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Predictive value of combined serum biomarkers for adverse pregnancy outcomes

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ABSTRACT

Objective: To determine if a combination of first and second trimester serum biomarkers (pregnancy-associated plasma protein A (PAPP-A), free βhCG, and maternal serum alpha-fetoprotein (msAFP)) may be utilized to develop a predictive model for adverse pregnancy outcomes.

Study design: We conducted a retrospective analysis including all women who delivered at our institution between 2007 and 2010. We estimated the area under the ROC curve (AUC) to compare predictive abilities of PAPP-A, free βhCG, and msAFP singularly, and in combination for adverse pregnancy outcomes. We sought to predict the risks of preeclampsia, preterm delivery (PTD, <37 weeks gestational age) and low birth weight (LBW, <2500 g). Using logistic regression analysis, we created models that controlled for maternal age, race, parity, body mass index, and histories of chronic hypertension and tobacco use.

Results: The final sample included 2199 women. Determining the AUC and optimal cutoff probability values for each of the biomarkers, we found that for PTD and LBW, the combination of all three biomarkers was most predictive, while for preeclampsia the combination of msAFP and PAPP-A was most predictive. The AUC of the three biomarker combination to detect adverse pregnancy outcomes are as follows: LBW 67%, PTD 72%, and preeclampsia 77%. We created race-specific logistic regression models to predict the risk probabilities. To illustrate, the predictive probability for a 33-year-old African American, nullipara with a BMI of 50, chronic hypertension, tobacco use, PAPP-A 0.3, msAFP 2.0 and free βhCG 0.98 MOMs are: PTD 59%, LBW 61% and Preeclampsia 91%.

Conclusion: The combination of biomarkers currently utilized in Down syndrome screening may also be used to predict additional adverse pregnancy outcomes. Further studies are needed to determine optimal maternal and fetal surveillance, if and when increased risks are identified.

Introduction

Combinations of first and second trimester serum markers are highly effective in screening for aneuploidy [1]. Pregnancy-associated plasma protein A (PAPP-A) and free βhCG are used as a first-trimester serum screen, while maternal serum alpha-fetoprotein (msAFP), hCG, unconjugated estriol and inhibin A comprise the standard second-trimester screen [2–5]. Maternal serum levels of these markers have been shown to be associated with adverse pregnancy outcomes in addition to aneuploidy, such as fetal growth restriction, preeclampsia, and fetal death; the likelihood of these outcomes increases with increasing extremity of an abnormal serum marker level [6,7]. These serum markers have independently shown predictive value for adverse pregnancy outcomes; their individual predictive values however, are too low to reliably use as a screening method.

PAPP-A is a protease for insulin-like growth factor (IGF) binding protein-4 [8]. If the level of PAPP-A is insufficient to successfully cleave IGF, IGF remains in its bound, inactive form, possibly leading to diminished fetal and placental growth [9]. Krantz et al.'s study showed a high positive predictive value of extremely low PAPP-A levels for intrauterine growth restriction (IUGR) [7]. While several other publications have shown statistically significant associations between low PAPP-A levels and preeclampsia, fetal loss, preterm birth, and IUGR, they have failed to demonstrate high sensitivity

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and high positive predictive values to deem a patient high or low risk for the adverse outcomes [10–14,6,15–17].

Free βhCG is a syncytiotrophoblast-derived promoter of cell growth and differentiation in the embryo [18]. Evidence is lacking to support an association between free βhCG and non-chromosomal adverse pregnancy outcomes [19,7,16].

Maternal serum AFP is a well-known glycoprotein excreted into fetal urine, which travels via the placenta or fetal membranes to maternal serum [20]. Elevated msAFP levels have previously been associated with preeclampsia, fetal death, preterm delivery, IUGR, and placental abruption [21–25].

In summary, many of the serum markers currently used for Down syndrome screening have independently been found to have some predictive value for other adverse pregnancy outcomes. We hypothesized that using these markers in combination (from both first and second trimesters) and incorporating maternal characteristics may increase their predictive value and ultimately result in a useful screening tool.

Materials and methods

This was a retrospective, case-control study including all women delivered of a singleton gestation at Mount Sinai Medical Center from 2007 to 2010 for whom first and second trimester serum marker analysis as well as outcome data were available. The Mount Sinai School of Medicine institutional review board approved this study. Maternal and neonatal data were extracted from the electronic medical records. Serum analyte assays were performed by NTD laboratories. We sought to correlate a combination of first and second trimester serum markers with adverse pregnancy outcomes. The primary outcomes of interest included preeclampsia, preterm delivery, and low birth weight. We had first and second trimester serum marker data for 2756 patients; however, only 2463 of these women delivered at our institution. Among these patients, 5 were missing data on either gestational age or birth weight, 10 were missing parity, 58 were missing race, and 191 were missing BMI, leaving 2199 patients for final analysis. In the case where a patient had more than one pregnancy during the study interval, only the initial pregnancy was included for analysis. The three patients who experienced intrauterine fetal demise were also excluded due to the small number.

