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# Value of Placental Volume and Vascular Flow Indices as Predictors of Early and Late Preeclampsia at First Trimester

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**Keywords**
Preeclampsia · Early preeclampsia · Late preeclampsia · Placental volume · Vascular indices · Preeclampsia prediction models

**Abstract**
***Introduction:*** We evaluated the utility of placental volume and three-dimensional (3D) vascular flow indices to predict early and late preeclampsia. ***Material and Methods:*** In 1,004 pregnancies attending routine care, we recorded first-trimester screening program for aneuploidy (FTSA) parameter and measured uterine artery pulsatility index (uterine-a PI). Placental volume and vascular flow indices were obtained using 3D power Doppler and VOCAL techniques. ***Results:*** Placental volume was lower and uterine-a PI was higher in both early and late preeclampsia groups versus nonaffected pregnancies. The prediction rate of placental volume in late preeclampsia was higher than that of uterine-a PI (AUROC 0.707 vs. 0.581, $p < 0.011$). The inclusion of placental volume improved significantly the prediction rate of total and late preeclampsia in the models constructed with maternal characteristics, FTSA, and uterine-a PI (AUROC 0.745 vs. 0.818, $p < 0.004$, and 0.740 vs. 0.812, $p < 0.012$, respectively). The inclusion of vascular indices did not improve the predictive value of these models. ***Discussion:*** Placental volume was an independent predictor of total, early, and late preeclampsia and its inclusion in combined predictive models significantly improved prediction rates. Reduced placental volume observed at first trimester in women with early and late preeclampsia suggests that these entities are the clinical expression of a similar pathophysiological process.



## Introduction

Preeclampsia is a multisystem complication that can cause considerable maternal and fetal morbidity and mortality. Late preeclampsia (with delivery >34 weeks) is more frequent and less serious than early preeclampsia (with delivery <34 weeks). Poor early placentation has been especially associated with early disease. Early identification of women at risk of preeclampsia is currently a crucial aim of antenatal care since they may benefit from prophylactic treatment and increased surveillance [1].



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There is wide variability in the performance of existing predictive models and markers which include maternal characteristics and biochemical and/or biophysical factors, alone or combined. The best models for risk of early and late preeclampsia built by Crovetto et al. [2] included mean arterial pressure, uterine artery pulsatility index (uterine-a PI), placental growth factor, and soluble Fms-like tyrosine kinase-1 achieving detection rates of 91.2 and 76.4%, respectively. Screening by maternal characteristics, uterine-a PI, mean arterial pressure, serum pregnancy-associated protein-A (PAPP-A) and placental growth factor detected 96% of cases of early preeclampsia and 54% of all cases of preeclampsia at a fixed false-positive rate (FPR) of 10% [3]. Kim et al. [4] have recently demonstrated the potential utility of combined first-trimester cell-free fetal DNA and cell-free total DNA, and PAPP-A for the early prediction of preeclampsia.

The introduction of three-dimensional (3D) ultrasound techniques, with the option of calculating placental volume and measuring vascular volumes, has created an excellent opportunity to study early changes in the uteroplacental circulation space, which includes the maternal spiral arteries and the intervillous space. This technology may allow a more direct evaluation of the abnormal placentation process thought to herald the development of preeclampsia. In agreement with the observations of other authors [4–8], we have shown that women with preeclampsia have significantly lower placental volume and vascularization indices at first trimester [9]. However, the use of 3D ultrasound parameters as risk factors for preeclampsia has been little studied, with discrepancies in the results published to date.

The aim of this study was to assess the usefulness of placental volume and 3D vascular indices as predictors of early and late preeclampsia, alone or combined with other factors.

## Methods

We performed a cohort study with prospective recruitment and follow-up of all consecutive pregnant women with singleton pregnancies routinely screened at our center, which attends a high-risk population of pregnant women. Between May 1, 2011 and March 30, 2014, chromosomal abnormalities were routinely tested by measurement of fetal nuchal translucency (NT) thickness and maternal serum free beta-human chorionic gonadotropin (β-hCG) and PAPP-A at $11^{+0}$ to $13^{+6}$ weeks of pregnancy. All pregnancies were dated by first-trimester ultrasound. Written informed consent was obtained from the women agreeing to participate in the study, which was approved by the Institutional Review Board. This population has been used in a previous study [9].

