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Efficiency of First-Trimester Uterine Artery Doppler, A-Disintegrin and Metalloprotease 12, Pregnancy-Associated Plasma Protein A, and Maternal Characteristics in the Prediction of Preeclampsia

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Abbreviations

ADAM12, A-disintegrin and metalloprotease 12; AUC, area under the curve; CI, confidence interval; MoM, multiples of the median; NPV, negative predictive value; PAPP-A, pregnancy-associated plasma protein A; PI, pulsatility index; PPV, positive predictive value

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Objectives—The purpose of this study was 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 preeclampsia.

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

Results—Among 578 patients with complete outcome data, there were 54 cases of preeclampsia (9.3%) and 13 cases of early preeclampsia (2.2%). Median ADAM12 levels were significantly lower in patients who developed preeclampsia compared to those who did not (0.81 versus 1.01 MoM; $P = .04$). For a fixed false-positive rate of 10%, ADAM12, PAPP-A, and uterine artery Doppler parameters in combination with maternal characteristics identified 50%, 48%, and 52% of patients who developed preeclampsia, respectively. Combining these first-trimester parameters did not improve the predictive efficiency of the models.

Conclusions—First-trimester ADAM12, PAPP-A, and uterine artery Doppler characteristics are not sufficiently predictive of preeclampsia. Combinations of these parameters do not further improve their screening efficiency.

Key Words—A-disintegrin and metalloprotease 12; pregnancy-associated plasma protein A; placental dysfunction; preeclampsia; uterine artery Doppler sonography

Preeclampsia affects 5% to 8% of pregnancies and remains a substantial contributor to perinatal morbidity and mortality worldwide.[1,2] Abnormal invasion of the placental trophoblast into 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 preeclampsia.

The use of biochemical and sonographic parameters to detect these pathologic changes and identify patients at high risk of developing preeclampsia 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 preeclampsia later in pregnancy. However, PAPP-A alone has demonstrated only modest predictive efficiency for adverse pregnancy outcomes, including preeclampsia.[3–6] More recent studies have evaluated the association between low levels of a novel serum analyte, A-disintegrin and metalloprotease 12 (ADAM12), and preeclampsia 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 have been subject to bias. In addition, 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 screening tools to detect increased vascular resistance in patients destined to develop preeclampsia, with reported sensitivity values ranging from 7% to 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 preeclampsia. We hypothesized 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 preeclampsia, the ability to predict patients at high risk of developing this disorder not only may provide an opportunity to affect pregnancy management but also may provide an opportunity to identify an enriched population of patients who can serve as target patients for future interventional studies.

Materials and Methods

We conducted a prospective cohort study of patients presenting to Washington University Medical Center from 2008 to 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 their sonographic examinations. The standard of care for first-trimester aneuploidy screening at our institution includes fetal crown-rump length measurement to confirm pregnancy dating (within ±7 days of menstrual dating), nuchal translucency measurement, and serum PAPP-A and free β-human chorionic gonadotropin measurements. Serum PAPP-A and free β-human chorionic gonadotropin measurements 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 10 mL of blood, which was used to measure the ADAM12 concentration. Maternal blood was collected into nonheparinized tubes and centrifuged at 1500g for 15 minutes. Maternal serum was then extracted and stored at –80°C until analyzed. A 25-μL aliquot of maternal serum was used to determine the ADAM12 concentration by a time-resolved fluorescent immunoassay, in which the concentration of ADAM12 was directly proportional to the fluorescence measured at 615 nm (DELFIA/AutoDELFIA ADAM12 research kit; PerkinElmer Life and Analytical Sciences, Turku, Finland). All serum analyte levels were converted into multiples of the median (MoM), adjusted for gestational age, for analysis.

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

Maternal demographics, medical histories, and obstetric histories were obtained from a detailed questionnaire routinely administered at the time of all initial sonographic examinations in our unit. Delivery outcome information was obtained from an electronic medical record review by a dedicated nurse coordinator. Patients who delivered outside our institution signed a consent for release of medical records at the time of study enrollment.

The primary outcome for this study was preeclampsia, defined as systolic blood pressure higher than 140 mm Hg or diastolic blood pressure higher than 90 mm Hg on at least 2 occasions separated by at least 4 hours in the presence of proteinuria (≥0.3 g in a 24-hour specimen or ≥1+ protein on a urine dipstick) after 20 weeks' gestation. Secondary outcomes included early preeclampsia, defined as preeclampsia requiring delivery before 34 weeks, and gestational hypertension, defined as blood pressure higher than 140/90 mm Hg in the absence of proteinuria after 20 weeks' gestation.[1,16]

Baseline maternal characteristics as well as ADAM12, PAPP-A, and uterine artery PI MoM values were compared between patients who developed preeclampsia and those who did not. Categorical variables were compared by χ^2 tests, and continuous variables were compared by an independent samples *t* test and the Mann-Whitney *U* test, as appropriate. Normality of distribution was evaluated by the Kolmogorov-Smirnov test. Logistic regression was then used to model the prediction of preeclampsia, incorporating various combinations of first-trimester parameters as well as maternal factors identified as significant in the univariate analysis. There was no evidence of colinearity between the first-trimester parameters and maternal characteristics of interest, thereby justifying their inclusion together in the various models. Receiver operating characteristic curves were generated for each model, and the area under the curve (AUC) was compared between each model by nonparametric *U* statistics. Sensitivity and specificity values at both 10% and 20% fixed false-positive rates were also calculated for each model. $P < .05$ was considered statistically significant. All statistical analyses were performed with STATA 12 Special Edition software (StataCorp, College Station, TX).

