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First-Trimester Prediction of Preterm Birth Using ADAM12, PAPP-A, Uterine Artery Doppler and Maternal Characteristics

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Abstract

Objective—To estimate the efficiency of first-trimester ADAM12, PAPP-A, uterine artery Doppler and maternal characteristics in the prediction of preterm birth (PTB).

Methods—A prospective cohort study of patients presenting for first-trimester aneuploidy screening. Maternal serum ADAM12 and PAPP-A levels were measured by immunoassay, and mean uterine artery Doppler pulsatility indices were calculated. The primary outcome was preterm birth (PTB) <34 weeks' gestation, and the secondary outcome was PTB <37 weeks' gestation. Logistic regression was used to model the prediction of PTB using ADAM12, PAPP-A, uterine artery Doppler, and maternal characteristics, individually and in combination. Sensitivity, specificity, and area under the receiver-operating characteristic curves were compared between models.

Results—Of 578 patients, 36 (6.2%) delivered <34 weeks and 78 (13.5%) delivered <37 weeks. For a 20% fixed false positive rate, ADAM12, PAPP-A, and uterine artery Doppler identified 58%, 52%, and 62% of patients with PTB <34 weeks and 42%, 48%, and 50% of patients with PTB <37 weeks, respectively. Combining these first-trimester parameters did not improve the predictive efficiency of the models.

Conclusion—First-trimester ADAM12, PAPP-A, and uterine artery Doppler are each modestly predictive of PTB; however, combinations of these parameters do not further improve their screening efficiency.

Keywords

ADAM12; PAPP-A; preterm birth; uterine artery Doppler

Introduction

Preterm birth (PTB) remains the leading cause of perinatal morbidity and mortality, affecting 12–13% of deliveries annually in the United States.¹ Both progesterone and cerclage have been shown to decrease the incidence of PTB in patients deemed to be high-risk; however, available evidence-based therapies for risk reduction are limited to patients with a prior obstetrical history of PTB and/or short cervical length.^{2–5} While the etiology of

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spontaneous PTB is likely multifactorial, impaired placentation and placenta ischemia likely play a role. This has been demonstrated in multiple histological and Doppler studies performed during the second half of pregnancy.⁶⁻⁹ Investigation into first-trimester markers of placental dysfunction may allow for the identification of an additional subset of high risk patients whom may benefit from early intervention and increased antenatal surveillance.

Pregnancy-associated plasma protein A (PAPP-A) and A Disintegrin and Metalloprotease (ADAM12) are placenta-derived proteins with proteolytic activity against insulin-like growth factor binding proteins. Low levels of these serum analytes in the first trimester may serve as markers of placental dysfunction.¹⁰⁻¹³ In addition, uterine artery Doppler studies are non-invasive measurements of placental vascular flow. Measures of increased resistance in the uterine arteries may reflect impaired trophoblastic invasion.¹⁴ Prior studies have shown that these first-trimester parameters may be altered in syndromes of placenta dysfunction such as pre-eclampsia and intrauterine growth restriction; however, the role of these first-trimester parameters in the prediction of PTB remains unclear.¹⁵⁻²² The objective of this study was to estimate the efficiency of first-trimester ADAM12, PAPP-A, uterine artery Doppler and maternal characteristics, both individually and in combination, in the prediction of PTB.

Methods

This was a prospective cohort study of patients presenting to Washington University Medical Center from 2008–2010 for first-trimester aneuploidy screening. Institutional review board approval from our institution was obtained, and patients provided written, informed consent for participation. Patients with singleton gestations between 11 weeks 0 days and 13 weeks 6 days gestation were approached for participation in the study. Exclusion criteria included multiple gestations, known aneuploidy and major congenital malformations.