*Maternal Characteristics*

Maternal characteristics were recorded before ultrasound examination, including age, parity (parous or nulliparous considered as no previous conception or pregnancy progressing beyond 23 weeks), weight, height, body mass index (BMI), smoking status, medical history (including chronic hypertension, and pregestational diabetes mellitus), and obstetric history (including hypertensive pregnancy complications). Obesity was defined as BMI >30 and smoking during pregnancy as >10 cigarettes per day. Preeclampsia and their severity were diagnosed in accordance with the definition of the International Society for the Study of Hypertension in Pregnancy [10].

*Ultrasound Study*

Transabdominal examination was carried out with NT measurement, diagnosis of any major fetal defects, and Doppler measurement of the uterine-a PI, as previously described [11]. When three similar consecutive waveforms were obtained, the PI was measured and the mean PI of the left and right arteries was calculated. The methods for obtaining placental volume and vascularization indices have been previously described [9, 12].

*Outcome Measures*

We compared the group of women who developed early preeclampsia (with delivery <34 weeks) with the group developing late preeclampsia (with delivery >34 weeks) during pregnancy, and each preeclampsia group was compared with the control group (women without hypertensive complications of pregnancy).

Data on pregnancy outcomes were prospectively collected and the following perinatal outcomes were recorded: gestational age (GA) at delivery, mode of delivery, birthweight and birthweight percentile, fetal sex, Apgar test score, and umbilical pH. Small for GA was defined as birth weight less than the 10th percentile for GA using a growth chart developed for the Spanish population [13].

*Statistical Method*

Comparisons

Normal distribution of the data was confirmed using Kolmogorov-Smirnov test (natural log transformed when necessary). Numerical data are shown as mean and standard deviation. Qualitative variables are expressed as frequencies and percentages. Differences between groups for parametric variables were compared using Student *t* test. Comparison between proportions was performed using $\chi^2$ test and Fisher exact test for small samples (expected values <5). After identifying the maternal characteristics that differed between the preeclampsia and control groups, linear regression analysis was used to assess their effect on placental parameters and perinatal outcomes.

Predictive Models

The performance of the models constructed to predict total preeclampsia and early and late preeclampsia was examined by multivariate logistic regression of:

1. Maternal characteristics: age, weight, height, BMI, race, smoking, parity, chronic hypertension, previous gestational hypertension or preeclampsia, pregestational diabetes mellitus, and assisted reproduction techniques.
2. First-trimester screening of aneuploidy (FTSA) parameters (crown-rump length, Δ NT + β-hCG MoM, and PAPP-A MoM).

**Table 1.** Maternal characteristics, first-trimester screening for aneuploidy (FTSA) parameters, first-trimester uterine artery pulsatility index, and perinatal outcomes in women with and without preeclampsia

