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Placental volume at 11 to 14 gestational weeks in pregnancies complicated with fetal growth restriction and preeclampsia

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Abstract

Objective: The study aims to evaluate the predictive value of first trimester placental volume in pregnancies destined to develop fetal growth restriction (FGR) and preeclampsia (PE).

Methods: Prospective observational study including placentas from 34 FGR, 12 PE, 15 GH (gestational hypertension) pregnancies, and 265 controls. Placental volume (PV) was obtained using VOCAL technique, and a *z* score was calculated (*z*-PV). The association of PV with other first trimester variables and maternal characteristics was assessed with Spearman's correlation.

Results: PV increased exponentially with crown-rump length (CRL) and was unrelated to maternal factors (weight, age, parity, and smoking status) as well as first trimester uterine artery Doppler, free β-hCG, nuchal translucency, or fetal heart rate. However, PV was positively associated with maternal height, CRL, PAPP-A, and birth weight. *z*-PV was a strong predictor for FGR with abnormal fetal Dopplers (AUC = 0.9472, $P < 0.001$). *z*-PV provided moderate prediction of FGR with normal fetal Dopplers (AUC = 0.8396, $P < 0.001$), PE (AUC = 0.8312, $P < 0.001$), and GH (AUC = 0.7640, $P < 0.001$). The addition of maternal weight, PAPP-A, β-hCG, and uterine artery Doppler improved our models.

Conclusion: At 11 to 14 weeks, PV is an independent predictor of pregnancy complications related to placental insufficiency, and the predictive ability is greater for FGR pregnancies with abnormal fetal Dopplers.

1 | INTRODUCTION

First trimester assessment at 11 to 14 weeks, which is often done for dating purposes or in the context of aneuploidy screening, can allow early identification of pregnancies at high risk for a wide variety of complications related to placental insufficiency, and thus implementation of preventative therapies.[1] First trimester predictive modes based on biochemical and biophysical markers of placentation combined with maternal factors and data from previous obstetric history can effectively identify pregnancies at risk to develop fetal growth restriction (FGR) and preeclampsia (PE).[2] The introduction of three-dimensional (3D) ultrasound has made possible the measurement of the placental volume (PV) at 11 to 14 weeks.[3]

Previous studies have examined the association of first trimester PV with placental-related pregnancy complications and have presented rather conflicting results.[4-11] Plasencia et al[5] found that PV is smaller in FGR pregnancies even after adjustment for maternal weight and fetal crown-rump length (CRL). In line with these results, two other studies confirmed an association between PV measurement at 11 to 14 gestational weeks and birth weight (BW).[6,7] However, other research groups have found that PV was not significantly different in FGR pregnancies compared with the control group.[8,9] In addition, the same inconsistency exists among few studies that have described how first trimester PV is altered in pregnancies that subsequently developed PE.[10,11]

The aim of the present study was to investigate the hypothesis that first trimester PV can be a predictive marker for pregnancy

complications related to placental dysfunction such as FGR and PE. In addition, we examined the possible associations between PV and first trimester biophysical parameters, biochemical indices and demographic characteristics.

What's already known about this topic?

- First trimester predictive algorithms have been developed to identify women at high risk to develop later complications related to placental insufficiency.
- Studies that examined the predictive value of first trimester placental volume in pregnancies with preeclampsia and fetal growth restriction have reached conflicting results.

What does this study add?

- Placental volume at 11 to 14 weeks' gestation is an independent predictor of pregnancy complications such as fetal growth restriction, preeclampsia, and gestational hypertension.
- The predictive ability of placental volume is greater for the subgroup of pregnancies with fetal growth restriction and abnormal fetal Doppler findings, which are known to be associated with a higher incidence of adverse outcome

2 | METHODS

This was a prospective observational case-control study derived from a cohort registry. The study included singleton, viable pregnancies with CRL between 44 and 84 mm presenting for routine first trimester screening for chromosomal abnormalities by fetal nuchal translucency thickness (NT) and maternal biochemical measurements, namely, free beta human chorionic gonadotrophin (β-hCG) and pregnancy associated plasma protein-A (PAPP-A). All ultrasound examinations were performed by Fetal Medicine Foundation (FMF) certified sonographers.

