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Correlation between First-Trimester Maternal Serum Markers, Second-Trimester Uterine Artery Doppler Indices and Pregnancy Outcome

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Key Words
Preterm delivery · Pre-eclampsia · Low birth weight · Pregnancy-associated plasma protein A · Free beta HCG · Uterine artery Doppler

Abstract

Aims: The aim of this study was to assess the correlation between first trimester maternal serum free beta-human chorionic gonadotropin (fBHCG), pregnancy-associated plasma protein A (PAPPA), second-trimester uterine artery (UA) Doppler measurements and adverse pregnancy outcomes. ***Methods:*** Serum levels of PAPPA and fBHCG were determined at the first trimester, and patients underwent bilateral UA Doppler assessments at 20–25 weeks of gestation. A serum PAPPA level <0.4 MoM was termed as low and the abnormal Doppler findings were the presence of bilateral notches and RI >0.52 (mean) or unilateral notch and RI >0.66 (90th percentile). ***Results:*** Mean PAPPA level was significantly lower in cases with unilateral or bilateral notches (1.09; 0.79 and 0.80 MoM for 0, 1 and 2 notches, $p < 0.001$). Fifty-two cases (12.8%) had a low PAPPA level; in this group the incidence of abnormal Doppler was significantly higher (34.6 vs. 18.4%, $p = 0.011$). In the presence of abnormal Doppler in a case with a low serum PAPPA the risk of pregnancy-induced hypertension (OR = 4.56, $p = 0.0067$), low birth weight (OR = 6.8, $p = 0.0002$) and the risk of at least one complication (OR = 7.6, $p = 0.00001$) were significantly high. ***Conclusion:*** Combination of first- and second-trimester findings might improve the efficiency of screening for pregnancy complications.

Introduction

Maternal serum pregnancy-associated plasma protein A (PAPPA) and free subunit β human chorionic gonadotropin (fBHCG) in low levels are reported to be associated with an increased risk of adverse outcome in pregnancy [1–3]. An abnormal uterine artery Doppler velocimetry (high pulsatility index or presence of notch) in the first and second trimester has been proposed as a good screening test to predict pre-eclampsia [4].

Although these markers represent measurable manifestations of abnormal placentation and reduced placental perfusion, first-trimester uterine artery Doppler measurements were not found to be correlated with their serum levels [5]. Uterine artery (UA) Doppler ultrasonography at 20–24 weeks of gestation is reported to be an effective method of screening women in the second trimester [6, 7]. It has been suggested that the combination of

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maternal serum markers with Doppler findings at second trimester may allow better prediction capabilities for pregnancy complications [8–10]. In a recent study from Cooper et al. [11] UA Doppler at 22 weeks was found to be a useful adjunct in patients with low PAPPA. The authors suggested that a negative Doppler does not rule out all adverse outcomes and clinical judgment was advised in the management of these patients.

The aim of our study was to assess the correlation between first-trimester maternal serum PAPPA and fBHCG levels, second-trimester uterine artery Doppler measurements and adverse pregnancy outcome in our population.

Materials and Methods

Patients attending for routine examination at 11–14 weeks of gestation to undergo first-trimester combined screening for trisomy 21 were included in this prospective study. PAPPA and fBHCG were assayed in maternal serum by chemiluminescent enzyme immunoassay methods (DPC®, Los Angeles, Calif., USA) at the first ultrasound scan. Values were corrected for maternal weight, smoking and ethnicity [12, 13]. Absolute concentrations of the analytes were converted into multiples of the median (MoM) for gestational age. MoM values and adjusted risk were calculated by Prisca 4.0 package screening programme (Typolog Software GmBH, Germany). A cut-off value of 0.4 MoM for serum level of PAPPA was chosen on the basis of the previous studies [1, 2]. After the determination of FTS aneuploidy risk, the cases with normal fetal anatomy were invited for a second evaluation at 20–25 weeks of gestation.

At the second examination, the resistance index (RI) and pulsatility index (PI) of uterine artery were measured and recorded bilaterally, as well as the presence or absence of an early diastolic notch [14]. Mean levels of PI and RI were calculated. Abnormal Doppler findings were the presence of bilateral notches and RI >0.52 (mean) or unilateral notch and RI >0.66 (90th percentile). The cut-off values were derived from the data of our study population.

Women with a history of recurrent miscarriage (if they were using aspirin, heparin or low-molecular-weight heparin), type 1 diabetes mellitus or pregnancies later determined to have fetal anomalies were excluded from the study. Following delivery, primary outcomes were obtained from medical records and patients themselves: pregnancy-induced hypertension (PIH) (diastolic blood pressure >90 mm Hg after 20 weeks of gestation with or without proteinuria), low birth weight (LBW) (<2,500 g) and preterm delivery (<37 weeks of gestation). Institutional review board approval was obtained for this study.

