Maternal haemodynamics in normal pregnancies and in pregnancies affected by pre-eclampsia

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Short title: Maternal haemodynamics in pre-eclampsia with FGR

Key words: Pregnancy, Pre-eclampsia, Haemodynamics, Hypertension, Fetal Growth Restriction, Cardiac Output

Abstract

Objectives: To determine if in a high risk group in the first half of pregnancy, women who developed pre-eclampsia (PE) with fetal growth restriction (PE-FGR) demonstrate distinct haemodynamics compared to those with PE in the absence of FGR (PE-only).

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Methods: Cardiac output (CO), peripheral vascular resistance (PVR) and mean arterial pressure (MAP) were measured at the first hospital visit at 9-24 weeks' gestation in 69 women who had chronic hypertension and 67 who had a hypertensive disorder in a previous pregnancy. In total, 19 subsequently developed PE-only, 22 developed PE-FGR, 17 developed pregnancy induced hypertension and 78 had uncomplicated pregnancies and the haemodynamic values in each of these groups were compared to those of a cohort of 300 low-risk women with normal pregnancies.

Results: In all the high risk groups, compared to normal pregnancies, PVR and MAP were increased, but CO in the group of PE with FGR was reduced whereas in the other high risk groups it was not significantly different from normal.

Conclusions: In women that develop PE there is evidence of high PVR and MAP from the first half of pregnancy and those with PE and FGR demonstrate evidence of failure in the physiological expansion in CO.

Introduction

Traditionally, preeclampsia (PE) has been defined as hypertension in the second half of pregnancy accompanied by proteinuria. However, it has recently been recognised that the syndrome can develop in the absence of proteinuria and a new definition of PE has been introduced, whereby hypertension can either by accompanied by proteinuria or by evidence of maternal liver or haematological complications or fetal growth restriction (FGR)[1]. There is uncertainty as to whether the pathogenesis of PE with a predominantly maternal component is the same or different from that of PE with a predominantly fetal component.

The main objective of this study is to compare the haemodynamic profile at the booking visit in the first half of pregnancy of women that subsequently develop PE with FGR to those with PE in the absence of FGR, in a high risk population. As these women were recruited from a high risk cohort, i.e. women with chronic hypertension or a hypertensive disorder in a previous pregnancy, we also sought to assess haemodynamics in those with an uncomplicated index pregnancy and in those with pregnancy induced hypertension (PIH). The haemodynamic profile was assessed by measurement of maternal cardiac output (CO), peripheral vascular resistance (PVR) and mean arterial pressure (MAP). Assessment of CO and PVR was undertaken non-invasively using a bioreactance monitor.

Methods

Study population

Two groups of singleton pregnancies were included in this study. The first group, comprised of 136 ‘high risk’ pregnancies recruited from the antenatal hypertension clinic, at King’s College Hospital, London from February 2013 to March 2015. These women had either chronic hypertension (n=69, 51%) or a hypertensive disorder in a prior pregnancy (n=67,

49%) and were referred for optimisation of their pregnancy management. This high risk group was subdivided into five subgroups according to pregnancy outcome: PE with FGR (n=22), PE without FGR (n=19), PIH (n=17), chronic hypertension without PE or FGR (n=39), and hypertensive disorder in a prior pregnancy without PE, PIH or FGR (n=39) in the index pregnancy. The second group, comprised of 300 women at 'low risk' of pregnancy complications who were attending midwifery-led antenatal care. We recruited 340 such women between February 2013 and August 2016, but subsequently excluded 40 because they developed pregnancy complications.

Haemodynamic studies were carried out in all patients by the same group of researchers using the same equipment and protocol. In the 'high risk' group, assessment was undertaken in the first visit to the hypertension clinic, which took place between 9-24 weeks' gestation. In the 'low risk' group, women were selected at random so that there was a balance of cases at different gestations to establish a reference range at 9-41 weeks.

Pregnancies were dated by crown-rump length recorded in the first trimester. Maternal and fetal outcomes were obtained from local databases and birthweight centiles were calculated using local reference ranges[2]. The definitions of PE and PIH were those of the International Society of Hypertension in Pregnancy, 2014[1]. FGR was diagnosed if the birth weight was $<3^{rd}$ percentile or if the weight was $\geq 3^{rd}$ percentile, or if there was a Doppler finding of cerebroplacental ratio $<5^{th}$ percentile, an umbilical artery pulsatility index (PI) $>95^{th}$ percentile, a middle cerebral artery PI $<5^{th}$ percentile, or uterine artery PI $>95^{th}$ centile[3].

Ethical approval for the study was given by the National Research Ethics Service (Reference: 12/LO/1593) and written, informed consent was obtained from all participants.

Maternal hemodynamics

A non-invasive portable cardiac monitor was used to record central maternal haemodynamics (NICOM, Cheetah Medical Ltd, Maidenhead, Berkshire, UK). This device uses bio-reactance technology to calculate stroke volume by recording the relative phase shifts that occur want an alternating electrical current traverses the thorax. An average from five cycles of haemodynamic recordings were used in the analysis, in order to control for differences in stroke volume that can occur owing to the negative intrathoracic pressure in inspiration. CO was calculated as the product between stroke volume and heart rate.

Systolic (SBP) and diastolic blood pressure (DBP) was taken in accordance with the British Hypertension Society guidance[4] and recorded with an automated device, which has been validated for use in pregnancy and PE[5] and MAP was defined as ((2xDBP)+SBP)/3.

Peripheral vascular resistance was calculated by the equation PVR = (MAP (mmHg)/CO[L/min]) x 80.