Maternal demographic characteristics (weight, height, parity, and smoking status), method of conception (spontaneous or assisted conception, including ovulation induction and in vitro fertilization), and ultrasound parameters (CRL and NT) were recorded in an electronic database (Astraia software; Astraia GmbH, Munich, Germany). Gestational age (GA) in days was defined by the last menstrual period. In women, unsure of their dates and in cases where the difference between the menstrual dates and the CRL-derived dates was 7 days or more, the GA was corrected by CRL. Parity was defined as one or more previous deliveries at or beyond 24 weeks. All cases had a third trimester growth scan with Doppler studies. Cases with chronic hypertension and superimposed PE were excluded. Other criteria of exclusion from our cohort were miscarriage, termination of pregnancy, and stillbirth. For each case about four controls assessed the same week were chosen.

The blood samples for PAPP-A and β-hCG were analyzed by Kryptor (Kryptor system, Brahms, Berlin, Germany). The values were converted to multiples of the median (MoM) according to the FMF formulas (www.fetalmedicine.com). The present study is part of I.P.'s PhD thesis, which has been approved by the Hospital's ethics committee (protocol number: 8/20-7-11). The study was conducted in the period January 2011 to June 2014.

2.1 | Three-dimensional (3D) ultrasound placental volumetry

PV measurements were performed off-line in electronically stored images by virtual organ computer-aided analysis (VOCAL) software. A 3D volume of the placental plate was acquired by transabdominal sonography (RAB 4-8L probe, Medison XQ, Korea) and stored electronically. The sweep angle was 85°, and the probe was perpendicular to the placental plate. With this sweep angle, we obtained a sequence of 12 sections of the placenta, each after a 15° rotation from the previous one. The contour of the placenta was drawn manually in each one of the different planes trying to exclude the uterine wall. Then, PV was automatically calculated using the VOCAL program. Finally, a 3D reconstruction of the placenta along with the PV measurement was displayed. Placental datasets with adequate quality, where PV calculation was possible, were defined as the ones in which the placental contour could be clearly visualized in all rotational planes. Every measurement was done off-line after the scan by the same operator (I.P.). The off-line calculation of PV in stored images was done in the same day of the examination in most cases or in the following day by an operator who was blinded to maternal characteristics or biochemical/screening results. The data regarding PV measurement were prospectively collected, and the pregnancy outcome was not known at the time of the collection.

2.2 | Uterine artery pulsatility index measurement

After completion of the transabdominal scan, women were asked to empty their bladder and were placed in the lithotomy position.[12] The transvaginal probe was inserted in the vagina and placed in the anterior fornix, and the internal and external cervical osses were identified. The probe was then moved laterally, and the uterine artery was identified using color Doppler as an alliasing vessel running along the side of the cervix at the level of the internal os. Pulsed wave Doppler was used to obtain clear, consistent, similar flow velocity waveforms. The uterine artery pulsatility index (Ut-PI) was measured bilaterally, and the mean Ut-PI was calculated.

2.3 | Outcome measures and definitions

Fetuses with estimated fetal weight (EFW) below 10th centile for gestation, with or without fetal Doppler abnormalities were classified as FGR. We applied reference ranges derived from the Greek population.[13] Fetal Doppler abnormalities were defined as increased umbilical artery pulsatility index (>95th centile) and/or low

cerebroplacental ratio (umbilical artery pulsatility index/middle cerebral artery pulsatility index less than fifth centile).

The definitions of PE and gestational hypertension (GH) used were those of the International Society for the Study of Hypertension in Pregnancy,[14] according to which in GH the systolic blood pressure should be 140 mmHg or more and the diastolic blood pressure of 90 mmHg or more on at least two occasions 4 hours apart developing after 20 weeks of gestation in previously normotensive women in the absence of significant proteinuria, whereas PE was diagnosed in the presence of GH with proteinuria of 300 mg or more in 24 hours or two readings of at least ++ on dipstick analysis of midstream or catheter urine specimens if no 24-hour collection was available.

The control group included normotensive women that fulfilled the abovementioned criteria with a normal third trimester ultrasound scan and fetuses with appropriate weight at delivery.