A maternal dried blood spot sample is analyzed for two biochemical markers in the first trimester: free beta human chorionic gonadotropin (free βhCG) and pregnancy associated plasma protein-A (PAPP-A). Blood specimens are collected in one of two ways, through a simple finger stick method, or with venipuncture. The venous blood is immediately spotted onto a dried blood spot card provided by PerkinElmer Labs/NTD using a Diff-Safe device, or the blood is spotted directly from the finger. The serum markers evaluated in the first trimester, PAPP-A and free βhCG hormone, are obtained between 10 and 13 weeks gestation. These serum markers are analyzed strictly based on embryonic crown rump length (CRL) of 37–84 mm, which correlates with this gestational age interval. NTD laboratories will not analyze these samples unless the CRL data is provided and falls within the aforementioned interval. With regard to second trimester samples, these were analyzed between 15 and 22 weeks gestation. Specifically, we assessed four biomarkers found in the mother's serum: alpha-fetoprotein (AFP), free βhCG, unconjugated estriol, and inhibin A.

Eligible charts were identified and data extracted for maternal height and weight (BMI was then calculated), race, history of tobacco use, history of chronic hypertension, maternal date of birth (age at delivery was then calculated), parity, gestational age at delivery (preterm delivery was subsequently defined as <37 gestational weeks), mode of delivery, birth weight (low birth weight was defined as <2500 g) (World Health Organization), and diagnosis of preeclampsia and/or gestational hypertension during index pregnancy. Preeclampsia was defined as new onset hypertension with coexistent proteinuria. Gestational hypertension was defined as new onset hypertension with blood pressure >140/90 mmHg on two separate occasions, four or more hours apart.

Statistical analyses were performed using SAS/STAT Version 9.2 (SAS Institute Inc., Cary, NC). Multivariable logistic regression models were used to estimate odds ratios and 95% confidence intervals for preeclampsia, preterm delivery and low birth weight, comparing groups of patients with different demographic characteristics (including age, BMI, parity, race, tobacco use, and hypertension) and serum biomarker levels. In another set of logistic regression models, again one for each adverse pregnancy outcome, interactions among the serum biomarkers were examined by adding three pairwise interaction terms (PAPP-A and msAFP, PAPP-A and free βhCG, free βhCG and msAFP) and one three-way interaction term (PAPP-A, msAFP and free βhCG) to the aforementioned models. Receiver operating characteristic (ROC) curves were then generated from these logistic regression models and areas under the ROC curves (AUCs) were estimated for each biomarker alone, in combination with another biomarker, and finally for all three biomarkers (considered the full model). From the full regression models, Youden's index was used to determine the optimal cutpoints on the probability scale for best discriminating between patients with and without each adverse pregnancy outcome. Youden's index is defined as the maximum difference between the sensitivity and false positive rate and ranges between 0 and 1. The predicted probability from the full multivariable regression model that corresponds to the Youden's index was defined as the optimal cutpoint, as it is the one point that maximizes both the sensitivity and specificity. Formulas (derived from these full logistic regression models) for computing race-specific predicted probabilities of adverse pregnancy outcomes for patients with specific demographic characteristics and serum biomarker levels can be furnished upon request. By comparing a patient's predicted probability of adverse outcome to the optimal cutpoint discussed earlier, we then computed sensitivity, specificity, positive predictive value and negative predictive value, to assess the screening capabilities of these biomarker values. All hypothesis testing was conducted at the 5% level of significance.

Results

The final analysis included 2199 patients. The mean maternal age was 32 [4.3] years, with a range of 16 to 48 years. The mean parity was 0.58, ranging from 0 to 7; 1233 women were nulliparous (56%). Most of the women were white (63%) or Hispanic (14%). Asian women comprised 11%, while African–American women comprised 9% of the study group; the remaining 3% were classified as other. The mean body mass index (BMI) was 24 [4.8]. 57 patients (3%) in the study group had preexisting hypertension, while only 49 women (2%) admitted to tobacco use during pregnancy.

Of the patients included in the study, 150 (7%) experienced preterm delivery, 148 (7%) were diagnosed with preeclampsia, and 106 (5%) gave birth to a low birth weight neonate. Of the 7% who delivered preterm, 61% of these patients were spontaneous preterm delivery, and 39% were iatrogenic. Of the 148 patients classified in our statistical analyses as having preeclampsia (defined as hypertension on two separate readings plus proteinuria), 8.5% of these patients were more specifically diagnosed with gestational hypertension.