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The efficacy of first-trimester PAPP-A and free βhCG levels for predicting adverse pregnancy outcome

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Abstract

Objective: To determine whether first-trimester measurements of maternal serum PAPP-A and free βhCG levels were associated with adverse pregnancy outcomes.
Study Design: First trimester maternal serum free βhCG and PAPP-A were measured in 490 singleton pregnancies. Pregnancies were followed by the fetal-maternal unit, and predictive efficacy of these markers for small for gestational age (SGA) babies, gestational diabetes mellitus and hypertensive disorders were analyzed by cut-off values determined by using a ROC analysis, and also, by using the fifth percentile as the cut-off value.
Results: The sensitivities for PAPP-A in predicting pregnancies with a SGA baby and those complicated by a hypertensive disorder were 49% and 73%, respectively, when optimal cut-off values were used. Specificities were 76% and 65%, respectively. Serum free βhCG had no predictive value for individual pregnancy outcomes.
Conclusion: Efficacy of first trimester maternal serum markers in predicting adverse pregnancy outcome is low. Even after optimization of cut-off values, these markers do not appear to be clinically acceptable as an effective tool for screening for adverse pregnancy outcomes.

Keywords: Diabetes; hCG; PAPP-A; preeclampsia; pregnancy outcome; screening; SGA.

Introduction

Second-trimester maternal serum markers, which have been used primarily as a screening method for open neural tube defects and trisomy 21, can also warn against certain impending perinatal complications [5, 17]. In recent years, first-trimester screening using fetal nuchal translucency, free β human chorionic gonadotropin (βhCG), and pregnancy-associated plasma protein A (PAPP-A) has been shown to provide an effective and noninvasive tool for the identification of women at increased risk for aneuploidies [1, 7, 16]. Since it would be advantageous to identify in the first trimester pregnancies with an increased risk for a subsequent adverse outcome, the usefulness of first-trimester biochemical markers as predictors of pregnancy complications has been recently studied [4, 6, 15]. However, results of the initial studies were conflicting [4, 6, 8, 9, 17]. Recent studies showed an association [4, 6]. However, low predictive values, which have been observed in these large studies, do not justify close surveillance of women with abnormal markers. This may be due to the selection of non-optimal cut-off values for the markers. Percentiles were used to define cut-offs in these studies [4, 6]. Therefore, we aimed to determine whether first-trimester measurements of maternal serum PAPP-A and free βhCG levels were associated with adverse pregnancy outcomes after optimal cut-off values were defined by using a receiver operating characteristic (ROC) analysis. We also aimed to compare this predictive efficacy with the optimal cut-off to that with the percentile approach.

Methods

In our clinic, first-trimester screening for trisomy 21 has been performed by using a combination of nuchal translucency (NT), serum free βhCG and PAPP-A levels. NT is measured according to the Fetal Medicine Foundation (FMF) guidelines by using a Voluson 730 Expert (GE Medical Systems, Milwaukee, WI, USA), and the data are analyzed by an FMF computer program for risk calculation and the risk is reported to the woman [14]. Women with a singleton pregnancy and who attended the screening program between July 2001 and July 2004 were asked for a blood sample for the present study. Maternal serum free βhCG and PAPP-A were measured by the Kryptor analyzer (Brahms AG, Berlin), which is a rapid random access immunoassay analyzer using time-resolved amplified cryptate emission (TRACE) technology.

Demographic data, maternal weight, smoking status, obstetric history and the results of the NT scan were entered into a database. Women with multiple pregnancy, chronic hypertension, previously diagnosed diabetes, or pregnancy with a prenatal or postnatal diagnosis of a chromosomal or structural abnormality, were excluded from the study. Women with a history of previous pre-eclamptic pregnancy, previous gestational hypertension, gestational diabetes or IUGR were also excluded. All pregnancies were followed by the fetal-maternal unit in our Department. Most frequent pregnancy complications, i.e. small for gestational age (SGA) babies, gestational diabetes mellitus (GDM), and

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hypertensive disorders, were the primary outcomes in the present study.

Babies weighing below the 10th centile for gestational age were included in the SGA group. Gestational diabetes mellitus was diagnosed using a 3-h 100-g oral glucose tolerance test and the National Diabetes Data Group Criteria [2]. Gestational hypertension and preeclampsia were diagnosed according to the criteria of the 2000 Working Group [11], and these were included in one group. The study was approved by the institutional review board at the Marmara University.

Statistical analysis

Gestational ages were estimated from the last menstrual period for women who had regular (21–35 days) menstrual cycles or from ultrasonographic scans in the first trimester for women who had irregular menstrual cycles.