2.4 | Statistical analysis

Exploratory data analysis was carried out for all the examined variables. Shapiro-Wilk test was used to assess the distribution of the continuous parameters. PV, Mean Ut-PI, MoM-PAPP-A, and MoM-β-hCG were $\log_{10}$ transformed to approximate Gaussian distributions.

To establish reference ranges for PV, the following steps were taken:

1. We computed the predicted PV values ($PV_{Predicted}$) by applying the anti-$\log_{10}$ function to the predicted values derived from the regression of $\log_{10}$ PV against CRL.
2. We calculated the standardized absolute residuals (SAR_S) by the equation

$$SAR_S = 1.25 \mid PV_{Observed} - PV_{Predicted} \mid$$

where $PV_{Observed}$ was the measured placenta volume.

3. We regressed the SAR_S against the CRL to calculate the CRL specific SD of PV (SD_{PV})

Finally, we computed *z* scores for PV (*z*-PV) by the equation

$$z - PV = (PV_{Observed} - PV_{Predicted})/SD_{PV}$$

Residual statistics were used out to identify outliers that have significant impact on our regression modeling. We used previous published formulas to calculate delta values for NT (d-NT), CRL (d-CRL), and fetal heart rate (d-FHR).[15,16] Delta values were computed by subtracting the expected value from the observed. Similarly, we used our previously published ranges for Ut-PI and BW to compute *z*-mean Ut-PI and *z*-BW.[15,17,18] Spearman's correlation coefficient and regression analysis were used to investigate the association between PV and first trimester ultrasound parameters, biochemical indices, and demographic characteristics.

We used a frequentist approach where multiple logistic regression analysis with backward elimination was carried out to construct prediction models. Intermediate models were compared with Akaike information criterion and information criterion. Logit models were assessed by receiver operating characteristic curve (ROC) analysis.

3 | RESULTS

The cohort from which the study group for the case-control study was derived, included 3358 singleton low risk pregnancies with known outcomes. The rates of GH, PE, and FGR were 3.8%, 2.01%, and 9.6%, respectively. The study group for the case-control study included 326 pregnancies; 34 fetuses were growth restricted (EFW below 10th centile for gestation), nine of them with fetal Doppler abnormalities (as defined in the Section 2). Our study population also included 15 women with GH and 12 with PE (five cases also had FGR, two of which also with fetal Doppler abnormalities). The control group consisted of 265 women with no pregnancy complications. The demographic characteristics and the distributions of the examined parameters of the study's subgroups are presented in Table 1.

3.1 | Reference ranges for PV and Ut-PI

PV (in mm^3) exponentially increased with increasing CRL:

$$\log_{10}PV = 1.009112 + 0.0094097^{*}CRL$$
$$R^2 = 0.1559,\ p < 0.001$$

The PV exerted significant heteroschedasticity and the SD_{PV} significantly increased with CRL. The SD_{PV} was given by the equation:

$$SD_{PV} = -17.23787 + 0.5636015^{*}\ CRL$$

The reference ranges for PV were constructed and used to calculate *z*-PV.

3.2 | Association of PV with first trimester parameters

Spearman's correlation coefficient analysis revealed that *z*-PV was not related to maternal weight, age, parity, smoking status, mode of conception, d-NT, $\log_{10}$ MoM β-hCG, *z*-mean Ut-PI, and d-FHR. *z*-PV was positively associated with maternal height, d-CRL, $\log_{10}$ MoM PAPP-A (Figure 1), and *z*-BW (Figure 1). Details of the correlation analysis are presented in Table 2.

3.3 | Prediction of FGR

z-PV was lower in the FGR group compared with the normal control group ($P < 0.001$; Table 1). *z*-PV was a significant predictor of FGR (OR = 0.2757869, R^2 = 0.2187, AUC = 0.8396, $P < 0.001$). We assessed maternal-pregnancy characteristics and first trimester biophysical and biochemical parameters as predictors of FGR in a multiple logistic regression model. *z*-PV (OR = 0.2924952), maternal weight (OR = 0.9674059), and *z*-mean Ut-PI (OR = 1.785765) were the

TABLE 1 Distributions of first trimester variables and maternal-pregnancy characteristics for the study's groups, namely, PE, FGR, FGR-AD, GH, and control[a]

