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Placental vascularization indices and prediction of pre-eclampsia in high-risk women

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ABSTRACT

Objective: To assess ability of first and second trimester Placental Vascularization Indices (PVIs) to predict pre-eclampsia (PE) in high-risk pregnancies.

Method: PVIs derived from 3-Dimensional power Doppler imaging were measured at 11 + 0–13 + 6 (n = 194) and 19 + 0–21 + 6 weeks (n = 195). Logistic regression (LR) models used PE as the outcome. To quantify added value of PVIs to baseline characteristics in predicting PE, integrated discrimination improvement (IDI) and net reclassification improvement (NRI) indices were calculated.

Results: Overall rate of PE was 12% (n = 26). Lower first trimester PVIs were seen in women with PE (mean, SD); Vascularization Index (VI,%): 10.0 (6.2) *v* 14.7 (7.6), P = 0.005, Flow Index (FI): 37.7 (9.1) *v* 42.9 (10.4), P = 0.03, Vascularization Flow Index (VFI): 3.8 (2.5) *v* 6.6 (4.0), P < 0.001). All first trimester PVIs predicted PE in LR models adjusted for covariates. IDI and NRI analyses confirmed added clinical utility of VI (IDI 0.05, P = 0.004; NRI 0.66, P < 0.001) and VFI (IDI 0.06, P = 0.004; NRI 0.53, P = 0.91). In the second trimester, FI was lower in women with PE (39.6 (9.1) *v* 44.4 (8.6), P = 0.01) and predicted PE in adjusted LR models (standardised OR 0.53, 95% CI 0.29–0.97, P = 0.04). FI discriminated between cases and non-cases of PE (IDI 0.04, P = 0.04).

Conclusion: First trimester placental vascularization indices (VI, FI and VFI) have the potential to predict PE in high-risk pregnancies, with FI remaining predictive in the second trimester.

1. Introduction

Worldwide, hypertensive disorders of pregnancy are responsible for around 18% of maternal deaths each year (62,000–77,000 deaths/annum) [1,2]. Pre-eclampsia (PE) is a major cause of maternal and perinatal morbidity and mortality affecting approximately 2% of all pregnant women [3]. Women with type 1 and 2 diabetes mellitus (DM), a body mass index (BMI) > 35 kg/m^2, essential hypertension, a previous history of PE, thrombophilia or autoimmune disease are at increased risk of adverse pregnancy outcomes, including PE [4].

The clinical significance of PE has resulted in it being the focus of research designed to improve our understanding of its aetiology and to develop better models of prediction. Predictive models have included maternal characteristics, assessment of previous obstetric history and inclusion of biophysical parameters such as maternal blood pressure, BMI and measurement of uterine artery Doppler. More recently, there has been increasing interest in 3 Dimensional Power Doppler (3DPD) acquisition of placental volume and placental vascularization indices (PVIs) and whether these might add to the predictive ability of established clinical and maternal serum and urine biomarkers [5–12].

Given that PE is in part attributed to a failure of placentation and remodelling of the maternal vasculature [13]; 3DPD evaluation of the placenta has the unique potential to offer clinicians a non-invasive means of assessing placental volume and PVIs [14]. A number of studies across general obstetric cohorts have shown significantly lower first trimester PVIs in women who subsequently develop PE [15], however little is known about the performance of PVIs for prediction of PE in high-risk women. The aim of this study was to assess the ability of PVIs measured in the first and second trimester to predict PE in a carefully characterised high-risk population. An additional aim was to evaluate

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the added clinical utility of PVIs for prediction of PE to that of established risk factors in high-risk women.

2. Materials and methods

The study population comprised high-risk women recruited to the PREDICT study (Prediction of PE in high-risk women) from a tertiary maternity unit in Northern Ireland (NI) between December 2014 and August 2016. The PREDICT study evaluated the clinical utility of whole volume derived 3DPD PVIs and serum biomarkers to predict PE in high-risk women in the first and second trimester of pregnancy. Written informed consent was obtained from all women. The Office for Research Ethics Committees NI (ORECNI) provided ethical approval (14/NI/1068).

Eligible women aged ≥18 years with a singleton pregnancy were recruited to one of four high-risk groups at 11 + 0–13 + 6 weeks gestation: (1) diabetes; pre-existing type 1 and type 2 diabetes (2) obesity; booking BMI > 35 kg/m^2 (3) hypertension; essential hypertension, a previous obstetric history of PE, intrauterine growth restriction (IUGR) or renal disease (4) autoimmune; known thrombophilia or autoimmune disease. A group of low-risk women (control group) were also recruited, however data reported in this paper concerns only high-risk women.

The primary outcome was PE, defined as hypertension after 20 weeks gestation and the co-existence of one or more of the following new-onset conditions: (1) proteinuria (2) maternal organ dysfunction or (3) uteroplacental dysfunction (i.e.) fetal growth restriction, in accordance with the International Society for the Study of Hypertension in Pregnancy (ISSHP) guidelines [16]. The diagnosis of PE was independently confirmed by three clinicians.

