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The Efficiency of First-Trimester Uterine Artery Doppler, ADAM12, PAPP-A and Maternal Characteristics in the Prediction of Pre-Eclampsia

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Abstract

Objective—To estimate the efficiency of first-trimester uterine artery Doppler, A-disintegrin and metalloprotease 12 (ADAM12), pregnancy-associated plasma protein A (PAPP-A) and maternal characteristics in the prediction of pre-eclampsia.

Methods—This is a prospective cohort study of patients presenting for first-trimester aneuploidy screening between 11-14 weeks' gestation. Maternal serum ADAM12 and PAPP-A levels were measured by immunoassay, and mean uterine artery Doppler pulsatility indices (PI) were calculated. Outcomes of interest included pre-eclampsia, early pre-eclampsia, defined as requiring delivery at <34 weeks' gestation, and gestational hypertension. Logistic regression analysis was used to model the prediction of pre-eclampsia using ADAM12 multiples of the median (MoM), PAPP-A MoM, and uterine artery Doppler PI MoM, either individually or in combination. Sensitivity, specificity, and area under the receiver-operating characteristic curves (AUC) were used to compare the screening efficiency of the models using non-parametric U-statistics.

Results—Of 578 patients with complete outcome data, there were 54 (9.3%) cases of preeclampsia and 13 (2.2%) cases of early pre-eclampsia. Median ADAM12 levels were significantly lower in patients who developed pre-eclampsia compared to those who did not. (0.81 v. 1.01 MoMs; $p<0.04$) For a fixed false positive rate (FPR) of 10%, ADAM12, PAPP-A, and uterine artery Doppler in combination with maternal characteristics identified 50%, 48%, and 52% of patients who developed pre-eclampsia, 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 not sufficiently predictive of pre-eclampsia. Combinations of these parameters do not further improve their screening efficiency.

Keywords

ADAM12; PAPP-A; placental dysfunction; pre-eclampsia; uterine artery Doppler

Introduction

Pre-eclampsia affects 5-8% of pregnancies and remains a significant contributor to perinatal morbidity and mortality worldwide.[1,2] Abnormal invasion of the placental trophoblast into

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the maternal spiral arterioles, as early as the first trimester, is the proposed pathophysiologic mechanism for the development of this disorder. This abnormal placentation results in a high resistance uteroplacental circulation bed and persistent placental underperfusion, leading to the phenotype of pre-eclampsia.

The use of biochemical and ultrasound parameters to detect these pathologic changes and identify patients at high risk for developing pre-eclampsia has been an area of intense research focus over recent years. Prior studies have demonstrated an association between low levels of pregnancy-associated plasma protein A (PAPP-A), a serum analyte routinely measured as part of first-trimester aneuploidy screening, and the subsequent development of pre-eclampsia later in pregnancy. However, PAPP-A alone has demonstrated only a modest predictive efficiency for adverse pregnancy outcomes, including pre-eclampsia.[3-6] More recent studies have evaluated the association between low levels of a novel serum analyte, A Disintegrin and Metalloprotease 12 (ADAM12), and pre-eclampsia and have produced conflicting results.[7-9] These studies mainly have been limited to case-control designs performed in populations with a low prevalence of preeclampsia, and, therefore, may be subject to bias. Additionally, these studies have primarily been conducted in low risk populations, thereby precluding a rigorous evaluation of maternal risk factors which may increase the screening efficiency of these biomarkers. Finally, uterine artery Doppler studies have been proposed as a screening tool to detect increased vascular resistance in patients destined to develop pre-eclampsia, with reported sensitivites ranging from 7-80% when performed in the first trimester.[10-15]

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 pre-eclampsia. We hypothesize that a combination of these first-trimester parameters, in addition to maternal clinical risk factors, may allow for more accurate identification of women at risk. Although there is currently no known effective strategy for the prevention of pre-eclampsia, the ability to predict patients at high risk of developing this disorder not only may provide an opportunity to impact pregnancy management but may also provide an opportunity to identify an enriched population of patients who can serve as target subjects for future intervention studies.