Since the focus of this study was on the development of a highly sensitive prediction model for preeclampsia, the precision of our sample size estimates was based on the half-width of the 95% confidence interval (CI) and the incidence of preeclampsia in our patient population. With these assumptions, our study was powered to produce a prediction model with 70% sensitivity (95% CI, 57%–83%) for preeclampsia and 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) or elective abortion (n = 1) and those with incomplete outcome information (n = 15), 578 patients were available for analysis, constituting our final study cohort. Of these patients, 54 (9.3%) developed preeclampsia, 13 (2.2%) developed early preeclampsia, and 55 (9.5%) developed gestational hypertension. The mean gestational age ± SD at the time of sonography and study enrollment was 12.1 ± 0.6 weeks. Compared to patients who did not develop preeclampsia, patients who went on to develop preeclampsia were more likely to be African American, have a higher prepregnancy body mass index, and have a higher incidence of both chronic hypertension and pregestational diabetes (Table 1).

Patients who developed preeclampsia had significantly lower ADAM12 levels (0.81 versus 1.01 MoM; $P = .04$) and PAPP-A levels (0.88 versus 1.18 MoM; $P < .001$) compared to controls; however, there was no significant difference in uterine artery Doppler PI levels in preeclamptic patients compared to controls (1.00 versus 0.99 MoM; $P = .77$). There was no significant difference in ADAM12, PAPP-A, or uterine artery Doppler PI levels when comparing patients who developed early preeclampsia or gestational hypertension to those who did not (Table 2).

Individually, ADAM12, PAPP-A, and uterine artery Doppler parameters were not sufficiently predictive of preeclampsia, resulting in AUCs ranging from 0.49 to 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, $P < .001$; PAPP-A alone, $P = .01$; uterine artery Doppler alone, $P < .001$). 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

Table 1. Baseline Maternal Characteristics and Obstetric History

Characteristic	Preeclampsia (n = 54)	Control (n = 524)	*P*
Maternal age, y[a]	30.2 ± 6.1	31.3 ± 5.8	.23
Race, %			.03
White	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[a]	34.0 ± 9.2	28.1 ± 7.4	<.001
Nulliparity, %	20.4	27.5	.26
Tobacco use, %	13.2	8.7	.27
Chronic hypertension, %	38.9	6.7	<.001
Pregestational diabetes, %	22.2	5.6	<.001

[a]Data are expressed as mean ± SD.

artery Doppler parameters, with an AUC of 0.79 (95% CI, 0.71–0.87) and sensitivity values of 50% and 75% at 10% and 20% false-positive rates, respectively. However, this predictive efficiency still was not statistically different from that of the model containing maternal characteristics alone ($P = .77$; Table 3). The significant independent predictors of preeclampsia in this model included PAPP-A, body mass index, history of chronic hypertension, and history of pregestational diabetes.

Similar results were observed for the prediction of early preeclampsia and gestational hypertension. The ADAM12, PAPP-A, and uterine artery Doppler parameters alone were not predictive of the development of early preeclampsia or gestational hypertension. 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 preeclampsia 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 sensitivity values of 54% and 62% at 10% and 20% false-positive rates, respectively (Table 4). The best overall predictive efficiency for gestational hypertension was observed with the combination of maternal characteristics, ADAM12, PAPP-A, and uterine artery Doppler parameters, with an AUC of 0.66 (95% CI, 0.58–0.74) and sensitivity values of 15% and 28% at 10% and 20% false-positive rates, respectively (Table 5). The only significant independent predictor of early preeclampsia in this model was a maternal history of chronic hypertension.

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 sensitivity values of our models at a 10% false-positive rate, positive predictive values (PPVs) and negative predictive values (NPVs) were estimated for our models containing maternal characteristics alone as well as the combination of maternal characteristics with ADAM12, PAPP-A, and uterine artery Doppler parameters. For the outcome of preeclampsia, the PPV and NPV were 4.8% and 99.4%, respectively, in the low-prevalence population and 35.7% and 94.2% in the high-prevalence population for maternal characteristics alone. For the outcome of early preeclampsia, 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.