| | Preeclampsia | | | No preeclampsia ($n$ = 904) | $p$ (1) | $p$ (2) | $p$ (3) |
|---|---|---|---|---|---|---|---|
| | early ($n$ = 12) | late ($n$ = 72) | total ($n$ = 84) | | | | |
| Maternal characteristics | | | | | | | |
| Maternal age, years | 30.03±6.88 | 30.50±5.95 | 30.43±6.05 | 31.03±5.89 | 0.521 | 0.376 | 0.588 |
| Weight, kg | 69.41±10.19 | 75.93±17.58 | 75.00±16.84 | 69.12±14.69 | 0.503 | 0.729 | <0.001 |
| Height, cm | 163.3±9.05 | 163.5±5.98 | 163.5±6.43 | 162.3±6.17 | 0.858 | 0.666 | 0.208 |
| BMI | 26.16±4.50 | 28.39±6.28 | 28.07±6.09 | 26.21±5.28 | 0.611 | 0.748 | 0.001 |
| Obesity (BMI >30) | 2 (16.7) | 25 (34.7) | 27 (32.1) | 195 (21.6) | 0.184 | 0.505 | 0.010 |
| Nulliparity | 7 (58.3) | 53 (73.6) | 60 (71.4) | 522 (57.7) | 0.225 | 0.605 | 0.005 |
| Smoking | 3 (25.0) | 11 (15.3) | 14 (16.7) | 200 (22.1) | 0.318 | 0.518 | 0.181 |
| Pregestational diabetes | 0 (0.0) | 9 (12.5) | 9 (10.7) | 60 (6.6) | 0.231 | 0.441 | 0.060 |
| Chronic hypertension | 2 (16.7) | 9 (12.5) | 11 (13.1) | 20 (2.2) | 0.491 | 0.031 | <0.001 |
| FTSA parameters | | | | | | | |
| Crown-rump length | 62.22±7.26 | 64.54±8.32 | 64.20±8.17 | 63.92±7.78 | 0.314 | 0.426 | 0.561 |
| Nuchal translucency | 1.71±0.42 | 1.69±0.39 | 1.69±0.39 | 1.74±0.43 | 0.826 | 0.684 | 0.285 |
| β-hCG MoM | 1.53±0.91 | 1.07±0.63 | 1.14±0.69 | 1.26±0.91 | 0.048 | 0.351 | 0.187 |
| PAPP-A MoM | 0.85±0.46 | 1.07±0.57 | 1.04±0.56 | 1.20±0.70 | 0.225 | 0.097 | 0.139 |
| Uterine artery pulsatility index | 2.71±0.46 | 2.16±0.75 | 2.24±0.74 | 1.85±0.55 | 0.002 | <0.001 | <0.001 |
| Perinatal outcomes | | | | | | | |
| GA at delivery, weeks | 29.6±3.2 | 37.7±1.9 | 37.4±3.3 | 39.5±1.9 | <0.001 | <0.001 | 0.001 |
| Birth weight, g | 999±412.7 | 2,980±749.2 | 2,697±994.5 | 3,185±570.6 | <0.001 | <0.001 | 0.001 |
| Spanish growth centiles | 3.5±6.8 | 35.7±35.1 | 31.1±34.5 | 41.3±32.6 | 0.005 | <0.001 | 0.066 |
| Small for GA | 9 (75.0) | 27 (37.5) | 36 (42.9) | 213 (23.6) | 0.004 | <0.001 | 0.016 |
| Apgar score at 5 min | 4.2±4.39 | 9.1±1.26 | 8.4±2.64 | 9.2±1.11 | <0.001 | <0.001 | 0.381 |
| Umbilical artery pH | 7.26±0.079 | 7.17±0.095 | 7.18±0.096 | 7.20±0.082 | 0.062 | 0.117 | 0.039 |
| Umbilical vein pH | 7.32±0.040 | 7.27±0.076 | 7.28±0.075 | 7.31±0.079 | 0.289 | 0.702 | 0.005 |

Values are given as mean ± standard deviation or $n$ (%). The $p$ values are obtained on comparing the groups of women with (1) early versus late preeclampsia, (2) early versus no preeclampsia, and (3) late versus no preeclampsia; considering the effect of obesity, nulliparity, chronic hypertension, and maternal weight. BMI, body mass index; PAPP-A, pregnancy-associated plasma protein-A; β-hCG, beta-human chorionic gonadotropin; GA, gestational age.

3. Uterine-a PI.
4. Placental volume.
5. Vascular indices (vascularization index, flow index, and vascularization flow index),
6. Maternal characteristics + FTSA parameters + uterine-a PI.
7. Maternal characteristics + FTSA parameters + uterine-a PI + placental volume, and
8. All factors considered.

The performance of these models was described by the areas under the receiver operating characteristic (AUROC) curve. Detection rates of preeclampsia at a fixed FPR of 10% were calculated. Bonferroni corrections were applied.

SPSS 19.0 (Statistics for Windows, Version 19.0; IBM Corp., Amonk, NY, USA) was used for data analyses and to construct the models. MedCalc 11 [14] was used to compare model prediction rates with a two-by-two approach and homogeneous subset analysis was performed to assess model performance.

Validation of Models

Model validation was performed with Weka 3.6.3 (Waikato Environment for Knowledge Analysis, GNU-GPL) [15] using a 10-fold cross-validation method.