Materials and Methods

This was a prospective cohort study of patients presenting to Washington University Medical Center from 2008-2010 for first-trimester aneuploidy screening. Women with singleton pregnancies between 11 and 14 weeks' gestation were eligible for inclusion. Exclusion criteria were known aneuploidy and major congenital malformations. Institutional review board approval was obtained, and all patients provided written, informed consent.

All consecutive eligible patients were approached for participation in the study at the time of ultrasound exam. Standard of care for first-trimester aneuploidy screening at our institution includes a measurement of fetal crown-rump length to confirm pregnancy dating (within ±7 days from menstrual dating), nuchal translucency measurement, and serum measurement of PAPP-A and free β-human chorionic gonadotropin (β-hCG). Serum measurements of both PAPP-A and free β-hCG are routinely performed by Perkin Elmer laboratories (Melville, NY) for all samples collected at our institution. Patients who consented to study participation provided an additional 10ml of blood which was used to measure ADAM12 concentration. Maternal blood was collected into non-heparinized tubes and centrifuged at 1500 *g* for 15 minutes. Maternal serum was then extracted and stored at -80° C until analyzed. A 25μl aliquot of maternal serum was used to determine ADAM12 concentration through a time-resolved fluorescent immuno-assay, in which the concentration of ADAM12

was directly proportional to the fluorescence measured at 615nm. (DELFIA/AutoDELFIA ADAM12 research kit, PerkinElmer Life and Analytical Sciences, Turku, Finland) All serum analyte levels were converted into multiples of the median (MoMs), adjusted for gestational age, for analysis.

Patients who consented to the study also underwent bilateral uterine artery Doppler assessment. This assessment was performed using a transabdominal approach with color flow mapping. A mid-sagittal view of the uterus was obtained and the cervical canal identified. The transducer was then rotated until the paracervical vessels were identified. Each uterine artery was then isolated, and the pulsatility index (PI) measured and averaged. These measurements were also converted into MoMs, adjusted for gestational age. All participating sonographers were certified by the Fetal Medicine Foundation for first-trimester Doppler measurements.

Maternal demographics, past medical history, and obstetrical history were obtained through a detailed questionnaire routinely administered at the time of all initial ultrasound exams in our unit. Delivery outcome information was obtained through electronic medical record review by a dedicated nurse coordinator. Patients who delivered outside of our institution signed a consent for release of medical records at the time of study enrollment.

The primary outcome for this study was pre-eclampsia defined as systolic blood pressure >140 mmHg or diastolic blood pressure >90 mmHg on at least two occasions separated by at least 4 hours in the presence of proteinuria (≥0.3 grams in a 24 hour specimen or ≥1+ protein on urine dipstick) after 20 weeks' gestation. Secondary outcomes included early pre-eclampsia, defined as pre-eclampsia requiring delivery <34 weeks, and gestational hypertension (HTN), defined as blood pressure >140/90 mmHg in the absence of proteinuria after 20 weeks' gestation.[1,16]

Baseline maternal characteristics as well as ADAM12, PAPP-A, and uterine artery PI MoMs were compared between patients who developed pre-eclampsia and those who did not. Categorical variables were compared using chi-square tests, and continuous variables were compared using the independent sample t-test and Mann-Whitney U test, as appropriate. Normality of distribution was evaluated using the Kolmogorov-Smirnov test. Logistic regression was then used to model the prediction of pre-eclampsia incorporating various combinations of first-trimester parameters as well as maternal factors identified as significant in the univariate analysis. There was no evidence of collinearity between the first-trimester parameters and maternal characteristics of interest, thereby justifying their inclusion together in the various models. Receiver-operating characteristic curves (ROC) were generated for each model, and the area under the curve (AUC) was compared between each model using non-parametric U statistics. 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 12, Special Edition (College Station, TX).

Since the focus of this study was on the development of a highly sensitive prediction model for pre-eclampsia, the precision of our sample size estimates was based on the ½ width of the 95% confidence interval and the incidence of pre-eclampsia in our patient population. With these assumptions, our study was powered to produce a prediction model with a 70% (95% CI 57-83) sensitivity for pre-eclampsia and a 90% sensitivity (95% CI 75-100) for early preeclampsia.