Table 2. Comparison of First-Trimester Marker Levels Between Study Groups

Marker	Preeclampsia (n = 54)	Control (n = 524)	*P*
ADAM12 MoM	0.81 (0.61–1.30)	1.01 (0.74–1.36)	.04
PAPP-A MoM	0.88 (0.62–1.27)	1.18 (0.60–1.63)	<.001
Uterine artery Doppler PI MoM	1.00 (0.85–1.22)	0.99 (0.79–1.23)	.77
Marker	**Early Preeclampsia (n = 13)**	**Control (n = 565)**	***P***
ADAM12 MoM	0.82 (0.57–1.21)	1.00 (0.73–1.35)	.11
PAPP-A MoM	1.02 (0.73–1.53)	1.14 (0.76–1.58)	.55
Uterine artery Doppler PI MoM	1.00 (0.79–1.22)	1.00 (0.89–1.43)	.22
Marker	**Gestational Hypertension (n = 55)**	**Control (n = 523)**	***P***
ADAM12 MoM	0.81 (0.63–1.22)	1.01 (0.73–1.35)	.07
PAPP-A MoM	1.18 (0.82–1.73)	1.13 (0.76–1.58)	.51
Uterine artery Doppler PI MoM	0.96 (0.78–1.13)	1.01 (0.80–1.24)	.10

Data are expressed as median (interquartile range).

Discussion

Findings from our prospective cohort demonstrate that both ADAM12 and PAPP-A levels are significantly reduced in patients who develop preeclampsia. Similar to PAPP-A, ADAM12 is a protease for insulin-like growth factor–binding proteins. Low levels of this analyte reflect an increased amount of insulin-like growth factor 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

Table 3. Predictive Efficiency of First-Trimester Markers for Preeclampsia

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	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

FPR indicates false-positive rate. Maternal characteristics included African American race, body mass index, history of chronic hypertension, and history of pregestational diabetes.

Table 4. Predictive Efficiency of First-Trimester Markers for Early Preeclampsia

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	0.65 (0.48–0.82)	35	46
Maternal characteristics + ADAM12	0.77 (0.62–0.93)	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

FPR indicates false-positive rate. Maternal characteristics included African American race and history of chronic hypertension.

actually have superior test performance characteristics for the prediction of preeclampsia, 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 preeclampsia. Both Laigaard et al[7] and Spencer et al[8] demonstrated decreased serum concentrations of ADAM12 in the first-trimester in women who went on to develop preeclampsia. Consistent with our results, Spencer et al[8] also demonstrated only a modest predictive efficiency of ADAM12 for preeclampsia, with an AUC of 0.694 for ADAM12 alone and an AUC of 0.714 when ADAM12 and PAPP-A were combined. Alternatively, Poon et al[9] found that first-trimester ADAM12 levels were not significantly lower in patients who developed preeclampsia compared to controls. 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. Although 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 preeclampsia.

Our study did not demonstrate any significant difference in uterine artery PI measurements between preeclamptic 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[20] demonstrated a significant increase in the first-trimester uterine artery Doppler PI in patients who developed both early- and late-onset preeclampsia compared to controls. In that study, the sensitivity of the maternal history plus uterine artery Doppler parameters for detecting early- and late-onset preeclampsia were 43.8% and 28.3%, respectively, at a 10% false-positive rate.[20] Although our study did not demonstrate a significant difference in absolute uterine artery PI values, the sensitivity of maternal characteristics and uterine artery Doppler parameters were similar to that observed by Parra-Cordero et al,[20] at 54% and 52%, respectively, at a 10% false-positive rate. Again, this finding suggests that the predictive value of these first-trimester parameters may be primarily driven by the contribution of maternal characteristics alone. In addition, Poon et al[21] demonstrated that first-trimester uterine artery Doppler parameters were significantly increased in patients who developed hypertensive disorders later in pregnancy. Differences between these studies and our study

Table 5. Predictive Efficiency of First-Trimester Markers 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	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

FPR indicates false-positive rate. Maternal characteristics included African American race and body mass index.

may be due to the varying criteria used to define an abnormal uterine artery Doppler PI. Both of the above-mentioned studies measured the right and left uterine artery PIs 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 that has been described previously.[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 parameters may not be reliable predictors of preeclampsia, 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 included its prospective cohort design and low rate of loss to follow-up. 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 that is often introduced in case-control studies through the process by which control patients are selected. In addition, given that our study was performed in a tertiary referral center, there was adequate representation of maternal comorbidities, which could then be rigorously evaluated as maternal risk factors for the development of preeclampsia.

Our study was not without limitations. Despite our large cohort, the small number of early preeclampsia cases (n = 13) left us underpowered to thoroughly evaluate this outcome. In addition, although we did adjust for gestational age, we did not perform an a priori adjustment of ADAM12 levels for other maternal characteristics. However, data in the literature as well as in our own population have 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 preeclampsia, we instead took the approach of controlling for these factors in our prediction model 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 contributed to the high prevalence of preeclampsia in our study population; however, this high prevalence of preeclampsia should not have affected the overall accuracy of our prediction model, given that sensitivity and specificity are independent of prevalence. Finally, the methods used in this study were aimed at population-based screening for hypertensive disorders in pregnancy. These risk factors may still play a substantial role in individualized patient risk assessment and counseling.

In conclusion, our study demonstrates that although first-trimester ADAM12 and PAPP-A levels are significantly reduced in patients who develop preeclampsia, 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 of novel serum and sonographic markers of placental dysfunction is warranted to more accurately identify this high-risk population.

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