## Results

Initially, 1,004 consecutive pregnant women undergoing first-trimester screening were included in the study and followed during pregnancy and after delivery. Sixteen (1.6%) were excluded due to miscarriage before 24 weeks' gestation (3 cases), interruptions (6 cases: 3 for aneuploidy and 3 for major malformations), and another 7 cases were lost to follow-up. In the remaining 988 pregnancies, 84 (8.5%) developed preeclampsia, 12 (1.21%)

**Table 2.** Three-dimensional (3D) ultrasound placental parameters in women with and without preeclampsia

| | Preeclampsia | | | No preeclampsia ($n$ = 904) | $p$ (1) | $p$ (2) | $p$ (3) |
|---|---|---|---|---|---|---|---|
| | early ($n$ = 12) | late ($n$ = 72) | total ($n$ = 84) | | | | |
| 3D ultrasound parameters | | | | | | | |
| Volume, $cm^3$ | 43.98±20.05 | 51.58±21.50 | 50.49±21.35 | 63.62±20.74 | 0.376 | 0.001 | <0.001 |
| Vascularization index | 8.08±5.49 | 8.35±5.02 | 8.31±5.06 | 9.34±4.58 | 0.733 | 0.295 | 0.135 |
| Flow index | 46.58±2.79 | 45.68±6.34 | 45.81±5.96 | 48.77±4.36 | 0.575 | 0.074 | 0.001 |
| Vascularization flow index | 3.84±2.72 | 3.95±2.63 | 3.93±2.63 | 4.65±2.55 | 0.732 | 0.235 | 0.047 |

Values are given as mean ± standard deviation. The $p$ values are obtained on comparing the groups of women with (1) early versus late preeclampsia, (2) early versus no preeclampsia, and (3) late versus no preeclampsia; considering the effect of obesity, nulliparity, chronic hypertension, and maternal weight.

**Table 3.** Screening for preeclampsia

| Variables included | Early preeclampsia | Late preeclampsia | Total preeclampsia |
|---|---|---|---|
| MC | 0.716 (0.569, 0.862) [38.5%] | 0.694 (0.626, 0.763) [31.7%] | 0.681 (0.616, 0.746) [30.1%] |
| Ut-a PI | 0.884 (0.811, 0.956) [61.5%] | 0.581 (0.499, 0.662) [20.0%] | 0.640 (0.566, 0.714) [28.8%] |
| Placental volume | 0.768 (0.626, 0.910) [38.5%] | 0.707 (0.638, 0.777) [35.0%] | 0.724 (0.661, 0.787) [37.0%] |
| Placental vascular indices | 0.676 (0.528, 0.823) [23.1%] | 0.659 (0.598, 0.720) [18.3%] | 0.670 (0.614, 0.725) [17.8%] |
| MC + FTSA + placental volume | 0.859 (0.772, 1.000) [69.2%] | 0.801 (0.736, 0.871) [51.7%] | 0.803 (0.754, 0.842) [49.3%] |
| MC + FTSA + Ut-a PI | 0.897 (0.791, 1.000) [76.9%] | 0.740 (0.676, 0.804) [35.0%] | 0.745 (0.683, 0.808) [41.1%] |
| MC + FTSA + Ut-a PI + placental volume | 0.904 (0.800, 1.000) [84.6%] | 0.812 (0.756, 0.869) [48.3%] | 0.818 (0.764, 0.872) [49.3%] |
| All variables | 0.907 (0.804, 1.000) [84.6%] | 0.815 (0.759, 0.871) [50.0%] | 0.820 (0.767, 0.874) [49.3%] |

Areas under the receiver operator characteristic curve (95% confidence interval) and sensitivity of the models for a false positive rate of 10% (percentages in brackets). MC, maternal characteristics; FTSA, first-trimester screening for aneuploidy fetal and biochemical parameters; Ut-a PI, uterine artery pulsatility index.

early and 72 (7.28%) late preeclampsia, while 904 (91.5%) pregnancies did not present this complication.

Maternal characteristics, FTSA parameters, uterine-a PI values at first trimester, 3D ultrasound placental parameters, and perinatal outcomes in women with preeclampsia, early and late preeclampsia, and controls, are shown in Table 1 together with the $p$ values obtained in the following comparisons: women with early versus late preeclampsia, early versus late group without preeclampsia, and late versus the group without preeclampsia.