Results

Of 618 patients enrolled, 13 were lost to follow up and 3 withdrew from the study before completion. After excluding patients who underwent spontaneous abortion (n=8), elective abortion (n=1), and those with incomplete outcome information (n=15), 578 patients were available for analysis, comprising our final study cohort. Of these patients, 54 (9.3%) developed pre-eclampsia, 13 (2.2%) developed early pre-eclampsia, and 55 (9.5%) developed gestational HTN. The mean gestational age at the time of ultrasound and study enrollment was 12.1 ± 0.6 weeks. Compared to patients who did not develop pre-eclampsia, patients who went on to develop pre-eclampsia were more likely to be African American, have a higher pre-pregnancy body mass index (BMI), and have a higher incidence of both chronic HTN and pre-gestational diabetes. (Table 1)

Patients who developed pre-eclampsia had significantly lower ADAM12 levels (0.81 vs. 1.01; p=0.04) and PAPP-A levels (0.88 vs. 1.18, p<0.001) compared to controls; however, there was no significant difference in uterine artery Doppler PI levels in pre-eclamptic patients compared to controls (1.00 vs. 0.99, p=0.77). There was no significant difference in ADAM12, PAPP-A, or uterine artery Doppler PI levels when comparing patients who developed early preeclampsia or gestational HTN compared to those who did not. (Table 2)

Individually, ADAM12, PAPP-A, and uterine artery Dopplers were not sufficiently predictive of pre-eclampsia, resulting in AUCs ranging from 0.49-0.64. In fact, maternal characteristics alone (AUC 0.78, 95% CI 0.71-0.75) were significantly more predictive of preeclampsia than any first-trimester parameter alone. (ADAM12 alone, p<0.001; PAPP-A alone, p=0.01; uterine artery Doppler alone, p<0.001) Combining these first-trimester parameters with maternal characteristics did improve the predictive efficiency of the models. The best overall predictive efficiency was observed with the combination of maternal characteristics, ADAM12, PAPP-A and uterine artery Doppler with an AUC of 0.79 (95% CI 0.71-0.87) and sensitivities of 50% and 75% at 10% and 20% FPR, respectively. However, this predictive efficiency still was not statistically different from the model containing maternal characteristics alone (p=0.77). (Table 3) The significant independent predictors of pre-eclampsia in this model included PAPPA, BMI, history of chronic hypertension and history of pre-gestational diabetes.

Similar results were observed for the prediction of early pre-eclampsia and gestational HTN. ADAM12, PAPP-A and uterine artery Doppler alone were not predictive for the development of early pre-eclampsia or gestational HTN. Combining these parameters with maternal risk factors did improve the predictive efficiencies; however, models containing the first-trimester parameters did not differ significantly from those containing maternal characteristics alone. The best overall predictive efficiency for early pre-eclampsia was observed with the combination of maternal characteristics, ADAM12 and PAPP-A with an AUC of 0.78 (95% CI 0.63-0.93) and sensitivities of 54% and 62% at 10% and 20% FPR, respectively. (Table 4) The best overall predictive efficiency for gestational HTN was observed with the combination of maternal characteristics, ADAM12, PAPP-A and uterine artery Doppler with an AUC of 0.66 (95% CI 0.58-0.74) and sensitivities of 15% and 28% at 10% and 20% FPR, respectively. (Table 5) The only significant independent predictor of early pre-eclampsia in this model was a maternal history of chronic hypertension.

In order to evaluate the predictive indices of our model, we created two hypothetical populations, one with a low prevalence of disease (1%) and one with a high prevalence of disease (10%). Using the calculated sensitivities of our models at a 10% FPR, positive (PPV) and negative predictive values (NPV) were estimated for our models containing maternal characteristics alone as well as the combination of maternal characteristics with

ADAM12 levels, PAPP-A levels, and uterine artery Doppler. For the outcome of pre-eclampsia, the PPV and NPV were 4.8% and 99.4%, respectively, in the low prevalence population and 35.7% and 94.2%, respectively, in the high prevalence population for maternal characteristics alone. For the outcome of early pre-eclampsia, the PPV and NPV were 5.3% and 99.5% in the low prevalence population and 37.9% and 94.7% in the high prevalence population for maternal characteristics alone. Finally, for the outcome of gestational hypertension, the PPV and NPV were 1.5% and 99.0% in the low prevalence population and 14.3% and 90.5% in the high prevalence population for maternal characteristics alone. When evaluating the models containing the combination of maternal characteristics and first-trimester markers of placental dysfunction, the predictive indices were identical to the models containing maternal characteristics alone.