All participants attended for two study visits at 11 + 0–13 + 6 (visit 1) and 19 + 0–21 + 6 weeks gestation (visit 2). Scans were performed by one trained operator blinded to outcomes using a Voluson E8 ultrasound machine (GE Healthcare, MDI Medical (NI) Ltd) equipped with a 3D/4D convex transducer (2–8 MHz). Initial machine settings were based on those reported by Odibo et al. in an unselected obstetric population [17]. Preliminary work was undertaken to explore the impact of maternal BMI on acquisition of placental volume images and performance of PVIs prior to recruitment. Machine settings were subsequently optimised and maintained for all scans to help standardize the imaging technique (3D power Doppler: depth 10.1 cm, zoom 1.1), frame rate 9 Hz, harmonics: high, power 97%, frequency: low, pulse repetition frequency (PRF): 0.9 Hz, wall motion filter (WMF): low, volume angle 85^0, quality - high 1, Compound Resolution Image (CRI): I, Speckle Reduction image (SRI): III. Transabdominal ultrasound was performed to obtain measurements of placental volume and PVIs Vascularization Index (VI): ratio of voxels to all voxels within the placenta (%) [number of vessels], Flow Index [FI]: mean power Doppler signal intensity from all colour voxels (unit-less) [intensity of flow] and Vascularization Flow Index (VFI): ratio of blood flow and vascularization) using a 3DPD whole volume placental imaging technique [18]. A longitudinal view of the placental mass was obtained using 2D grey-scale imaging. This was adapted where necessary depending on size and location of the placenta. Using VOCAL software (Virtual Organ Computer-aided AnaLysis), the largest image of the placenta was located and positioned within the image acquisition box (Fig. 1). The region of interest was then adjusted before proceeding to off-line volume analysis. A manual tracing method of the placental border via six 30^0 rotations was employed. Placental volumes were obtained twice for each participant to obtain optimal images and mean placental volume is reported throughout the analysis. Reliability analysis was conducted for a subset of images chosen at random (n = 30) and evaluated at both time points. Analysis of images evaluated twice by the same operator demonstrated good repeatability (r) for VI, FI and VFI in the first and second trimester. At 11 + 0–13 + 6 weeks gestation, intra class correlation-coefficients (ICC) for VI, FI and VFI were 0.95, 0.96 and 0.94, respectively. Co-efficient of variation (CV) measurement ranged from 5.0 to 11.4%. In the second trimester, ICC for VI, FI and VFI were 0.97, 0.68 and 0.95, respectively. Co-efficient of variation (CV) measurements were higher (range: 8.1–12.9%). Between image variation demonstrated fair repeatability in the first trimester; ICC was > 0.8 for all placental vascularization indices (PVIs) with CV measurements ranging from 4.3 to 18.6%. Between 19 + 0–21 + 6 weeks gestation, r and CV measurements (13.6–26.2%) were less reliable and ICCs were lower (0.40–0.79).

2.1. Statistical analysis

Preliminary comparison of baseline maternal characteristics in women who developed PE and those who did not was performed using independent sample t tests and χ^2 tests. Mean values (standard deviation, SD) of PV, VI, FI and VFI are reported for cases and non-cases of PE.

Logistic regression models using PE as the primary outcome were determined for each PVI in each high-risk group. To facilitate comparison of placental parameters in regression models, PVIs were standardized to have a mean of 0 and a standard deviation (SD) of 1 and results presented as standardized odds ratios. Covariates included: study group, age, BMI, smoking status, aspirin use (at visit 1 and visit 2), parity, material deprivation of area of residence and mean arterial pressure (MAP) (at visit 1 and visit 2). The area under the receiver operating characteristic (ROC) curve was used to assess the ability of each PVI to predict PE in high-risk women. Logistic regression analysis provided predicted probabilities of PE for a base model containing established risk factors and for models obtained by the addition of each PVI to the base model. These predicted probabilities were used to derive ROC curves, and the increase in the area under these curves was assessed for significance [19].

To quantify the added value of PVIs to that of established clinical risk factors for prediction of PE, Integrated Discrimination Improvement (IDI) and category-free Net Reclassification Improvement (NRI) indices were calculated [20]. These incorporated predicted probabilities of development of PE for each woman derived from logistic regression models [21]. These indices offer additional information regarding the incremental yield of a new biomarker over the area under the ROC curve. The NRI was calculated on a continuous, uncategorised basis [20]. Defining PE as the event, it is described as the sum of $NRI_{(events)}$ and $NRI_{(non\text{-}events)}$ and is interpreted as the proportion of women reclassified to a more appropriate risk on addition of the PVI to the logistic regression [21]. In women who developed PE, if the addition of the PVI results in more individuals being reclassified to a higher risk, then the $NRI_{(events)}$ is positive. For women who did not develop PE, if more women are assigned as lower risk, then the $NRI_{(non\text{-}events)}$ is positive. IDI was defined as the average increase in predicted risk of PE in women with PE added to the average decrease in predicted risk in women without PE [21].

A 20% incidence of PE was assumed in the high-risk groups [22–24]. With an assumed inter-patient SD in VFI of 5.2 [17], a sample size of 200 women in the high-risk groups was sufficient to give 90% power to detect a difference of 3.0 in mean VFI between women who did not develop PE (expected size 160) and women who did (expected size 40). Statistical analysis was performed using SPSS version 21 (IBM Corp., Armonk, NY), Stata release 14 (StataCorp, College Station, TX) and the Hmisc package in R version 3.1.3 (R Core Team, Vienna, Austria).

3. Results

A total of 232 women were enrolled in the PREDICT study. Analysis of placental parameters by primary outcome (PE) in high-risk women was performed at two time points; visit 1 at 11 + 0–13 + 6 weeks (n = 194) and visit 2 at 19 + 0–21 + 6 weeks gestation (n = 195). The overall rate of PE was 12% (n = 26).

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