Correlations between biochemical markers, PI, and RI and birth weight were assessed by Spearman's correlation coefficient. The efficiency of serum markers in predicting the abnormal Doppler findings was examined with the analysis of the area under the receiver operator characteristic (ROC) curves. Intergroup comparison of PAPPA, fBHCG levels and the presence of early diastolic notches was performed by means of analysis of variance.

Table 1. Spearman correlation coefficients (significance levels) between second-trimester uterine artery Doppler indices and multiples of the median of maternal serum markers

	PI	RI
PAPPA	−0.269 ($p < 0.0001$)	−0.273 ($p < 0.0001$)
fBHCG	−0.14 ($p = 0.004$)	−0.146 ($p = 0.0035$)

Separate Logistic regressions were used to determine if low levels of PAPPA at first trimester and/ or UA Doppler at second trimester were significant predictors of the outcome variables. Two by two tables were constructed to calculate test performance of positive and negative value, sensitivity and specificity. $p < 0.05$ was considered statistically significant. All calculations were performed with use of the MedCalc for Windows, version 8.1.00 (MedCalc Software, Mariakerke, Belgium).

Results

During the study period (January 2008–March 2009), 499 women underwent both first- and second-trimester screenings. The pregnancy outcome was determined in 429 of these cases. Twenty-five cases were excluded from the study (14 using aspirin, heparin or LMH, 3 cases of fetal cardiac anomaly, 8 type 1 diabetes mellitus). The study group consisted of 404 cases with a median age of 27 (range 17–44 years), 174 patients (43%) were nulliparous. The ethnic origin was Caucasian in 100% of the cases. In this group of 404 cases, 52 (12.8%) were found to have low levels of PAPPA and 83 cases (20.5%) had abnormal Doppler findings. In 18 of the cases (4.4%) both factors were present.

The serum levels of the markers had significant negative correlation with uterine artery Doppler indices (table 1). The serum level of fBHCG was significantly lower in cases with bilateral notches than those with absent early diastolic notch (1.2 and 1.0 MoM for 0 and 2 notches, respectively, $p = 0.047$). The mean PAPPA level was significantly lower in groups with uni- or bilateral notches compared to the group without an early diastolic notch (1.19, 0.79 and 0.80 MoM for 0, 1 and 2 notches, respectively, $p < 0.001$).

In this group, 83 of the 404 cases (20.5%) had abnormal Doppler findings. A cut-off value of <0.62 MoM for PAPPA (sensitivity 50.6%, specificity 74.45%) and 0.95 MoM for fBHCG (sensitivity 65%, specificity 54.83%) was determined for the prediction of the presence of ab-

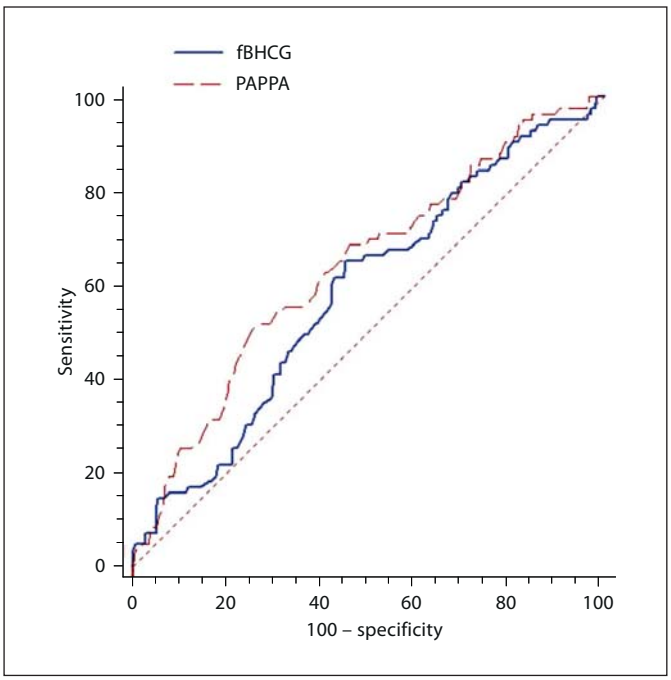

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Fig. 1. Comparison of the ROC curves for the prediction of abnormal Doppler of fBHCG (AUC 0.58, p = 0.013) and PAPPA (AUC 0.63, p = 0.0001); the difference was nonsignificant (p = 0.224).