Discussion

Findings from our prospective cohort demonstrate that both ADAM12 and PAPP-A levels are significantly reduced in patients who develop pre-eclampsia. Similar to PAPP-A, ADAM12 is a protease for insulin growth factor (IGF) binding proteins. Low levels of this analyte reflect an increased amount of IGF in the bound state which is then unavailable to promote placental growth and development, making this finding biologically plausible.[17,18] However, despite these associations, the predictive efficiency of ADAM12 and PAPP-A was overall modest and not sufficient for clinical use. In fact, our findings suggest that maternal characteristics alone actually demonstrate superior test performance characteristics for the prediction of pre-eclampsia which are not enhanced by the addition of these first-trimester markers, either individually or in combination.

Prior studies have been conflicting regarding the role of ADAM12 in the prediction of pre-eclampsia. Both Laigaard *et al.* and Spencer *et al.* demonstrated decreased serum concentrations of ADAM12 in the first-trimester in women who went on to develop preeclampsia.[7,8] Consistent with our results, Spencer *et al.* also demonstrated only a modest predictive efficiency of ADAM12 for pre-eclampsia with an AUC of 0.694 for ADAM12 alone and an AUC of 0.714 when ADAM12 and PAPP-A were combined.[8] Alternatively, Poon *et al.* found that first-trimester ADAM12 levels were not significantly lower in patients who developed pre-eclampsia compared to controls.[9] They attributed these negative findings to *a priori* adjustment of ADAM12 levels for race and maternal weight. When these maternal characteristics were evaluated in our population, we found no relationship between ADAM12 and maternal race. While there was a modest correlation between ADAM12 levels and maternal weight, we adjusted for this factor in our prediction model as an established maternal clinical risk factor for pre-eclampsia.

Our study did not demonstrate any significant difference in uterine artery PI measurements between pre-eclamptic and control patients. Given that maximal trophoblast invasion occurs during the first-trimester, it would seem justified that enhanced vascular resistance in the uterine arteries would be detectable at this early stage of gestation in patients with impaired placentation.[19] Recently, Parra-Cordero *et al.* demonstrated a significant increase in first-trimester uterine artery Doppler PI in patients who developed both early-onset and late-onset pre-eclampsia compared to controls. In this study, the sensitivity of maternal history plus uterine artery Doppler for detecting early-onset and late-onset pre-eclampsia were 43.8% and 28.3%, respectively, at a 10% FPR.[20] While our study did not demonstrate a significant difference in absolute uterine artery PI values, the sensitivity of maternal characteristics and uterine artery Doppler were similar to that observed by Parra-Cordero *et al.* at 54% and 52%, respectively, at a 10% FPR. Again, this finding suggests that the predictive value of these first-trimester parameters may be primarily driven by the contribution of maternal characteristics alone. Additionally, Poon *et al.* demonstrated that first-trimester uterine

artery Doppler studies were significantly increased in patients who developed hypertensive disorders later in pregnancy.[21] Differences between these studies and our study may be due to the varying criteria which was used to define an abnormal uterine artery Doppler PI. Both of the above-mentioned studies measured the right and left uterine artery PI and used the lowest recorded value in their analysis. Alternatively, our study used the average value of the right and left uterine artery PI measurements, a technique which has been previously described.[12,14] We believe that this average value is more representative of overall placental perfusion. This discrepancy between studies further supports the claim that first-trimester uterine artery Doppler may not be a reliable predictor of pre-eclampsia, as we would have expected to observe more consistent results across studies regardless of the criteria used to define an abnormal value. Furthermore, differences in study populations as well as variability in the maternal factors included in the prediction models may also account for some of the discrepancy observed between studies.