ROC analysis was performed to analyze the predictive value of markers for individual pregnancy outcomes and the whole group of women with any of these adverse pregnancy outcomes. Diagnostic sensitivity and specificity were calculated, and the ROC curve was constructed by plotting the sensitivity against the false-positive rate (1-specificity) of various cut-off values for predicting pre-eclampsia. The value with the optimal combination of sensitivity and specificity, which indicates the point with the highest sum of these, was chosen as the optimal cut-off value. Area under each ROC curve (AUC_{ROC}), which indicates the predictive power of the parameter, was calculated. The P value of the ROC analysis indicates the significance of the difference between the relevant variable and the coin test, which has an AUC of 0.5.

Since fifth percentile has been commonly used as the cut-off value in previous studies [6, 7], which analyzed the efficacy of maternal markers in predicting pregnancy outcomes, predictive values were determined also by using this cut-off value. Predictive efficacy of maternal markers with the fifth percentile as the cut-off value was analyzed by using the χ^2 or Fisher's exact tests, where appropriate. SPSS, version 11.5 (SPSS, Inc, Chicago, IL, USA) was used for the statistical analysis. P values <0.05 were considered significant.

Results

Four-hundred and ninety singleton pregnancies were enrolled for the study. Six women did not complete the antenatal follow-up and could not be reached. Two women had abortion, one woman had a stillbirth, two women had a fetus with a chromosomal abnormality, and three women had a fetus with a cardiac anomaly. The mean ($\pm$SD) for maternal age and weight were 30.4 ± 5.0 years and 61.9 ± 9.8 kg, respectively. Two-hundred and forty women (50.4%) were nulliparous.

ROC analysis revealed that neither of the serum markers could predict GDM (Table 1). Also, serum β-hCG was not associated with any individual perinatal outcome, but associated with adverse pregnancy outcome, when all individual outcomes were evaluated in one group (Table 1). Serum PAPP-A could predict SGA babies and hypertensive disorders of pregnancy (Table 1, Figure 1). Serum free βhCG had no predictive value for individual pregnancy outcomes (Table 1). Optimal cut-off values for PAPP-A were 0.69 MoM and 0.87 MoM for SGA babies and hypertensive disease of pregnancy, respectively (Table 1). When the fifth percentile, which corresponds to 0.40 MoM, was chosen as the cut-off value, there was significance for hypertensive diseases of pregnancy. The P value was higher than, but close, to the level of significance for PAPP-A in the prediction of pregnancies with an SGA baby (Table 1).

Sensitivity for these markers, which was between 7 and 13 when the fifth percentile was used as the cut-off value, improved to values between 48 and 73 when the optimal cut-off values were used (Table 1). However, specificity decreased in a similar magnitude from above nineties. Also, increasing the cut-off values increased the rate of women with a positive test to values between 25% and 44% (Table 1).

Both PAPP-A and hCG were predictive of all 3 outcomes as a whole (Table 1); however, predictive values were low (Table 1).

Discussion

Our results confirm previous studies associating IUGR with first-trimester PAPP-A [4, 6, 9, 10, 12, 13, 15]. In large series, the fifth percentile for the serum PAPP-A level, which corresponds to a value between 0.42 and 0.44 MoM, has been accepted as the cut-off, and positive and negative predictive values between 14–18 and 91–94%, respectively, have been reported [4, 6]. Although there appears an association between IUGR and serum PAPP-A level, these predictive values do not strongly suggest this marker as an effective screening tool. In the present study, we also observed comparable predictive values when we chose the fifth percentile (0.40 MoM) as the cut-off value. After the ROC analysis, in an effort to optimize the predictive power, the sensitivity improved from 11.4 to 48.6%, although positive and negative predictive values were comparable. This means a decrease in the number of missed diagnoses. However, this also increased the cut-off to 0.69 MoM, and therefore, increased the number of women with a positive test, and thus require more women to have close surveillance. The cost-effective analysis should be done with these optimal cut-offs.

Previous studies of first-trimester free β-hCG and subsequent IUGR failed to find an association [3, 8, 9, 12, 13, 19]. The present study also supports these results. However, a recent large study suggested an association between β-hCG and IUGR, when the lowest (1st) percentile was used as the cut-off [6]. We did not observe an association between β-hCG and individual perinatal outcomes in the present study. Free β-hCG was predictive with the optimal cut-off value of 1.01 MoM, when all

Table 1 Results of the ROC analysis: Optimum cut-off values for individual maternal serum hormones and their predictive values for individual and different combinations of adverse pregnancy outcomes.

