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Clinical Paper

An Assessment of Fetal Cerebral and Hepatic Perfusion in Normal Pregnancy and Pre-Eclampsia Using Three-Dimensional Ultrasound

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ABSTRACT

Background: Pre-eclampsia and placental causes of intrauterine growth restriction (IUGR) are part of the same spectrum of disorders. In IUGR, there is preferential shunting of blood to the fetal brain at the expense of other organs. We wanted to demonstrate that this also occurs in pre-eclampsia using three dimensional (3D) ultrasound. The 3D indices of perfusion are: flow index (FI), vascular index (VI) and vascularisation flow index (VFI) which reflect tissue vascularity and flow intensity.

Methods: Fourteen normal pregnant women and 14 with diagnosed pre-eclampsia were recruited. Scanning was conducted by 2 observers using a Voluson E8 machine. Perfusion was measured at a pre-defined position within the fetal brain and fetal liver. The power Doppler signals were quantified using the 'histogram facility' to generate 3 indices of vascularity: FI, VI and VFI. The unpaired t-test was used to compare differences between groups. The hypothesis was that fetal brain FI, VI and VFI would be similar between women with normal pregnancy and women with pre-eclampsia, but measurements would be reduced in the fetal liver in women with pre-eclampsia.

Results: Maternal characteristics of age, body mass index and gestation were not different between groups. The depth of insonnation did not differ between groups.

Fetal cerebral perfusion was not different between women with a normal pregnancy compared to women with pre-eclampsia. The mean (SD) for FI was 22.4 (5.7) vs. 21.1 (4.3) respectively (p=0.49). For VI, the mean (SD) was as 64.7 (40.4) vs. 79.1 (27.4) respectively (p=0.28). For VFI, the mean (SD) was 14.8 (10.3) vs. 16.1 (5.5) respectively (p = 0.66).

Fetal hepatic perfusion was not different between women with a normal pregnancy compared to women with pre-eclampsia. The mean (SD) for FI was 34.4 (19.9) vs. 27.8 (11.0) respectively (p = 0.28). For VI, mean (SD) was 67.6 (36.0) vs. 87.3 (25.8) respectively (p=0.11). For VFI, the mean (SD) was 19.6 (11.6) vs. 23.1 (10.6) respectively (p=0.42).

Conclusion: Using 3D ultrasound, we were not able to demonstrate preferential shunting of blood to the fetal brain at the expense of the fetal liver. Due to the high variability of our data, no definite conclusions can be derived from this work. A larger study may be required.

Key words: Pre-eclampsia, 3D ultrasound, perfusion.

INTRODUCTION

The patho-physiology of pre-eclampsia is believed to be placental in origin, with inadequate trophoblastic invasion of spiral arteries compromising placental blood flow[1]. The disease of pre-eclampsia overlaps with placental causes of intrauterine growth restriction (IUGR), where 20% of women with pre-eclampsia will have a growth restricted baby below the 10th centile[2]. Previous research studying IUGR has demonstrated preferential vascular shunting to the fetal brain as a compensatory measure for poor placental perfusion[3].

The current study aims to investigate whether this 'brain-sparing' effect is also demonstrable in pre-eclampsia. In other words, is there preferential shunting to the fetal brain at the expense of vascular flow to other major organs, such as the fetal liver?

With the advent of three dimensional (3D) ultrasound, physicians have been able to obtain in-vivo indices of perfusion [4,5]. These indices are flow index (FI), vascular index (VI) and vascularisation flow index (VFI) which are believed to reflect vascularity and flow intensity.

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In order to demonstrate preferential vascular shunting to the fetal brain in pre-eclampsia, we hypothesise the following:

1. Fetal cerebral perfusion is similar in pre-elampsia compared to normal pregnancy using the indices of FI, VI and VFI. .
2. Fetal hepatic perfusion is reduced in pre-eclampsia compared to normal pregnancy using the indices of FI, VI and VFI.