Variable	FGR (N = 34)	FGR-AD (N = 9)	GH (N = 15)	PE (N = 12)	Control (N = 265)
Maternal weight, kg	65 (14.2)	65.3 (19.5)	78.8 (13.3)	79.9 (12.2)	68.5 (13.6)
Maternal height, cm	162.8 (6.2)	163.8 (2.3)	163.4 (7.5)	164 (6.4)	164.3 (5.9)
Parity (nulliparous %)	65%	77%	66%	66%	65%
Maternal age, y	30.4 (4.2)	29.7 (5.5)	31.6 (5.7)	31.9 (3.7)	31 (4.2)
Smoking status (smokers %)	30%	33.3%	20%	7.6%	11.4%
Conception (assisted reproduction %)	5.8%	0%	13.3	8.3%	1.9%
Gestational age at delivery, wk	36.8 (3.5)	36.9 (1.8)	36.3 (3.8)	34.9 (4.5)	38.8 (1.6)
d-CRL	−2.1 (5)	−5.6 (4.5)	−2.4 (5.2)	1.3 (4.9)	0.3 (4.9)
d-NT	0 (0.3)	0 (0.20)	0 (0.2)	0 (0.1)	0 (0.3)
d-FHR	−0.6 (9)	−3 (10)	−1.3 (8.8)	3.4 (7.9)	0.5 (5.8)
$\log_{10}$ MoM PAPP-A	−0 (0.2)	−0.1 (0.3)	−0.1 (0.3)	0 (0.1)	0 (0.2)
$\log_{10}$ MoM β-hCG	0 (0.2)	0 (0.2)	−0.1 (0.2)	0 (0.2)	0 (0.2)
z-BW	−2.1 (0.5)	−2.2 (0.8)	−1 (1.3)	−0.64 (1.5)	0.3 (1)
z-mean Ut-PI	1 (1.3)	1.3 (1.7)	0.69 (0.9)	1 (1.4)	0.19 (1)
z-PV	−0.7 (0.7)	−1.2 (0.3)	−0.4 (0.9)	−0.5 (0.6)	0.7 (1.1)

Abbreviations: BW, birth weight; CRL, crown-rump length; FGR, fetal growth restriction; FHR, fetal heart rate; GH, gestational hypertension; MoM, multiples of the median; NT, nuchal translucency thickness; PAPP-A, pregnancy associated plasma protein-A; PE, preeclampsia; PV, placental volume; Ut-PI, uterine artery pulsatility index; β-hCG, beta human chorionic gonadotrophin.

[a]Data are presented as mean (standard deviation) for continuous variables and percentage (%) for binary variables.