	AUC ± SE	95% CI	P*	Cut-off	Rate of + test (%)	Sn (%)	Sp (%)	PPV (%)	NPV (%)	P**
SGA (n = 35; 7.4%)										
Serum PAPP-A (MoM)	0.61 ± 0.05	0.50–0.71	0.03	0.69	25.5	48.6	76.3	14.0	94.9	0.001
				0.40	5.0	11.4	95.4	16.7	93.1	0.074
Serum HCG (MoM)	0.57 ± 0.05	0.47–0.68	NS	NA	NA	NA	NA	NA	NA	NA
HT [Gestational hypertension (n = 32; 6.7%) + pre-eclampsia (n = 12; 2.5%)]										
Serum PAPP-A (MoM)	0.69 ± 0.05	0.60–0.78	< 0.001	0.87	38.0	72.7	65.4	17.7	95.9	< 0.001
				0.40	5.0	11.4	95.6	20.8	91.4	0.045
Serum HCG (MoM)	0.57 ± 0.05	0.48–0.67	NS	NA	NA	NA	NA	NA	NA	NA
SGA or HT										
Serum PAPP-A (MoM)	0.67 ± 0.04	0.59–0.74	< 0.001	0.84	36.1	63.4	68.6	26.2	91.4	< 0.001
				0.40	5.0	12.7	96.3	37.5	86.3	0.004
Serum HCG (MoM)	0.58 ± 0.04	0.50–0.66	0.04	0.74	26.5	40.8	76.0	23.0	88.0	0.005
				0.40	5.0	8.5	95.5	25.0	85.6	NS
Gestational DM (n = 18; 3.8%)										
Serum PAPP-A (MoM)	0.48 ± 0.07	0.35–0.62	NS	NA	NA	NA	NA	NA	NA	NA
Serum HCG (MoM)	0.57 ± 0.06	0.46–0.68	NS	NA	NA	NA	NA	NA	NA	NA
SGA or HT or GDM										
Serum PAPP-A (MoM)	0.64 ± 0.04	0.57–0.71	< 0.001	0.85	36.3	59.8	68.8	30.1	88.4	< 0.001
				0.40	5.0	10.3	96.1	37.5	82.7	0.026
Serum HCG (MoM)	0.58 ± 0.04	0.52–0.65	0.015	1.01	43.9	57.5	59.0	23.9	86.1	0.007
				0.40	5.0	6.9	95.4	25.0	82.0	NS

* Significance of the difference from a coin test, which has an AUC of 0.5.

** Significance of the difference in the rates of disease between pregnancies with the relevant hormone below the cut-off value and those with the relevant hormone above the cut-off value. AUC = area under the curve, SE = standard error, CI = confidence interval, Sn = sensitivity, Sp = specificity, PPV = positive predictive value, NPV = negative predictive value, HT = Hypertension, SGA = small for gestational age, NS = not significant, NA = nonapplicable.

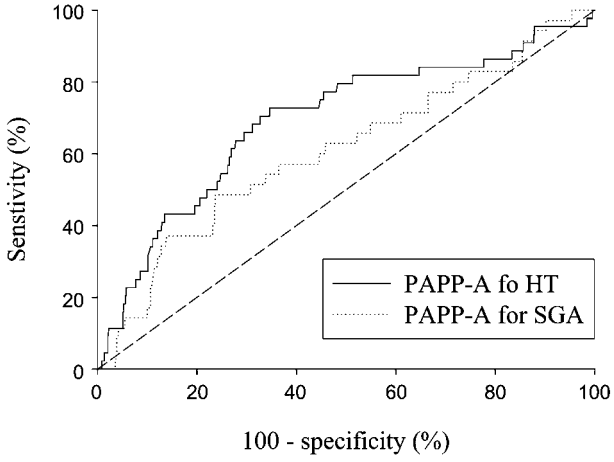

Figure 1 ROC curves for the serum PAPP-A level in the prediction of pregnancies with small for gestational age (SGA) babies and those with hypertension (HT). Both curves had significantly higher AUC values than a coin test, i.e. a test that approximates a coin flip, which is shown by a diagonal from the lower left to the upper right corner of the graph (dashed line) and also signifies an AUC of 0.5.

adverse outcomes in the present study were evaluated as one group. However, this does not appear to be clinically significant, since approximately 44% of women had a positive test with this cut-off value.

Few studies have observed an association between first trimester βhCG and gestational diabetes mellitus [9]. However, no associaton has been observed in a recent large series [4]. We also could not observe such association. Serum PAPP-A has been suggested to be associated with gestational DM in contrast to our findings in the present study [4, 9]. The absence of both of these associations may be due to a type II error. Low PAPP-A level has been associated with both gestational hypertension and pre-eclampsia [4, 9]. No association between βhCG and hypertension has been observed previously [4, 19]. Our results in the present study are consistent with these reports.

Previous results on the use of PAPP-A for screening of adverse pregnancy outcome are not promising. It has a high negative predictive value (90–99%), but also, a low positive predictive value (2–26%) for major pregnancy outcomes, when cut-off values between first and tenth percentiles are used [4]. Low sensitivity also has been reported [6]. The present study confirms these previous findings, and also, shows that this predictive efficacy may not be a clinically acceptable level by using optimal

cut-off values. The use of optimal cut-off values, which were determined by using the ROC analysis, improves the predictive efficacy of PAPP-A relative to the use of the fifth percentile as the cut-off value. The improvement in sensitivity decreases the number of missed diagnoses, but also increases the rate of subjects with a positive test. Therefore, this improvement does not appear to be clinically acceptable to suggest maternal serum PAPP-A level as an effective tool for screening of adverse pregnancy outcome.

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