Strengths of our study include its prospective cohort design and low loss to follow up rate. This study design allowed us to ensure that our unaffected patients were derived from the same population as our affected patients, thereby eliminating the bias which is often introduced in case-control studies through the process by which controls patients are selected. Additionally, given that our study was performed in a tertiary referral center, there was adequate representation of maternal co-morbidities which could then be rigorously evaluated as maternal risk factors for the development of pre-eclampsia. Our study is not without limitations. Despite our large cohort, the small number of early pre-eclampsia cases (n=13) left us under-powered to thoroughly evaluate this outcome. Additionally, while we did adjust for gestational age, we did not perform *a priori* adjustment of ADAM12 levels for other maternal characteristics. However, data in the literature as well as in our own population has been conflicting as to which factors truly have a significant effect on this analyte. Given that these proposed adjustment factors are also well-established risk factors for pre-eclampsia, we instead took the approach of controlling for these factors in our prediction model in order to provide a more individualized risk assessment based on maternal characteristics and history. Furthermore, our medical center is a high-risk, tertiary referral center which likely contributes to the high prevalence of preeclampsia in our study population; however, this high prevalence of pre-eclampsia should not affect the overall accuracy of our prediction model, given that sensitivity and specificity are independent of prevalence. Finally, the methods used in this study are aimed at population-based screening for hypertensive disorders in pregnancy. These risk factors may still play a significant role in individualized patient risk assessment and counseling.

In conclusion, our study demonstrates that while first-trimester ADAM12 and PAPP-A levels are significantly reduced in patients who develop pre-eclampsia, the predictive efficiency of these first-trimester serum markers as well as uterine artery Doppler studies, both individually and in combination, are not superior to that achieved by maternal characteristics alone. Continued investigation into novel serum and ultrasound markers of placental dysfunction is warranted in order to more accurately identify this high risk population.

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Table 1

Baseline maternal characteristics and obstetrical history

	Pre-Eclampsia (n=54)	Control (n=518)	p-value
Maternal Age (years)*	30.2 ± 6.1	31.3 ± 5.8	0.23
Race			0.03
Caucasian	42.6%	57.4%	
African American	48.1%	28.1%	
Hispanic	0%	2.6%	
Asian	5.6%	9.0%	
Other	3.7%	2.9%	
Body Mass Index (kg/m^2)*	34.0 ± 9.2	28.1 ± 7.4	<0.001
Nulliparity	20.4%	27.5%	0.26
Tobacco Use	13.2%	8.7%	0.27
Chronic Hypertension	38.9%	6.7%	<0.001
Pre-gestational Diabetes	22.2%	5.6%	<0.001

* Data expressed as mean ± standard deviation

Table 2

Comparison of First-Trimester Marker Levels Between Study Groups

Pre-Eclampsia			
Marker	**Pre-Eclampsia (n=54)**	**Control (n=518)**	**p-value**
ADAM12 MoM	0.81 (0.61-1.30)	1.01 (0.74-1.36)	0.04
PAPP-A MoM	0.88 (0.62-1.27)	1.18 (0.60-1.63)	<0.001
Uterine Artery Doppler PI MoM	1.00 (0.85-1.22)	0.99 (0.79-1.23)	0.77
Early Pre-Eclampsia			
Marker	**Early Pre-Eclampsia (n=13)**	**Control (n=565)**	**p-value**
ADAM12 MoM	0.82 (0.57-1.21)	1.00 (0.73-1.35)	0.11
PAPP-A MoM	1.02 (0.73-1.53)	1.14 (0.76-1.58)	0.55
Uterine Artery Doppler PI MoM	1.00 (0.79-1.22)	1.00 (0.89-1.43)	0.22
Gestational HTN			
Marker	**Gestational HTN (n=55)**	**Control (n=523)**	**p-value**
ADAM12 MoM	0.81 (0.63-1.22)	1.01 (0.73-1.35)	0.07
PAPP-A MoM	1.18 (0.82-1.73)	1.13 (0.76-1.58)	0.51
Uterine Artery Doppler PI MoM	0.96 (0.78-1.13)	1.01 (0.80-1.24)	0.10