MATERIALS AND METHODS

Full research ethical and governance approvals were granted for this study (Research ethics no: 11/NI/0082; Research governance no: IRAS 57428). 14 normal pregnant patients and 14 with pre-eclampsia were recruited, and informed consent obtained. Normal pregnancy was defined as women with no pre-existing maternal co-morbidities, on no medication and no antenatal complications or concerns regarding fetal growth. Pre-eclamptic patients met the criteria of confirmed hypertension (BP >140/90mmHg on two consecutive occasions four hours apart); and significant proteinuria (>2+ on urinalysis; or >0.5g/24h on urine collection). Exclusion criteria included gestation less than 20 weeks; multiple pregnancy; and pregnancy with an abnormal fetus.

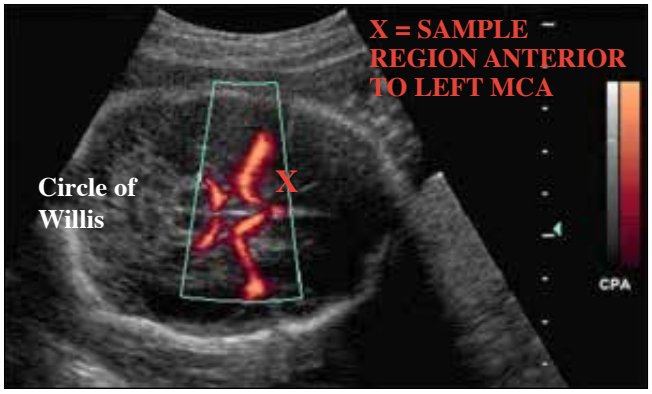

Fig 1. Fetal Cerebral Perfusion

Ultrasound scanning was conducted by one of two observers who had received identical training in the technique. A Voluson E8 machine with a 6 MHz trans-abdominal probe was used. The Voluson default settings were kept constant at: frequency 'mid'; dynamic 'set 3'; balance '>150'; smooth '4/5'; ensemble '11'; line density '8'; power Doppler map '4'; artefact suppression 'off'; power Doppler line filter 'off'; and, quality 'high'. Gain, signal power, pulse repetition frequency and speed of acquisition were controlled for. When measuring an area of perfusion, colour flow and 3D power Doppler angiography (3D-PDA) were applied to a pre-defined anatomical location, and the depth of insonnation also recorded. From within the area measured, a constant spherical sample volume was chosen. The power Doppler signals were then semi-quantified utilising the 'histogram facility', generating the three indices of vascularity: FI, VI and VFI.

Identifying fetal cerebral blood flow and measuring perfusion

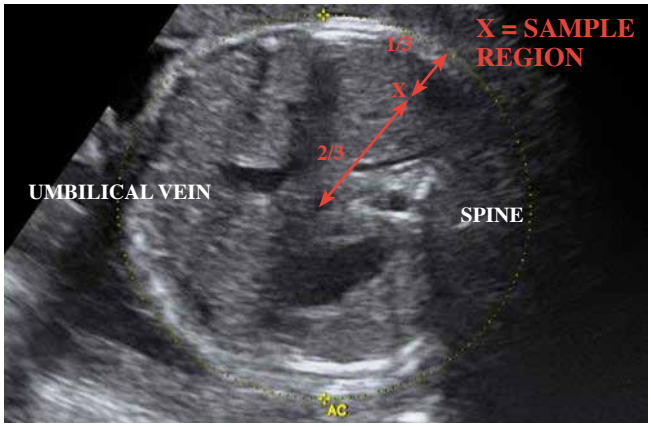

Fig 2. Fetal Hepatic Perfusion

Colour flow Doppler was used to identify the fetal Circle of Willis in the standard biparietal diameter view. The left middle cerebral artery (MCA) was visualised and the half way point of this vessel was identified. The region of vascularity sampled was arbitrarily fixed as 1cm anterior to this half way point of the left MCA (Figure 1). 3D-PDA was applied to this region.

Identifying fetal hepatic blood flow and measuring perfusion

The standard view used in measuring abdominal circumference was obtained. An imaginary line was drawn from the centre of the abdomen to the periphery, and 3D-PDA was applied to the hepatic region 2/3 of the distance from the centre along this line (Figure 2).