Placental volume was lower, and uterine-a PI higher, in the groups with early and late preeclampsia versus controls. The magnitude of the increase in uterine-a PI was significantly greater in the group with early preeclampsia compared to that with late preeclampsia. The differences were calculated considering the effect of obesity, nulliparity, chronic hypertension, and maternal weight. Table 2 shows the $p$ values obtained in two-by-two comparisons.

Placental volume and vascular indices were independent predictors of preeclampsia and early and late preeclampsia. For a 10% FPR, the detection rate for placental volume for preeclampsia was 37%, 38.5% for early and 35% for late preeclampsia. Sensitivity for all vascular indices together was 23.1, 18.3, and 17.8% for total, early, and late preeclampsia, respectively (Table 3).

The prediction rate of preeclampsia, and of early preeclampsia, for uterine-a PI and placental volume was similar (AUROC curve 0.640 vs. 0.724, and 0.884 vs. 0.768, respectively). Regarding late preeclampsia, the prediction rate of placental volume was higher than that of uterine-a PI (AUROC curve 0.707 vs. 0.581, $p < 0.011$). The inclusion of placental volume increased the AUROC curve value of multifactorial models to predict preeclampsia and late preeclampsia constructed with maternal characteristics, FTSA parameters, and uterine-a PI (AUROC curve 0.745 vs. 0.818, $p < 0.004$, and 0.740 vs. 0.812, $p < 0.012$, respectively), but not that of early preeclampsia (0.897 vs. 0.904).