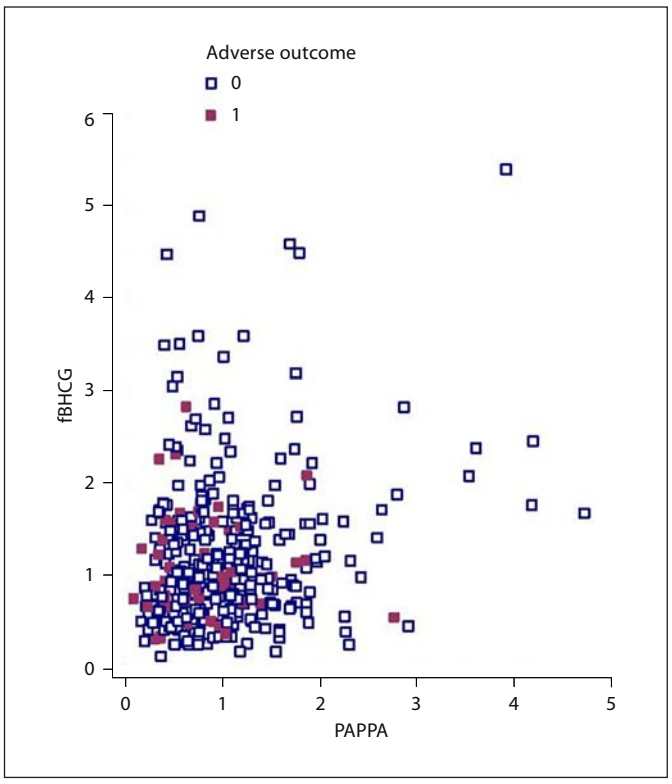

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Fig. 2. Scatter diagram of the cases showing the correlation PAPPA and fBHCG (colored points indicate the cases with any of the adverse outcomes).

normal Doppler. ROC curves for the predictive value of the markers are compared in figure 1. Fifty-two of the cases (12.8%) had a low PAPPA (<0.4 MoM). Below this cut-off, the rate of the cases with abnormal Doppler was significantly higher (34.6 vs. 18.4%, p = 0.011).

In the study group, the incidence of PIH was 8.6%, LBW was 9.9% and preterm delivery was 5.9%. Four cases resulted with neonatal demise related with the complications of severe prematurity (<28 weeks). Sixty-four of the cases (15.8%) had at least one of these complications. Maternal serum fBHCG level was not correlated with the birth weight (r = 0.017, p = 0.73), and PAPPA level showed a positive correlation (r = 0.127, p = 0.01).

In pregnancies resulting in any of the adverse outcomes, the mean maternal serum level of PAPPA was significantly lower (1 vs. 0.8 MoM; p = 0.01), whereas the mean levels of fBHCG did not show any significant difference (1.19 vs. 1.05 MoM; p = 0.16).

The scatter diagram for PAPPA, fBHCG values and the presence of any adverse outcome is presented in figure 2.

Low PAPPA or abnormal UA Doppler were significant predictors of PIH, LBW and preterm delivery (table 2). In the presence of abnormal Doppler in a case with a low serum PAPPA, the risk of PIH (OR = 4.56, CI 1.5–13.6; p = 0.0067), LBW (OR = 6.8, CI 2.4–18.7; p = 0.0002) and the risk of at least one complication (OR = 7.6, CI 2.9–20; p = 0.00001) were significantly higher. The sensitivity, specificity, positive and negative predictive values of low PAPPA and abnormal Doppler for the outcomes of interest are presented in table 3.

Discussion

Pathophysiological changes in pre-eclampsia are believed to occur in early pregnancy and antedate clinical manifestation of the disease and there is evidence that it is associated with a failure of trophoblastic invasion of the maternal spiral arteries [15, 16]. The clinical manifestations of this failed placentation are pre-eclampsia, IUGR and preterm birth. Despite the presence of numerous studies about the association between abnormal angio-

Table 2. Low levels of PAPPA and abnormal Doppler as predictors of adverse outcomes

	Low PAPPA	Abnormal Doppler
Pregnancy-induced hypertension	OR = 2.6 (95% CI 1.15–5.9, p = 0.02)	OR = 4.9 (95% CI 2.4–10.12, p = 0.00001)
Low birth weight	OR = 2.98 (95% CI 1.3–6.4, p = 0.005)	OR = 6 (95% CI 3–11.9, p = 0.00001)
Preterm delivery	OR = 3.8 (95% CI 1.54–9.4, p = 0.0037)	OR = 9.3 (95% CI 3.8–22.7, p = 0.00001)
At least one adverse outcome	OR = 3.15 (95% CI 1.63–6, p = 0.0006)	OR = 5.6 (95% CI 3.19–10, p = 0.00001)

Table 3. Sensitivity, specificity, positive and negative predictive values for the prediction of various adverse outcomes