RESULTS

There was no statistically significant difference in age, body mass index or gestation between women with a normal

TABLE I:

Patient Demographics

	Normal n=14 mean (SD)	**Pre-eclampsia n=14 mean (SD)**	**t test P value**
Age (years)	29.5 (7.0)	28.4(6.0)	0.67
Body Mass Index (kg/m2)	23.6 (4.9)	26.2 (5.9)	0.22
Mean Arterial Pressure (mmHg)	89.2(6.5)	118.2 (5.1)	< 0.01
Gestation at scanning (weeks)	35+4	34+0	0.40
Depth of insonnation (cm) – Cerebral cortex	6.1 (1.7)	5.7 (1.3)	0.47
Depth of insonnation (cm) – Fetal liver	6.6 (1.6)	7.1 (2.2)	0.49

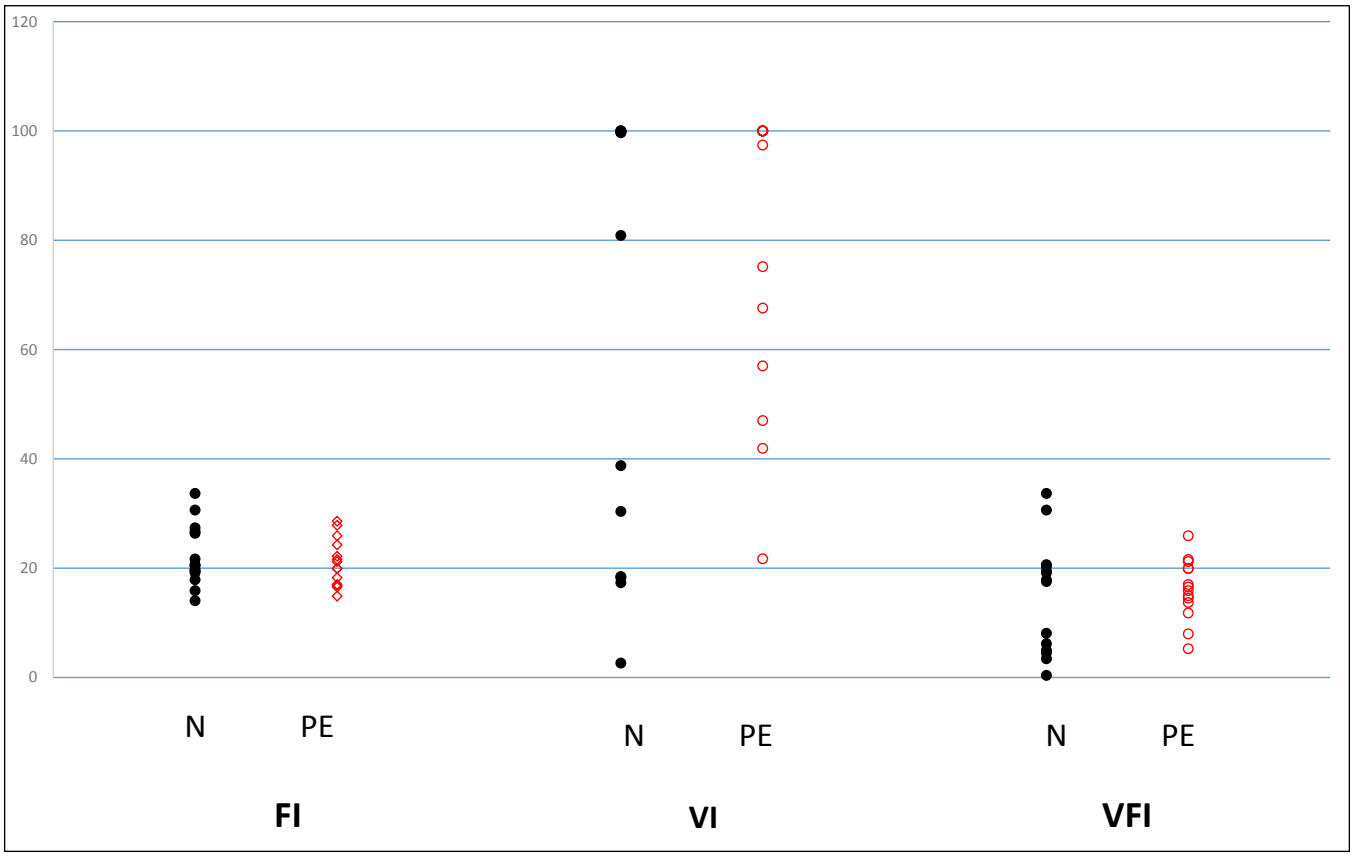

Fig 3. Data distribution of fetalcerebral perfusion indices

TABLE II:

Fetal Cerebral Perfusion

	Normal (n=14) Mean (SD)	**Pre-eclampsia (n=14) Mean (SD)**	**t test p-value**
FI	22.4 (5.7)	21.1 (4.3)	0.49
VI	64.7 (40.4)	79.1 (27.4)	0.28
VFI	14.8 (10.3)	16.1 (5.5)	0.66

TABLE III:

Fetal Hepatic Perfusion

	Normal (n=14) Mean (SD)	**Pre-eclampsia (n=14) Mean (SD)**	**t test p-value**
FI	34.4 (19.9)	27.8 (11.0)	0.28
VI	67.6 (36.0)	87.3 (25.8)	0.11
VFI	19.6 (11.6)	23.1 (10.6)	0.42

pregnancy and women with pre-eclampsia (Table 1). Women with pre-eclampsia had a higher mean arterial pressure (MAP). Depth of insonnation was not different between groups for either cerebral or hepatic perfusion measurements.

For women with pre-eclampsia, 5 of 14 delivered a baby that was growth restricted as defined by plotting birthweight on a customized growth chart.

Indices of fetal cerebral perfusion were not different between women with a normal pregnancy in comparison to women with pre-eclampsia (Table 2). The mean (SD) for FI, VI and VFI was not different between groups. For FI, the mean (SD) was 22.4 (5.7) vs. 21.1 (4.3) for normal vs pre-eclampsia groups respectively (p=0.49). For VI, the mean (SD) was 64.7 (40.4) vs. 79.1 (27.4) respectively; p = 0.28. For VFI, the mean (SD) was 14.8 (10.3) vs. 16.1 (5.5) respectively; p= 0.66. The overall distribution of this data is shown in Figure 3.

Fetal hepatic perfusion was not different between women with a normal pregnancy compared to women with pre-eclampsia (Table 3). The mean (SD) for FI was 34.4 (19.9) vs. 27.8 (11.0) between the normal and pre-eclampsia groups (p = 0.28). For VI, mean (SD) was 67.6 (36.0) vs. 87.3 (25.8) respectively (p=0.11). For VFI, mean (SD) was 19.6 (11.6) vs. 23.1 (10.6) respectively (p=0.42). The overall distribution of this data is shown in Figure 4.

DISCUSSION

The main findings were that three-dimensional indices of perfusion were not different in the fetal brain or fetal liver in women with pre-eclampsia compared to normal pregnancy. Hence the concept of a 'brain sparing effect' has not been demonstrated in this sample population.

The strengths of this study are that the 3D ultrasound technique was robustly standardized and the two groups of patients were matched for general characteristics.