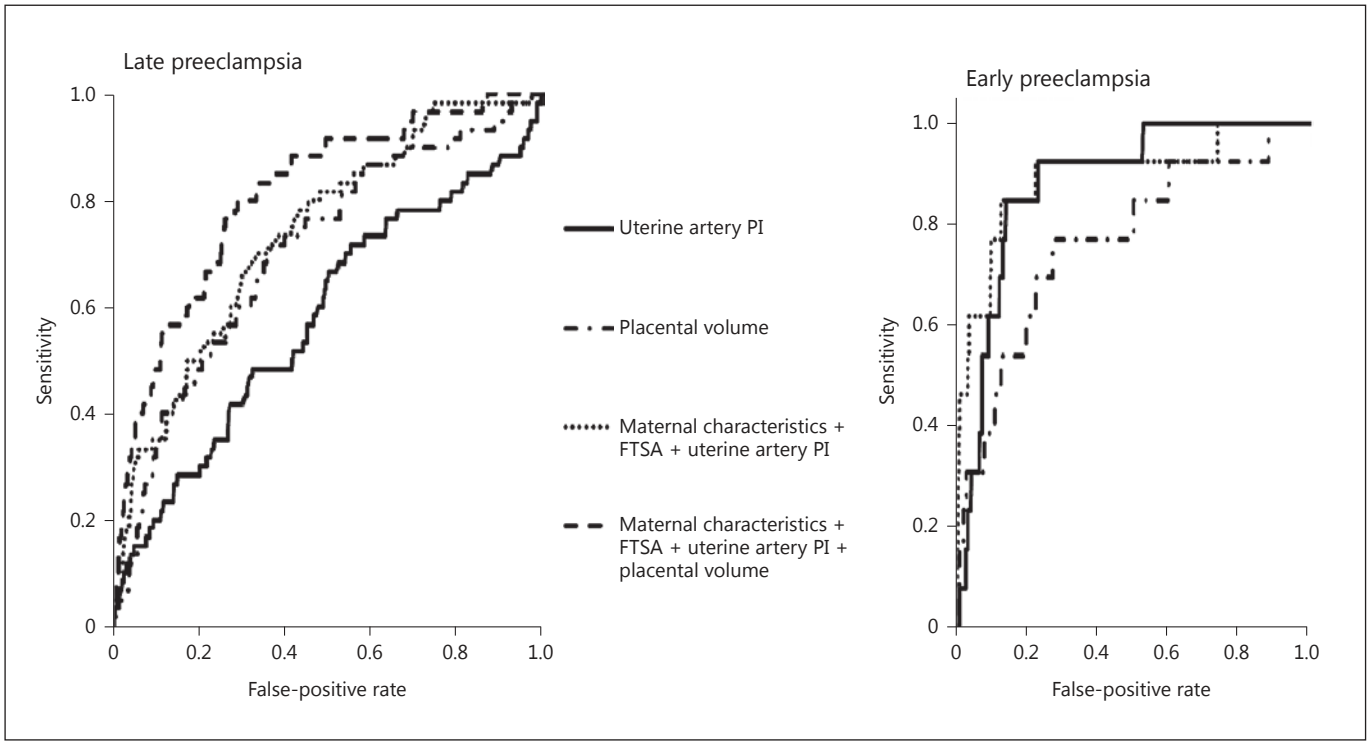


**Fig. 1.** Receiver operator curves for the prediction of late preeclampsia and early preeclampsia on inclusion of the following factors: uterine artery pulsatility index (PI), placental volume, maternal characteristics + first-trimester screening of aneuploidy (FTSA) parameters + uterine artery PI, and maternal characteristics + FTSA parameters + uterine artery PI + placental volume.

The incorporation of vascular indices in these models did not improve their predictive value. AUROC curve values and sensitivities for the factors considered, alone or in multifactorial models, for preeclampsia and early and late preeclampsia are shown in Table 3 and Figure 1. *p* values obtained on two-by-two comparisons are included in Table 4.

The results obtained in the analysis of homogenous subsets indicated that the combined models with greatest prediction rate for preeclampsia and late preeclampsia were those that included maternal characteristics, FTSA parameters, uterine-a PI, and placental volume, with or without vascular indices (AUROC curve value 0.818 and 0.820, and 0.812 and 0.815, respectively), as shown in Table 5.

The predictive value for early preeclampsia of the combined models that included maternal characteristics, FTSA parameters, and uterine-a PI (AUROC curve 0.897) was similar to that of the more complex models constructed with these factors plus placental volume (AUROC curve 0.904) and vascular indices (AUROC curve 0.907), as shown in Table 5.

Table 6 shows the results of the internal validation test for all predictive models of early and late preeclampsia.

## Discussion

The present study showed that placental volume was lower and uterine-a PI higher at the first trimester in pregnancies with early and late preeclampsia. 3D ultrasound and power-Doppler showed altered placentation not only in women with early preeclampsia but also those with late preeclampsia. Plasencia et al. [9] had previously shown that placental volume and vascular indices were lower in pregnancies with preeclampsia, without differentiating between early and late.

These results coincide with those of Eastwood et al. [16], who found mean differences in vascularization indices in preeclampsia and non-preeclampsia. On the other hand, Arakaki et al. [17] observed high uterine-a PI and low placental volume more often in cases of early pre-

**Table 4.** *p* values obtained on two-by-two comparison of areas under the receiver operator characteristic curves of the different models constructed to predict early and late preeclampsia

| Variables included in the models | Ut-a PI | Placental volume | Vascular index | MC + FTSA + placental volume | MC + FTSA + Ut-a PI | MC + FTS + Ut-a PI + placental volume | MC + FTSA + Ut-a PI + vascular index + placental volume |
|---|---|---|---|---|---|---|---|
| *Early preeclampsia* | | | | | | | |
| MC | 0.018 | 0.679 | 0.685 | 0.104 | 0.007 | 0.016 | 0.013 |
| Ut-a PI | | 0.168 | 0.028 | 0.673 | 0.600 | 0.566 | 0.509 |
| Placental volume | | | 0.355 | 0.130 | 0.152 | 0.066 | 0.062 |
| Vascular index | | | | 0.045 | 0.025 | 0.016 | 0.014 |
| MC + FTSA + placental volume | | | | | 0.464 | 0.142 | 0.133 |
| MC + FTSA + Ut-a PI | | | | | | 0.754 | 0.654 |
| MC + FTSA + Ut-a PI + placental volume | | | | | | | 0.266 |
| *Late preeclampsia* | | | | | | | |
| MC | 0.050 | 0.798 | 0.437 | 0.001 | 0.134 | <0.001 | <0.001 |
| Ut-a PI | | 0.011 | 0.082 | <0.001 | 0.001 | <0.001 | <0.001 |
| Placental volume | | | 0.282 | 0.002 | 0.530 | <0.001 | <0.001 |
| Vascular index | | | | 0.008 | 0.041 | <0.001 | <0.001 |
| MC + FTSA + placental volume | | | | | 0.077 | 0.257 | 0.205 |
| MC + FTSA + Ut-a PI | | | | | | 0.012 | 0.009 |
| MC + FTSA + Ut-a PI + placental volume | | | | | | | 0.423 |
| *Total preeclampsia* | | | | | | | |
| MC | 0.439 | 0.365 | 0.794 | <0.001 | 0.046 | <0.001 | <0.001 |
| Ut-a PI | | 0.064 | 0.471 | <0.001 | 0.001 | <0.001 | <0.001 |
| Placental volume | | | 0.174 | 0.002 | 0.639 | <0.001 | <0.001 |
| Vascular index | | | | <0.001 | 0.041 | <0.001 | <0.001 |
| MC + FTSA + placental volume | | | | | 0.087 | 0.250 | 0.199 |
| MC + FTSA + Ut-a PI | | | | | | 0.004 | 0.002 |
| MC + FTSA + Ut-a PI + placental volume | | | | | | | 0.356 |