* Data expressed as medians and interquartile ranges

* HTN=hypertension; MoM=multiples of the median

Table 3

Predictive Efficiency of First-Trimester Parameters for Pre-Eclampsia

Marker	AUC (95% CI)	Sensitivity 10% FPR	Sensitivity 20% FPR
Maternal Characteristics Alone	0.78 (0.71-0.85)	50%	62%
ADAM12 Alone	0.58 (0.50-0.67)	12%	30%
PAPP-A Alone	0.64 (0.57-0.72)	18%	32%
Uterine Artery Doppler Alone	0.49 (0.41-0.56)	5%	16%
ADAM12 +PAPP-A + Uterine Artery Doppler Alone	0.64 (0.57-0.72)	22%	42%
Maternal Characteristics + ADAM12	0.78 (0.70-0.85)	50%	62%
Maternal Characteristics + PAPP-A	0.79 (0.72-0.86)	48%	64%
Maternal Characteristics + Uterine Artery Doppler	0.77 (0.69-0.86)	52%	64%
Maternal Characteristics + ADAM12 + PAPP-A	0.79 (0.71-0.86)	50%	70%
Maternal Characteristics + ADAM12 + Uterine Artery Doppler	0.78 (0.70-0.86)	52%	62%
Maternal Characteristics + ADAM12 + PAPP-A + Uterine Artery Doppler	0.79 (0.71-0.87)	50%	75%

* Maternal characteristics: African American race, body mass index, history of chronic hypertension, history of pre-gestational diabetes

Table 4

Predictive Efficiency of First-Trimester Parameters for Early Pre-Eclampsia

Marker	AUC (95% CI)	Sensitivity 10% FPR	Sensitivity 20% FPR
Maternal Characteristics Alone	0.71 (0.54-0.88)	55%	58%
ADAM12 Alone	0.63 (0.46-0.80)	22%	30%
PAPP-A Alone	0.55 (0.38-0.71)	16%	22%
Uterine Artery Doppler Alone	0.60 (0.44-0.75)	10%	38%
ADAM12 +PAPP-A + Uterine Artery Doppler Alone	0.65 (0.48-0.82)	35%	46%
Maternal Characteristics + ADAM12	0.77 (0.620.93)	54%	62%
Maternal Characteristics + PAPP-A	0.75 (0.60-0.90)	54%	54%
Maternal Characteristics + Uterine Artery Doppler	0.71 (0.53-0.90)	54%	62%
Maternal Characteristics + ADAM12 + PAPP-A	0.78 (0.63-0.93)	54%	62%
Maternal Characteristics + ADAM12 + Uterine Artery Doppler	0.77 (0.61-0.93)	54%	62%
Maternal Characteristics + ADAM12 + PAPP-A + Uterine Artery Doppler	0.77 (0.62-0.93)	54%	62%

* Maternal characteristics: African American race and history of chronic hypertension

Table 5

Predictive Efficiency of First-Trimester Parameters for Gestational Hypertension

Marker	AUC (95% CI)	Sensitivity 10% FPR	Sensitivity 20% FPR
Maternal Characteristics Alone	0.62 (0.55-0.70)	15%	22%
ADAM12 Alone	0.57 (0.49-0.66)	15%	32%
PAPP-A Alone	0.53 (0.44-0.61)	20%	26%
Uterine Artery Doppler Alone	0.57 (0.49-0.64)	16%	22%
ADAM12 +PAPP-A + Uterine Artery Doppler Alone	0.59 (0.52-0.66)	12%	20%
Maternal Characteristics + ADAM12	0.62 (0.53-0.72)	12%	36%
Maternal Characteristics + PAPP-A	0.63 (0.55-0.71)	12%	28%
Maternal Characteristics + Uterine Artery Doppler	0.64 (0.56-0.71)	8%	30%
Maternal Characteristics + ADAM12 + PAPP-A	0.63 (0.54-0.73)	14%	42%
Maternal Characteristics + ADAM12 + Uterine Artery Doppler	0.65 (0.57-0.73)	10%	28%
Maternal Characteristics + ADAM12 + PAPP-A + Uterine Artery Doppler	0.66 (0.58-0.74)	15%	28%

* Maternal characteristics: African American race and body mass index