	Sensitivity %	Specificity %	PPV	NPV
Low PAPPA				
PIH	25.7	88.3	17.3	92.6
LBW	27.5	88.7	21.1	91.7
PTD	29.1	88.1	13.4	95.1
At least one adverse outcome	26.5	89.7	32.7	86.6
Abnormal Doppler				
PIH	51.4	82.3	21.6	94.7
LBW	55	83.2	26.5	94.4
PTD	66.6	82.3	19.2	97.5
At least one adverse outcome	50	85	38.5	90
Low PAPPA and abnormal Doppler				
PIH	14.2	96.4	27.7	92.2
LBW	17.4	96.9	38.8	91.4
PTD	29.1	97.1	38.8	95.5
At least one adverse outcome	15.6	97.6	55.5	86
Low PAPPA or abnormal Doppler				
PIH	62.8	74.7	19.1	95.5
LBW	62.5	75.2	21.7	94.8
PTD	66.6	64.6	13.9	95.7
At least one adverse outcome	59.3	77.3	33	91

PTD = Preterm delivery.

genic factors and subsequent pre-eclampsia, none of the previous studies provided adequate information on a cut-off value that could be clinically useful for the prediction of pre-eclampsia [17]. Maternal serum fBHCG levels in pregnancies that subsequently develop pre-eclampsia were reported to be mildly reduced at 11–14 weeks, but the median fBHCG was not significantly different than the normal outcome group [8, 18]. Low level of fBHCG in the first trimester was also found to be related to LBW, small for gestational age (SGA) [19] and fetal death [20]. In our study group, first-trimester fBHCG level was correlated with second-trimester Doppler indices. However, this marker was not correlated with the birth weight.

In the study by Spencer et al. [21], maternal serum PAPPA has been shown to be relatively low in the first trimester of pregnancies complicated by SGA and/or pre-eclampsia. Although low PAPPA levels reported to be at least as important as is abnormal Doppler at the first trimester in the prediction of SGA fetuses [22], the sensitivity of PAPPA in screening for pre-eclampsia remained low in studies with different populations and cut-off values [5, 8, 23]. Also, in our study the sensitivity of PAPPA levels at the first trimester were lower than abnormal Doppler findings at the second trimester for all of the various adverse outcomes.

Increased impedance to flow in the uterine arteries, as measured by the PI at 20–25 weeks' gestation is reported to be able to identify, for a 5% false-positive rate, about 45% of pregnancies that subsequently develop pre-eclampsia [24, 25]. The sensitivity of this test varies with the definition of abnormal Doppler findings. In our study we used both the presence of bilateral early diastolic notches and high levels of RI as in a study from Kurdi et al. [26] and found a sensitivity of 51.4% for PIH.

Palma Dias et al. [27] reported a relative risk of 4.5 (CI 3.2–6.4) for overall placental insufficiency after a positive Doppler screening at 22–24 weeks of gestation and suggested that this test could be used in combination with other markers to stratify the level of care offered in the third trimester. In our study the relative risk of adverse outcome in a case with abnormal Doppler was 5.6 (CI 3.19–10), and in the presence both of the factors (abnormal Doppler and low PAPPA) the relative risk was 7.6 (CI 2.9–20).

Comparing first-trimester Doppler findings with maternal serum markers, Prefumo et al. [5] reported that fBHCG and PAPPA levels did not significantly change with the number of notches. Spencer et al. [8] found a small but significant association only between first-

trimester PAPPA and second-trimester mean PI in the control group ($r = -0.177$, $p < 0.001$), but not in the pre-eclamptic group. In our population, we found a significant correlation between both of the markers and Doppler indices. Mean PAPPA and f BHCG levels of the cases with bilaterally notches were significantly lower than the cases without any early diastolic notch. We detected the serum level <0.62 MoM for PAPPA for the prediction of abnormal UA Doppler. It seems that PAPPA levels at the first trimester have a better correlation with second-trimester UA Doppler findings.

In two of the recent studies, the presence of significant association between PI of uterine artery and PAPPA in the first trimester has been reported [28, 29]. But the detection rate of early screening for pre-eclampsia by maternal variables and Doppler was not improved by inclusion of PAPPA [29]. Spencer et al. [2] combined first-trimester markers and second-trimester Doppler findings, and they reported that the detection rate of pre-eclampsia was 14% for PAPPA alone, 55% for UA mean PI alone and 62.1% for the combination of PAPPA and UA Doppler. In our study, the sensitivity for PIH was also higher if we used Doppler findings (25.7% for low PAPPA vs. 51.4% for abnormal Doppler), and if we combined these markers (62.8%).

One of the limitations of this study was the small number of the cases. Therefore, we included all of the cases with pregnancy-induced hypertension (early and late pre-eclampsia, gestational hypertension) in the same group, and both of the babies which were SGA or preterm were included in the group of LBW infants.

Although the aim of the routine antenatal care in the first trimester is to identify the women who are at high risk of fetal anomalies, the presence of low levels of the markers would be useful in patient selection for second-trimester Doppler screening. Combination of first- and second-trimester findings might improve the predictive value of screening tests.

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