MC, maternal characteristics; FTSA, first-trimester screening for aneuploidy fetal and biochemical parameters; Ut-a PI, uterine artery pulsatility index.

**Table 5.** Results obtained in the analysis of homogenous subsets

| Variables included in the models | Homogeneous subsets (α = 0.10) | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | early preeclampsia | | | | late preeclampsia | | | | total preeclampsia | | |
| | 1 | 2 | 3 | 4 | 1 | 2 | 3 | 4 | 1 | 2 | 3 |
| Ut-a PI | | | 0.884 | 0.884 | 0.581 | | | | 0.640 | | |
| Vascular indices | 0.676 | | | | | 0.659 | | | 0.670 | | |
| MC | 0.716 | 0.716 | | | | 0.694 | 0.694 | | 0.681 | 0.681 | |
| MC + FTSA | 0.780 | 0.780 | | | | 0.713 | 0.713 | | 0.696 | 0.696 | |
| Placental volume | 0.768 | 0.768 | 0.768 | | | 0.707 | 0.707 | | 0.724 | 0.724 | |
| MC + FTSA + Ut-a PI | | | 0.897 | 0.897 | | | 0.740 | | | 0.745 | |
| MC + FTSA + Ut-a PI + placental volume | | | | 0.904 | | | | 0.812 | | | 0.818 |
| MC + FTSA + Ut-a PI + vascular index + placental volume | | | | 0.907 | | | | 0.815 | | | 0.820 |

From left to right and in ascending order, each column shows the areas under the receiver operator characteristic curve obtained in the predictive models for preeclampsia. MC, maternal characteristics; FTSA, first-trimester screening for aneuploidy parameters; Ut-a PI, uterine artery pulsatility index.

**Table 6.** Validation of models for the prediction of early and late preeclampsia

| Variables included in the models | Training set | | | | 10-fold cross validation | | | |
|---|---|---|---|---|---|---|---|---|
| | AUROC | TP rate | F-measure | κ | AUROC | TP rate | F-measure | κ |
| *Early preeclampsia* | | | | | | | | |
| Ut-a PI | 0.884 | 0 | 0 | 0 | 0.875 | 0 | 0 | 0 |
| Vascular index | 0.675 | 0 | 0 | 0 | 0.633 | 0 | 0 | 0 |
| MC | 0.716 | 0 | 0 | 0 | 0.479 | 0 | 0 | 0 |
| MC + FTSA | 0.780 | 0 | 0 | 0 | 0.591 | 0 | 0 | 0 |
| Placental volume | 0.768 | 0 | 0 | 0 | 0.748 | 0 | 0 | 0 |
| MC + FTSA + Ut-a PI | 0.897 | 0.154 | 0.267 | 0.2641 | 0.812 | 0.077 | 0.133 | 0.1303 |
| MC + FTSA + Ut-a PI + placental volume | 0.904 | 0.231 | 0.375 | 0.3719 | 0.819 | 0.154 | 0.235 | 0.2305 |
| MC + FTSA + Ut-a PI + vascular index + placental volume | 0.907 | 0.231 | 0.375 | 0.3719 | 0.777 | 0.077 | 0.125 | 0.1207 |
| *Late preeclampsia* | | | | | | | | |
| Ut-a PI | 0.581 | 0 | 0 | 0 | 0.574 | 0 | 0 | 0 |
| Vascular indices | 0.659 | 0.014 | 0.028 | 0.0258 | 0.643 | 0.014 | 0.028 | 0.0258 |
| MC | 0.694 | 0.028 | 0.054 | 0.0485 | 0.612 | 0.028 | 0.051 | 0.0366 |
| MC + FTSA | 0.713 | 0.042 | 0.079 | 0.1258 | 0.603 | 0.028 | 0.051 | 0.0389 |
| Placental volume | 0.707 | 0 | 0 | 0 | 0.706 | 0 | 0 | 0 |
| MC + FTSA + Ut-a PI | 0.74 | 0.042 | 0.078 | 0.0675 | 0.641 | 0.042 | 0.074 | 0.0573 |
| MC + FTSA + Ut-a PI + placental volume | 0.812 | 0.056 | 0.100 | 0.0852 | 0.732 | 0.056 | 0.096 | 0.0772 |
| MC + FTSA + Ut-a PI + placental volume + vascular indices | 0.815 | 0.070 | 0.125 | 0.1106 | 0.727 | 0.070 | 0.116 | 0.0935 |