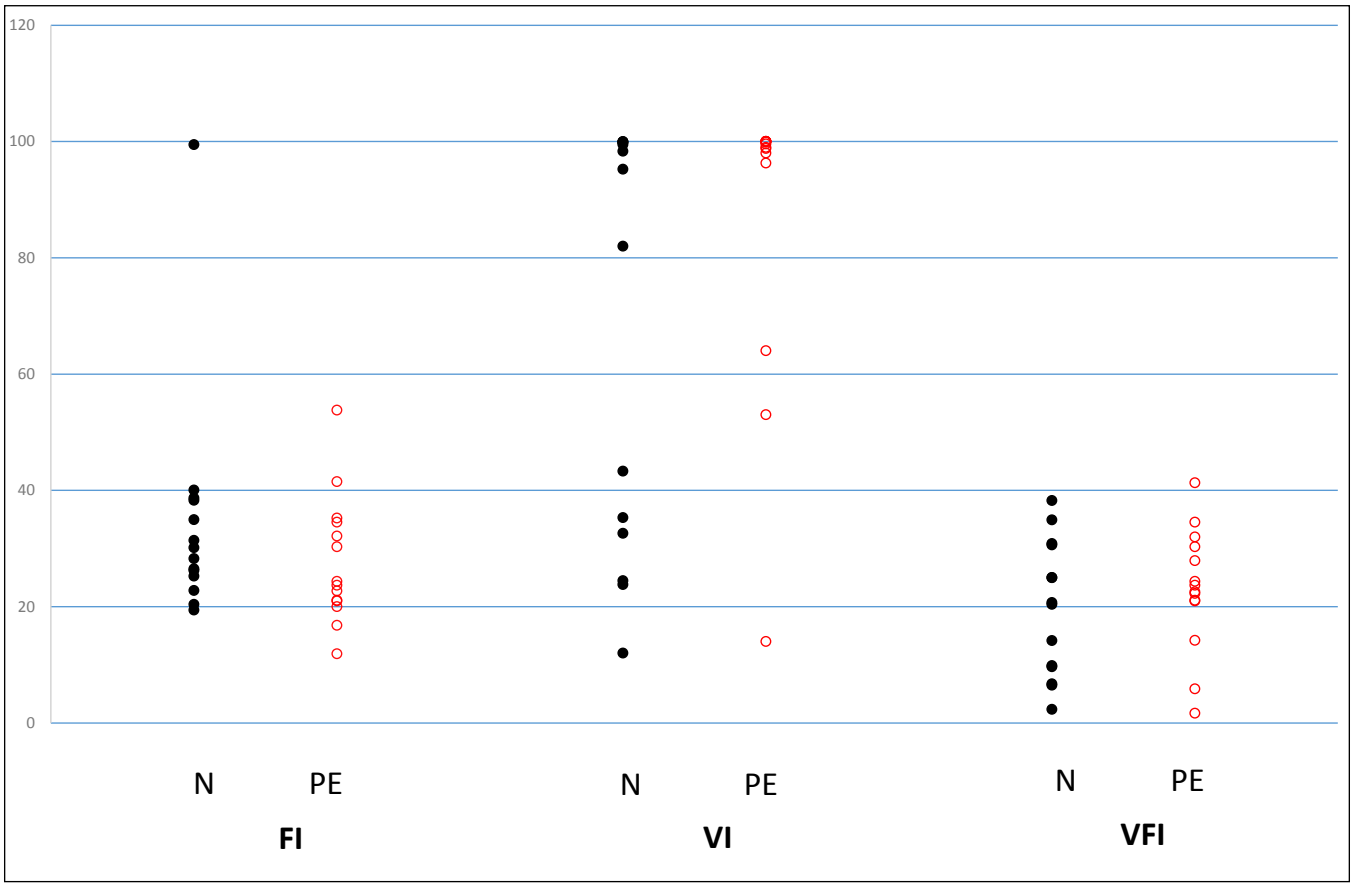

Fig 4. Data distribution of liver perfusion indices

A weakness of this study was the small sample size. Patients were also scanned by two different operators although every effort was made to ensure consistency in scanning techniques.

There are several possible explanations why no differences between groups were found. The first explanation is that there is truly no difference between these two populations in terms of fetal cerebral perfusion and fetal liver perfusion.

The second explanation is that the women selected who had pre-eclampsia had mild disease and therefore any differences would have been more difficult to detect, especially given the small number of patients. It would have been difficult to recruit women with severe pre-eclampsia to this study without compromising the safety of these women.

The third explanation is that the method used to assess perfusion is poor. In the current study, the variability of the data in both the normal population and the population with pre-eclampsia is wide. The methods of FI, VI and VFI have been criticized in a previous study as the measurements, particularly for VI and VFI, had wide variability[6]. Previous work from our unit concur with this assertion[7,8].

Despite our skepticism of 3D ultrasound as a method of assessing perfusion, we undertook this study as currently there are no other non-invasive methods of assessing perfusion in a fetus.

Taken together, we suggest that no clinical conclusion can be derived from our current study.

Previous work from our unit demonstrated a statistical difference in certain regions of the placenta in pre-eclampsia compared to normal pregnancy despite wide variability in measurements obtained[8]. The apparent poor performance of the test in the current study has prompted us to perform a sample size calculation using our current data. We chose to perform a sample size calculation using FI as this is believed to be most stable[6]. A sample size calculation for FI using an alpha or 0.05 and a Power of 80%, suggests a requirement of 302 women in each group to demonstrate a statistical difference. It may therefore be appropriate to consider performing a larger study.

DECLARATION OF INTEREST

No conflict of interest declared.

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