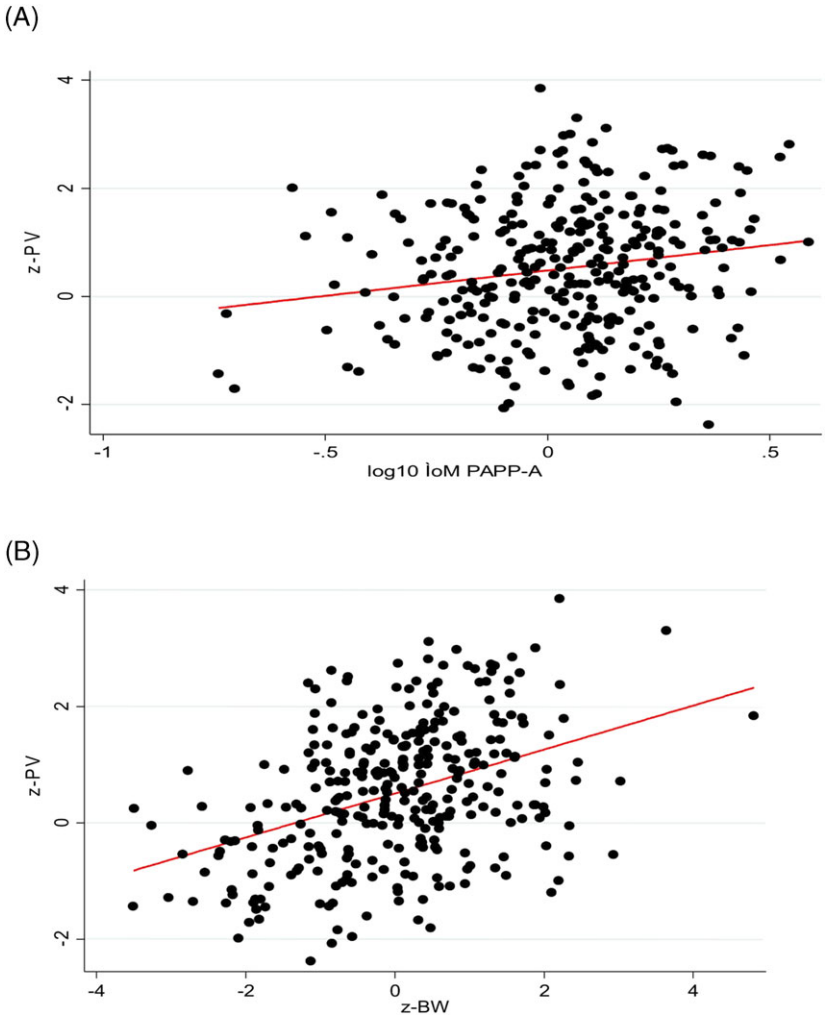

FIGURE 1 Association between placental volume (*z*-PV), log10 MoM PAPP-A (A) and birth weight (*z*-BW) (B). The regression line is superimposed [Colour figure can be viewed at wileyonlinelibrary.com]

TABLE 2 Correlation between *z* scores for placenta volume (*z*-PV) first trimester variables and maternal-pregnancy characteristics

z-PV		
Variable	**Correlation Coefficient**	***P* Value**
Maternal weight	0.105	0.1665
Maternal height	0.123	0.02
Parity (parous)	0.009	0.877
Maternal age	−0.089	0.111
Smoking status (smokers)	−0.040	0.476
Conception (assisted reproduction)	−0.020	0.654
Gestational age at delivery, wk	0.1604	0.004
d-CRL	0.158	0.005
d-NT	0.061	0.275
d-FHR	−0.044	0.441
$\log_{10}$ MoM PAPP-A	0.162	0.004
$\log_{10}$ MoM β-hCG	0.003	0.958
z-BW	0.376	<0.001
z-mean Ut-PI	0.035	0.539

Abbreviations: BW, birth weight; CRL, crown-rump length; FHR, fetal heart rate; MoM, multiples of the median; NT, nuchal translucency thickness; PAPP-A, pregnancy associated plasma protein-A; PV, placental volume; Ut-PI, uterine artery pulsatility index; β-hCG, beta human chorionic gonadotrophin.

significant predictors in the final model (AUC = 0.8766, R^2 = 0.2694, P < 0.001). The combined model was marginally better compared with the *z*-PV alone model (Figure 2; Table 3).

3.4 | Prediction of FGR with abnormal Doppler studies

z-PV was lower in the group of FGR with abnormal fetal Dopplers compared with the control group (P < 0.001; Table 1). *z*-PV was a strong predictor of FGR with abnormal Doppler (OR = 0.0950245, R^2 = 0.3681, AUC = 0.9472, P < 0.001). Multiple logistic regression showed that *z*-PV (OR = 0.0792666), *z*-mean Ut-PI (OR = 2.808554), and $\log_{10}$ MoM β-hCG (OR = 97.85784) were significant predictors in the final highly predictive model (AUC = 0.9738, R^2 = 0.4976, P < 0.001). The combined model was marginally better compared with the *z*-PV alone model (Figure 2; Table 3).

3.5 | Prediction of PE

z-PV was lower in the PE group compared with the control group (P < 0.001; Table 1). *z*-PV was predictive of PE (OR = 0.3276286, R^2 = 0.1443, AUC = 0.8312, P < 0.001). Multiple logistic regression revealed that *z*-PV (OR = 0.25), maternal weight (OR = 1.06), and *z*-mean Ut-PI (OR = 1.87) were significant predictors of PE (AUC = 0.9194, R^2 = 0.3216, P < 0.001). The combined model was better compared with *z*-PV alone (Figure 2; Table 3).