MC, maternal characteristics; FTSA, first-trimester screening for aneuploidy parameters; Ut-a PI, uterine artery pulsatility index; AUROC, area under the receiver operator characteristic curve; TP, true positive.

eclampsia compared with unaffected pregnancies. However, they did not find these differences, or worse perinatal outcomes, in cases of late preeclampsia.

Preeclampsia may have different etiologies and various authors have postulated that early and late preeclampsia may result from distinct entities. Uterine artery Doppler data, different maternal risk factor profiles, fetal outcomes, biochemical markers, heritability, and clinical features between early-onset and late-onset preeclampsia had suggested that early preeclampsia may be strongly associated with defective invasion of the spiral arteries, in contrast to the findings in late preeclampsia, which may be a consequence of placental deterioration at term [11, 17–19]. Our study findings do not support this rigid separation; on the contrary, they lend support to the alternative working hypothesis that preeclampsia is a spectrum disorder whose severity is reflected in GA at the time of delivery [20, 21].

*Early Preeclampsia*

Placental volume was an independent risk factor for early preeclampsia. This coincides with the findings of Rizzo et al. [5], who also indicated that the combined use of placental volume and uterine-a PI yielded better predictive value than their isolated use. However, the inclusion of placental volume in our predictive model including maternal characteristics, FTSA parameters, and uterine-a PI did not substantially improve the performance of the model (AUROC curve 0.904 vs. 0.897). Arakaki et al. [17] constructed a screening model of early preeclampsia with only placental volume and uterine-a PI as risk factors, which showed a sensitivity of 67% for a 5% FPR. Incorporating maternal characteristics and FTSA parameters to the model, as they suggested, allowed us to achieve a sensitivity of 84.6% for a FPR of 10% and 77% for a FPR of 5%.

*Late Preeclampsia*

Placental volume showed a significantly greater effect on prediction rate than uterine-a PI as independent risk factors in predictive models of late preeclampsia. The inclusion of placental volume significantly improved the prediction rate of the model which included maternal characteristics, FTSA parameters, and uterine-a PI. The

further addition of vascular indices did not improve the performance of this model. Dar et al. [6] suggested that measurement of vascularization index, flow index, and vascularization flow index in early pregnancy may provide an effective first-trimester screening method for preeclampsia, but their series was small. Odibo et al. [7] and Odeh et al. [8] indicated that placental volume vascular indices as independent risk factors for preeclampsia had limited value, but no distinction was made between early and late preeclampsia.

The main limitations of this study are small size of the early preeclampsia group and high preeclampsia rate. So, although internal validation of the built-in models has been performed, their effectiveness should be tested in the general obstetric population.

The main contribution of the present study is that placental alterations at first trimester were demonstrated, by 3D ultrasound and power-Doppler, in women with both early and late preeclampsia. Our findings lend support to the hypothesis that the two entities share common physiopathological mechanisms from the first trimester of pregnancy. We found that the inclusion of placental volume in combined predictive models of late preeclampsia significantly improved their performance, but better models are required to correctly identify women who will truly develop preeclampsia.

## Disclosure Statement

There is no conflict of interest.

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