Maternal demographics, past medical history, and past obstetrical history were obtained from a detailed patient questionnaire administered at the time of ultrasound. Standard of care for first-trimester aneuploidy screening at our institution includes ultrasound measurement of crown-rump length (CRL) to confirm pregnancy dating, nuchal translucency measurement, and maternal serum collection for PAPP-A and free β -hCG determination. All pregnancies were dated by last menstrual period (LMP) if consistent with CRL measurements (± 7 days) or by the CRL measurement if it was not consistent with menstrual dating. PAPP-A levels were measured by PerkinElmer laboratory (Melville, NY) as is standard for first-trimester screening at our institution. Patients who consented to the study also provided an additional 10 ml of maternal blood for use in determining ADAM12 concentrations. Maternal blood was collected into non-heparinized tubes and centrifuged at 1,500 *g* for 15 minutes. Maternal serum was then extracted and stored at -80°C until the time of ADAM12 analysis. A 25 μl aliquot of serum was used to measure the concentration of ADAM12 with a time-resolved fluorescent immunoassay, in which ADAM12 concentration was directly proportional to the fluorescence measured at 615nm. (DELFI/ AutoDELFI/ ADAM12 research kit, PerkinElmer Life and Analytical Sciences, Turku, Finland) Interassay mean coefficient of variation was 6%. Uterine artery Doppler studies were performed transabdominally using Voluson 730 Expert ultrasound machines (GE Medical Systems, Milwaukee, WI, USA). The pulsatility index (PI) of both the right and left uterine arteries was measured using pulse wave Doppler, and the average PI calculated. All participating sonographers are certified by the Fetal Medicine Foundation for first-trimester Doppler measurements. ADAM12, PAPP-A and uterine artery PI values were converted to multiples of the median (MoM), adjusted for gestational age, for analysis. Delivery information was extracted from electronic medical records from those patients who

delivered within our medical system. For patients who delivered outside of our medical system, a release of medical records form was obtained at the time of study enrollment.

Our primary outcome of interest was all PTB <34 weeks' gestation, and our secondary outcome was all PTB <37 weeks' gestation. A planned sub-analysis was also performed excluding all cases of pre-eclampsia and intrauterine growth restriction as surrogate markers of indicated PTB. Intrauterine growth restriction was defined as birth weight <10th percentile for gestational age using standards derived by Hadlock.²³ Pre-eclampsia was defined as blood pressure of >140 mm Hg systolic and/or 90mm Hg diastolic on two or more occasions with proteinuria of 0.3 gm or more in a 24-hour urine specimen occurring after 20 weeks gestation in a woman with previously normal blood pressure. If a 24-hour urine sample was not available, proteinuria was diagnosed as 1+ or greater on urine dipstick.²⁴ Baseline maternal characteristics, ADAM MoMs, PAPP-A MoMs, and uterine artery PI MoMs were compared between patients with and without the study outcomes of interest. Categorical variables were compared using chi-square tests. Continuous variables were compared using the independent sample t-test or Mann-Whitney U test, as appropriate. Normal distribution of variables was evaluated using the Kolmogorov-Smirnov test. Logistic regression analysis was then used to model the prediction of PTB. Models incorporating first-trimester parameters, both individually and in combination, were evaluated. Maternal characteristics and historical factors identified as significant in the univariable analysis were included in the models. Receiver-operating characteristic (ROC) curves were generated for each model, and the area under the curve (AUC) compared between models using non-parametric U statistics. The sensitivity and specificity at both 10% and 20% fixed false positive rates (FPR) were also calculated for each model. P-values <0.05 were considered statistically significant. All statistical analyses were performed using STATA 10, Special Edition (College Station, TX).

Since the focus of this study was on the development of a highly sensitive prediction model for PTB, the precision of our sample size estimates was based on the ½ width of the 95% confidence interval and the incidence of PTB in our patient population. With these assumptions, our study was powered to produce a prediction model with an 85% sensitivity for PTB <34 weeks and a 75% sensitivity for PTB <37 weeks.

Results

Over the study period, a total of 618 patients were enrolled. Three patients withdrew from the study after enrollment, and 13 patients were lost to follow up. After excluding patients experiencing spontaneous abortion (n=8), elective termination (n=1), and those with incomplete outcome information (n=15), 578 patients were available for analysis, comprising our final study cohort. The mean gestational age at the time of enrollment was 12.1 ± 0.6 weeks, and the mean gestational age at the time of delivery was 38.2 ± 2.7 weeks. 78 (13.5%) patients delivered <37 weeks, of which 36 (6.2%) were deliveries at <34 weeks.