3.6 | Prediction of GH

z-PV was lower in the GH group compared with the control group (P < 0.001; Table 1). *z*-PV was predictive of GH (OR = 0.4038118, R^2 = 0.1118, AUC = 0.7640, P < 0.001). Multiple logistic regression

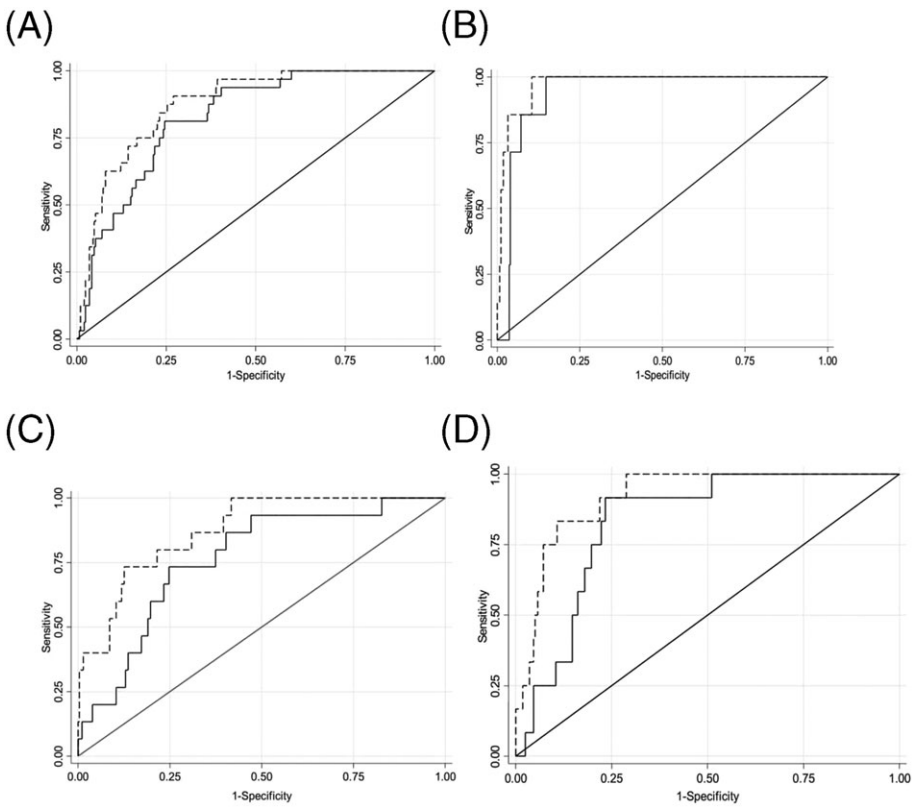

FIGURE 2 ROC curves for the various prediction models. (A) Fetal growth restriction (FGR), (B) FGR with abnormal Doppler, (C) gestational hypertension (GH), and (D) preeclampsia (PE). The solid line is the *z*-PV alo
ne whereas the dashed line is the combined model in all graphs. PV, placental volume

TABLE 3 Detection rates of FGR, FGR-abnormal Doppler, GH, PE, and preterm birth before 34 and 37 weeks due to placental-related disorders at different FPR[a]

Prediction Models	Detection Rate % 3% FPR	5% FPR	10% FPR	AUC
FGR				
z-PV	17.14	40.0	45.7	0.8396
z-PV, maternal weight, *z*-mean Ut-PI	21.8	43.7	62.5	0.8766
FGR-abnormal Doppler				
z-PV	11.0	77.8	88.8	0.9472
z-PV, *z*-mean Ut-PI, $\log_{10}$ MoM β-hCG	71.4	85.7	86.0	0.9738
GH				
z-PV	13.0	20.0	20.0	0.7640
z-PV, maternal weight, $\log_{10}$ MoM PAPP-A, $\log_{10}$ MoM β-hCG	33.0	40.0	53.0	0.8743
PE				
z-PV	8.3	16.6	25.0	0.8312
z-PV, maternal weight, *z*-mean Ut-PI	25.0	33.3	75.0	0.9194
Preterm birth before 37 weeks due to FGR or GH or PE				
z-PV	12.5	29.2	41.6	0.8329
z-PV, parity, *z*-mean Ut-PI	38.1	42.8	61.9	0.8782
Preterm birth before 34 weeks due to FGR or GH or PE				
z-PV	27.2	36.3	45.5	0.8341
z-PV, *z*-mean Ut-PI	60.0	70.0	80.0	0.9134

