <5th percentile for gestational age as IUGR and they found optimal thresholds associated with IUGR were AFP >2.0 MoM, HCG >2.5 MoM and uE3 <0.9 MoM. The sensitivity, specificity, positive and negative predictive values for predicting IUGR in the presence of at least one abnormal marker were reported to be 46%, 66%, 11% and 90%. The authors suggested that these thresholds might be used for the detection of cases that would benefit from sonographic screening.^[14] In our pregnant population only MSAFP level was effective in the prediction of SGA birth weight (<10th percentile for gestational age). Using a cut off value >1.09 MoM, we could detect SGA babies of hypertensive mothers with a sensitivity of 75% and specificity of 72.5%.

Morris et al. reviewed the literature with the aim to determine the accuracy of five serum markers used in Down syndrome screening for prediction of preeclampsia and SGA. They concluded that these markers might be useful means of risk assessment or of use in prediction when combined with other tests.^[15] Abnormal maternal uterine artery Doppler in association with elevated maternal serum AFP, hCG or inhibin A or decreased PAPP-A was reported to identify the women at higher risk of IUGR and preeclampsia. Uterine artery Doppler measurements were suggested to be used in the evaluation of unexplained abnormal level of either of these markers.^[12,16]

Audibert et al. evaluated a cohort of 2,615 women with maternal hCG, AFP levels and second trimester uterine artery Doppler findings. In women with subsequent preeclampsia mean values for hCG and AFP were reported to be significantly higher and the presence of an uterine notch was associated with a significantly higher risk of preeclampsia and IUGR. In their

study group the sensitivity of the different tests ranged from 2 to 40%.^[17] We also found in our pregnant population higher levels for MSAFP and MSHCG in cases of PIH. In cases with BLN+ we could predict PIH with a sensitivity of 65% and specificity of 63% using > 0.98 MoM as cut off for MSAFP level.

Cnossen et al. evaluated 219 studies for the accuracy of 27 tests for predicting preeclampsia. They found that none of the tests had a high level of both sensitivity and specificity of greater than 90%. Only Doppler measurements were over 60% sensitive. The authors pointed out that high sensitivity was more useful than specificity in order to minimize false negatives.^[18] New tests with higher levels of sensitivity should be determined in future.

In our group, we have a high rate of BLN+ cases as a limitation of the study. This might be related with the fact that the cases with high risk were frequently referred and the prognosis of them was therefore easy to find. In a new study including the cases at higher gestational age and lower rate of BLN+, the predictive value of these markers might be reevaluated.

Conclusion

High MSAFP, MSHCG levels, and abnormal uterine artery Doppler findings at second trimester are related with the development of PIH and SGA birth weight. In cases with bilateral notching, high levels of MSAFP may contribute to the prediction of PIH. MSAFP level have a better predictive value for SGA birth weight associated with PIH.

Conflicts of Interest: No conflicts declared.

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