A comparison of maternal characteristics between the study groups is shown in Table 1. On average, patients who delivered <34 weeks' gestation were younger, had a higher maternal body mass index (BMI), and were more likely to be of African American race compared to those who delivered at ≥34 weeks. Patients with PTB <34 weeks were also more likely to have a history of a prior preterm delivery, chronic hypertension, and pre-gestational diabetes. Both median ADAM12 (0.79 v. 1.01; p=0.010) and PAPP-A levels (0.83 v. 1.15; p=0.014) were significantly lower in patients with PTB <34 weeks compared to controls. In addition, median uterine artery Doppler PI MoM levels were significantly higher in patients with PTB <34 weeks compared to controls (1.09 v. 0.99; p=0.013). (Table 2)

Individually, ADAM12, PAPP-A and uterine artery Doppler each had a limited predictive efficiency for PTB <34 weeks with AUCs ranging from 0.62–0.63. Combinations of these first-trimester parameters along with maternal characteristics identified as significant in the univariable analysis improved the predictive efficiency of models. (Table 3) The best prediction of PTB <34 weeks was obtained by the combination of maternal characteristics, ADAM12, PAPP-A and uterine artery Doppler. This combination resulted in a prediction model with an AUC of 0.78 (95% CI 0.69–0.88) and sensitivities of 42% and 65% at 10% and 20% fixed FPRs, respectively. However, the predictive efficiency of this model was not statistically different from the predictive efficiency of any other combination of markers or from the predictive efficiency of the model containing maternal characteristics alone. There was no evidence of collinearity between the various first-trimester markers, thereby justifying their inclusion in the models in combination.

After excluding all cases of pre-eclampsia and intrauterine growth restriction (n=54), there were 23 remaining cases of PTB <34 weeks and 51 remaining cases of PTB <37 weeks. There was no statistically significant difference in the predictive efficiency of the models after excluding these cases, thereby demonstrating that our results are not primarily driven by the already established association between abnormal values of these first-trimester biomarkers and both pre-eclampsia and intrauterine growth restriction. (Figure 1)

Similar results were observed for our secondary outcome of PTB <37 weeks. Both ADAM12 and PAPP-A levels were significantly lower in those patients who delivered <37 weeks compared to controls; however, there was no statistically significant difference in uterine artery PI between the comparison groups. (Table 2) The predictive efficiency of the models was overall low. The best predictive efficiency was observed by combining maternal characteristics, ADAM12, PAPP-A, and uterine artery Doppler, resulting in an AUC of 0.71 (95% CI 0.63–0.79) with a sensitivity of 38% at a 10% FPR and a sensitivity of 50% at a 20% FPR. Again, this combination of parameters did not provide a significant improvement in predictive efficiency compared to the model incorporating maternal characteristics alone. (Table 4)

Comment

Findings from our study demonstrate that both first-trimester PAPP-A and ADAM12 levels are significantly reduced in patients who subsequently deliver preterm <34 weeks and <37 weeks. We also found that uterine artery Doppler studies were altered, but only in the subgroup of patients who delivered <34 weeks. Despite these findings, the predictive efficiency of these first-trimester markers, both individually and in combination, was modest and not superior to screening with maternal characteristics alone. Furthermore, our results were not altered after excluding cases of pre-eclampsia and intrauterine growth restriction, two common diagnoses leading to indicated preterm delivery. Findings from this sub-analysis suggest that the associations we observed are not primarily driven by the already well-established association between first-trimester markers of placental dysfunction and these disorders.^{19,25} These findings also substantiate prior research indicating that both spontaneous and indicated PTB may share some of the same underlying pathophysiologic pathways.^{26,27}

Our results are consistent with previous studies demonstrating low levels of PAPP-A in patients who deliver preterm; however, results from our study differ from those of other studies which have evaluated the association of ADAM12 and first-trimester uterine artery Doppler with PTB.^{15,16,20} A 2011 case control study by Beta *et al.* demonstrated no difference in ADAM12 levels or uterine artery Doppler indices in patients who delivered

preterm.²¹ Similarly, Soares *et al.* demonstrated no difference in first trimester uterine artery resistance when retrospectively comparing patients with preterm versus term deliveries.²²

The biologic plausibility of our findings stems from the role that abnormal placentation may play in the pathogenesis of PTB. Prior studies have demonstrated failure of physiologic transformation of the spiral arteries by the invading trophoblasts in a subset of patients with preterm labor and preterm premature rupture of membranes.^{8,28} This impaired trophoblast invasion has been reflected in second-trimester uterine artery Doppler studies showing increased impedance to vascular flow in patients who deliver preterm.²⁹ Additionally, an altered profile of placental-derived angiogenic and anti-angiogenic factors has been observed in a subset of patients who develop spontaneous preterm labor.³⁰ Given that abnormal placentation is established early in gestation, it may be possible to identify a subset of patients at risk for PTB by evaluating markers of placental dysfunction as early as the first trimester.