Abbreviations: FGR, fetal growth restriction; FPR, false positive rates; GH, gestational hypertension; MoM, multiples of the median; PAPP-A, pregnancy associated plasma protein-A; PE, preeclampsia; PV, placental volume; Ut-PI, uterine artery pulsatility index; β-hCG, beta human chorionic gonadotrophin.

[a]Comparison of screening performance by *z*-PV alone and combinations of maternal-pregnancy characteristics, biophysical, and biochemical indices. The AUCs for the different models are also presented.

demonstrated that *z*-PV (OR = 0.38), maternal weight (OR = 1.05), $\log_{10}$ MoM PAPP-A (OR = 0.04), and $\log_{10}$ MoM β-hCG (OR = 0.06) were significant predictors of GH (AUC = 0.8743, R^2 = 0.2883, $P < 0.001$), and their combination significantly improved the model compared with *z*-PV alone (Figure 2; Table 3).

3.7 | Prediction of preterm birth in pregnancies with placenta-related complications

GA at delivery (GAD) was proportional to PV in the whole study group (Table 2). We grouped the cases of PE, GH, FGR, and FGR with abnormal fetal Dopplers into a single group, and we categorized them into term delivery (after 37 weeks) and preterm delivery before 37 (PR37) and 34 weeks (PR34). *z*-PV was a strong predictor for both PR37 (OR = 0.2961188, R^2 = 0.1902, AUC = 0.8329, $P < 0.001$), and PR34 (OR = 0.2860767, R^2 = 0.1741, AUC = 0.8341, $P < 0.001$). For the PR37, the combination of *z*-PV (OR = 0.3206672), nulliparity (OR = 7.320416), and *z*-mean Ut-PI (OR = 2.104458) improved the prediction (AUC = 0.8782, R^2 = 0.2781, $P < 0.001$). Similarly, for the PR34 group, *z*-PV (OR = 0.2866452) combined with *z*-mean Ut-PI (OR = 2.948456) optimized the prediction model (AUC = 0.9134, R^2 = 0.3792, $P < 0.001$). Table 3 reports the detection rates for the preterm birth in cases with the examined pregnancy complications.

4 | DISCUSSION

The present study examined the possible predictive value of first trimester PV measurement in pregnancies destined to develop pregnancy complications related to placental insufficiency. PV has a linear positive association with BW centiles expressed in *z* scores and $\log_{10}$ MoM PAPP-A (Figure 1). These findings are in line with a previous report by Plasencia et al and imply a direct association between PV, placental biochemical profile as expressed by maternal serum levels of PAPP-A and fetal growth.[5] PAPP-A is a placental-derived hormone with a pivotal role in fetal and placental development and function.[19] Apart from PAPP-A levels, *z*-PV was related to maternal height and d-CRL, but not to other parameters among the set of first trimester indices or maternal-pregnancy characteristics included in our analysis. This observation facilitates the use of *z*-PV as first trimester predictive marker.

There is robust evidence that first trimester uterine artery Doppler reflects uteroplacental perfusion and has a value in the prediction of pregnancy complications related to abnormal placentation such as FGR and hypertensive disorders in pregnancy that develop in second and third trimester of pregnancy.[20] In our study, Ut-PI was not related with first trimester PV. Similarly, Yigiter et al[21] reported a univariate weak association between Ut-PI and placenta volume, which was not evident in the multiple regression model. It is interesting that a previous study from our research group showed that also first trimester fetal volume is unrelated to placenta invasion as reflected in uterine arteries blood flow.[17] However, uterine artery Doppler remains an independent predictor of PE and FGR.