Strengths of our study include its prospective cohort design and low loss to follow up rate. Additionally, given our robust dataset, we were able to perform a rigorous epidemiologic evaluation, capturing maternal characteristics, obstetrical history and first-trimester biomarkers in predicting PTB. Finally, our primary outcome encompasses all PTB, both spontaneous and indicated. Although prior studies have evaluated only spontaneous PTB, more recent research by Ananth and colleagues suggests that these two clinical subtypes of PTB may share common etiologies.²⁶ By including all cases of PTB as our primary outcome, we were able to further support this hypothesis. Additionally, we were also able to perform a subgroup analysis, excluding all cases of pre-eclampsia and intrauterine growth restriction as surrogate markers of indicated preterm delivery, thereby further characterizing the robustness of our findings.

Our study is not without limitations. Although the incidence of PTB in our cohort was comparable to the national average, our study was still somewhat limited by the overall small number of PTB cases despite our large prospective cohort. Due to this fact, we were unable to evaluate the outcomes of very early PTB <32 and <28 weeks' gestation. Additionally, given the low percentage of nulliparous patients in our cohort, we were unable to stratify our analysis based on parity, a significant component in the assessment of PTB risk. Despite this, we were able to control for the effect of a history of a prior PTB, one of the strongest predictors of subsequent PTB. It is certainly possible that these first-trimester biomarkers may provide a significant contribution to the prediction of PTB in nulliparous patients, given that these patients inherently have no prior obstetric history to consider in creating a prediction model. Finally, we were unable to separate patients who experienced preterm delivery secondary to preterm labor alone versus those with preterm premature rupture of membranes. While it is possible that these clinical scenarios may represent two different pathways in the pathogenesis of PTB, histologic changes consistent with impaired placentation and placental ischemia have been observed in both of these subgroups.^{8,28}

Although findings from our study support the hypothesis that abnormal first-trimester placentation plays a likely role in the pathogenesis of PTB, the addition of ADAM12, PAPP-A, and uterine artery Doppler does not significantly improve upon the prediction of PTB which is achieved by maternal characteristics alone. Our results suggest that in the identification of patients at high risk for PTB, first-trimester screening with biomarkers may be equivalent to screening by maternal and obstetrical history alone. Continued investigation into novel first-trimester markers of placental dysfunction in the prediction of PTB is warranted.

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What's already known about this topic?

- First-trimester markers of placental dysfunction have been linked to subsequent adverse perinatal outcomes.

What does this study add?

- First-trimester ADAM12 serum levels and uterine artery Doppler studies are altered in patients who deliver at <34 weeks' gestation, supporting the role of abnormal placentation in the pathogenesis of preterm birth.
- Screening for preterm birth risk with first-trimester markers of placental dysfunction is not superior to screening using maternal characteristics alone.

Figure 1.

Comparison of ROC curves for prediction of PTB <34 weeks. The curves highlighted in blue correlate to prediction of PTB with maternal risk factors alone. The curves highlighted in red correlate to prediction of PTB combining maternal risk factors, ADAM12, PAPP-A,

and uterine artery Doppler. A) All PTB<34 weeks; B) PTB<34 weeks excluding cases of pre-eclampsia and intrauterine growth restriction

Table 1

Baseline maternal characteristics and obstetrical history compared between the study groups.

	Preterm Birth <34 weeks (n=36)	Delivery 34 weeks (n=542)	p-value
Maternal Age (years) *	28.2 ± 6.1	31.4 ± 5.8	0.005
African American Race	63.9%	27.7%	<0.001
Body Mass Index (kg/m²) *	30.9 ± 7.7	28.5 ± 7.7	0.04
Nulliparity	25.0%	26.9%	0.80
Prior Preterm Birth	30.6%	8.5%	<0.001
Tobacco Use	13.9%	8.8%	0.30
Chronic Hypertension	33.3%	8.2%	<0.001
Pre-gestational Diabetes	16.7%	6.5%	0.02

* Data expressed as mean ± standard deviation

Table 2

Comparison of First-Trimester Marker Levels Between Study Groups

PTB <34 Weeks			
Marker	PTB <34 Weeks (n=36)	Delivery 34 Weeks (n=542)	p-value
ADAM12 MoM	0.79 (0.54–1.24)	1.01 (0.74–1.35)	0.010
PAPP-A MoM	0.83 (0.62–1.47)	1.15 (0.80–1.58)	0.014
Uterine Artery Doppler PI MoM	1.09 (0.95–1.54)	0.99 (0.78–1.22)	0.013
PTB <37 Weeks			
Marker	PTB <37 Weeks (n=78)	Delivery 37 Weeks (n=500)	p-value
ADAM12 MoM	0.83 (0.57–1.22)	1.02 (0.75–1.36)	0.003
PAPP-A MoM	0.92 (0.62–1.54)	1.17 (0.82–1.59)	0.009
Uterine Artery Doppler PI MoM	1.00 (0.84–1.28)	0.99 (0.79–1.22)	0.290

* Data expressed as medians and interquartile ranges

Table 3

Predictive Efficiency of First-Trimester Parameters for PTB <34 Weeks

Marker	AUC (95% CI)	Sensitivity 10% FPR	Sensitivity 20% FPR
Maternal Characteristics Alone	0.73 (0.61–0.84)	42%	58%
ADAM12 Alone	0.63 (0.52–0.73)	25%	42%
PAPP-A Alone	0.62 (0.52–0.73)	20%	42%
Uterine Artery Doppler Alone	0.62 (0.53–0.71)	25%	34%
ADAM12 +PAPP-A + Uterine Artery Doppler Alone	0.65 (0.55–0.75)	32%	42%
Maternal Characteristics + ADAM12	0.72 (0.59–0.84)	42%	58%
Maternal Characteristics + PAPP-A	0.77 (0.68–0.87)	38%	52%
Maternal Characteristics + Uterine Artery Doppler	0.76 (0.65–0.87)	38%	62%
Maternal Characteristics + ADAM12 + PAPP-A	0.77 (0.67–0.87)	42%	58%
Maternal Characteristics + ADAM12 + Uterine Artery Doppler	0.76 (0.65–0.87)	42%	62%
Maternal Characteristics + ADAM12 + PAPP-A + Uterine Artery Doppler	0.78 (0.69–0.88)	42%	65%

* Maternal Characteristics: African American Race, BMI, Prior PTB, history of chronic hypertension, history of pre-gestational diabetes

Table 4

Predictive Efficiency of First-Trimester Parameters for PTB <37 Weeks

Marker	AUC (95% CI)	Sensitivity 10% FPR	Sensitivity 20% FPR
Maternal Characteristics Alone	0.69 (0.61–0.77)	38%	45%
ADAM12 Alone	0.60 (0.53–0.68)	20%	38%
PAPP-A Alone	0.59 (0.52–0.66)	22%	36%
Uterine Artery Doppler Alone	0.54 (0.47–0.60)	10%	24%
ADAM12 + PAPP-A + Uterine Artery Doppler Alone	0.60 (0.52–0.68)	28%	40%
Maternal Characteristics + ADAM12	0.69 (0.61–0.77)	38%	45%
Maternal Characteristics + PAPP-A	0.70 (0.63–0.78)	38%	50%
Maternal Characteristics + Uterine Artery Doppler	0.69 (0.61–0.77)	38%	45%
Maternal Characteristics + ADAM12 + PAPP-A	0.71 (0.63–0.78)	38%	48%
Maternal Characteristics + ADAM12 + Uterine Artery Doppler	0.70 (0.62–0.77)	40%	45%
Maternal Characteristics + ADAM12 + PAPP-A + Uterine Artery Doppler	0.71 (0.63–0.79)	38%	50%

* Maternal Characteristics: African American Race, BMI, Prior PTB, history of chronic hypertension, history of pre-gestational diabetes