Three-dimensional evaluation of placental growth in the first trimester has received little attention, and published data on the correlation of PV with clinical outcomes are scarce. According to our results, PV was significantly lower in all groups with placenta-related disorders compared with the control group. These findings are in agreement with most published studies that also supported that PV is smaller at 11 to 14 weeks in pregnancies that develop PE, FGR, and GH at later stages.[5-7,10,11,22] In line with our results, a previous study also showed that first trimester PV tends to be smaller in pregnancies that subsequently developed early-onset but not late-onset GH compared with uncomplicated pregnancies.[23] This is an important observation as it is known that the early-onset PE is mostly related to placental dysfunction and poorer outcome. Authors also stated that the PV measurement is highly reproducible.[23]

Moreover, we investigated the hypothesis that PV could be a predictive marker for the group of pregnancy complications included in our study. Most of the relevant published studies examined if first trimester PV can predict the delivery of a growth-restricted fetus. Hafner et al[6] examined a total of 2489 singleton pregnancies at 11 to 13 weeks and reported a detection rate of 27% for FGR at a 10% false positive rate when first trimester PV was used as an isolated marker. Plasencia et al[5] combined the PV measurement with maternal factors and improved slightly the detection rate for FGR to 30% at a similar false positive rate. Interestingly, we found that PV alone is a strong predictor in the group of pregnancies with severe growth restriction (FGR and Doppler abnormalities). In particular, for a generally accepted 5% FPR, we were able to identify 77% of fetuses

destined to be growth restricted with severe deterioration in their hemodynamic status. The addition of other parameters increased significantly the detection rate (Table 3). To the best of our knowledge, this is the first study that distinguished this subgroup of FGR fetuses and examined its relation to first trimester PV. This observation has potentially clinical value as such pregnancies may benefit from low dose aspirin prophylaxis[1] and require intensive monitoring and referral to specialized fetal medicine units.[1,24] Due to the limited number of cases in this group, our observation should be confirmed in a larger study. Another limitation is that PV measurement can be time consuming, and this may restrict its wide clinical applicability. However, PV measurement can be easily done in an off-line setting at the end of the clinic or as a second line assessment in high-risk cases. Also, data on placental weight or histology are not available as not part of the protocol though a correlation would be interesting. We need to mention that PV could not be assessed only in two cases due to multiple fibroids and distorted uterine wall anatomy, whereas in all other cases, PV volumes were successfully obtained.

In pregnancies with gestational hypertensive disorders, we demonstrated that the PV measurement could provide a moderate prediction for both GH and PE subgroups and remained a significant predictor in the final models for these outcomes. Recent studies from another research group also showed that women with PE have significantly lower PV in the first trimester, and that this observation was also confirmed when the authors analyzed separately cases with early and late-onset PE.[22,25] At variance with this, Arakaki et al[23] showed that PV was significantly smaller only in the subgroup of PE and GH with early-onset. In the same study, authors also presented a predictive model based on first trimester PV and Ut-PI with 67% detection rate for the early-onset group for a 5% false positive rate. Another important observation in our study was that PV had predictive value for preterm birth before 34 and 37 weeks among cases with the pregnancy complications examined (Table 3). The sensitivity of the measurement was better for the identification of preterm birth before 34 weeks compared with 37 weeks, and the addition of uterine artery Doppler improved the performance of screening. At 10% FPR, 80% of cases with placenta-related complications that required delivery before 34 weeks could be identified from first trimester. These findings further support the clinical value of PV measurement given that prematurity is a major determinant of perinatal outcome in this group of pregnancies.[26,27]

Overall, we examined the potential association between PV and biochemical and biophysical markers of placental development in the first trimester of pregnancy. Our findings demonstrate that PV at 11 to 14 weeks of gestation is strongly related to PAPP-A with a mechanism unrelated to impaired placental perfusion, an observation consistent with our previous study about first trimester fetal volume. A possible explanation could be that first trimester PV is more strongly dependent on the anabolic effect of placenta-produced proteins rather than reflects the perfusion of the utero-placental unit. To the best of our knowledge, this is the first study that co-examines the predictive capacity of PV in different subgroups of pregnancies with pregnancy complications, all related to placental dysfunction. Our findings support that PV could have a role in first trimester prediction models for complications related to utero-placental problems, mainly in pregnancies with FGR and Doppler abnormalities.

CONFLICTS OF INTEREST

All authors report no conflicts of interest.

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