Statistical analysis

The sample size for the construction of the reference ranges was based on a report that at least 292 subjects were required for the creation of reference ranges in pregnancy[6]. The sample size for the two groups that developed PE was based on our previous study which demonstrated that in the first half of pregnancy there was a difference in cardiac output of 1.6 L/min between women whose pregnancies were complicated by FGR compared to those who had appropriately grown babies at delivery[7]. Given this difference in CO between the two groups, for a Type I error (a) of 0.05 and type II error of 0.05 (i.e. power of 95%) 8 women with FGR pregnancies and 16 women with appropriately grown babies would need to be recruited.

Gestation-specific haemodynamic reference ranges were derived from the cohort of 300 normal pregnancies. The normality of the distribution of measurements was assessed using the Kolmogoroff-Smirnoff test; in the case of PVR logarithmic transformation was necessary to normalize the data. Multivariate regression analysis was then used to determine the expected mean CO, log PVR and MAP adjusted for gestational age and maternal characteristics. In the normal outcome and the high risk cohort each measured value of CO, PVR and MAP was expressed as a Z-score (number of standard deviations from the expected normal mean). Comparison between the groups was by one-way ANOVA and the Kruskal-Wallis test for normally and non-normally distributed data, respectively. Categorical data were compared using the chi-square or Fisher's exact test where appropriate. The Bonferroni correction was used to control for multiple comparisons. In the women who developed PE, univariate regression analysis was used to determine the significance of the association between Z-score for CO, PVR and MAP with birthweight Z-score.

Results

Maternal demographics and pregnancy outcomes

The maternal demographic characteristics at booking in the first half of pregnancy, and the outcome variables for the cohort of women who had normal pregnancies, PE with FGR, PE without FGR (PE Only), PIH, chronic hypertension without PE or FGR and hypertension in a previous pregnancy without PE, PIH or FGR are presented in Table 1.

In both groups with PE, compared to the normal outcome group, there was a higher prevalence of multiparity, chronic hypertension and use of antihypertensive medications. In the PE FGR group, the birthweight percentile and gestational age at delivery were significantly lower than in the normal outcome group and the PE Only group. There were

significant differences between the normal outcome group and the PE group without FGR (PE Only) in age, weight, ethnicity and BSA; although the values in the two PE groups were similar there was no significant difference between the normal outcome group and the PE FGR group because of the small number of cases in the latter. There was a significant but unexplained difference in gestational age at presentation between the two PE groups.

The group with chronic hypertension was significantly shorter and heavier than the group with previous pregnancy hypertension, and had a significantly smaller proportion of white women and a significantly higher proportion of black women.

Reference ranges of maternal haemodynamics in pregnancies with normal outcome

Multivariate regression analysis demonstrated significant contributions from gestational age, maternal ethnicity and BSA in the prediction of CO, PVR and MAP (Table 2). Higher BSA was associated with a higher CO, MAP and lower PVR. Black and mixed ethnicity, compared to Caucasians, was associated with a higher CO and lower PVR. After controlling for BSA and ethnicity, multivariate logistic regression showed a quadratic relationship between gestational age and CO, MAP and PVR.

Maternal haemodynamics – differences between groups

The z-scores for MAP and PVR were significantly higher in all five subgroups of 'high risk' pregnancies than in the normal outcome group (Table 3, Figure 1). The Z-score for CO was significantly lower only in the subgroup of PE- FGR compared to all other subgroups. In terms of CO, there was no significant difference between the PE group without FGR (PE Only) and the normal outcome group, or between the normal outcome group or any of the other high risk groups.

Maternal haemodynamics in women with PE – association with birthweight

In the combined PE group, there was a significant association between birthweight z-score and CO z-score (CO z-score CO = -0.07 + 0.34 x birthweight z-score; P=0.004, R^2=0.2), MAP z-score (MAP z-score = 1.7- 0.48 x birthweight z-score; p=0.03, R^2=0.1) and log PVR z-score [log PVR z-score = 0.78 x (-0.51 x birthweight z-score); P=0.001, R^2=0.25) (Figures 2a, 2b, 2c).

Discussion

Non-invasive assessment of haemodynamics

New non-invasive cardiac monitoring methods have facilitated maternal haemodynamic assessment in hypertensive pregnancies. This has been done firstly, to determine the role of haemodynamics in the disorder's pathogenesis[8], secondly, to aid screening,[9, 10] and thirdly, to guide therapy[11, 12]. Echocardiography was used since the 1980s but requires operator expertise. Newer devices including NICOM are operator independent. NICOM validation studies have been conducted outside of pregnancy[13], however, within pregnancy there remain concerns regarding its limits of agreement with echocardiography[14].

Due to the gestational-age spread at presentation in the PE-FGR group, we had to control for gestational-age haemodynamic effects, and hence required gestation-specific reference ranges. One option was to use ranges derived from echocardiography. However, since the limits of agreement between NICOM and echocardiography seem to be above proposed levels of clinical acceptability[14], we elaborated reference ranges specific to the NICOM device.

Reference ranges - pregnancies with normal outcomes

The NICOM discerned the anticipated temporal cardiovascular changes associated with normal pregnancy, and also showed ethnic and BSA-variances in cardiac function. In the normal cohort, black women had about a 0.4L/min higher CO than Caucasians. This corresponds with work by Bamfo et al, who showed in a normal pregnant population black women had a 10% higher CO compared to white women[15]. BSA was positively correlated with CO, as previously demonstrated in pregnant[16] and non-pregnant individuals[17].

Larger stature confers greater metabolic demand[18] and consequently greater CO, but in pregnancy some studies show a weaker association between BSA and CO[19]. Duvekot et al[20] have speculated this is because the early increase in CO is driven by upregulation of the renin-angiotensin system, and thus only poorly related to BSA.

Women with a larger BSA had higher MAPs. This corresponds with Easterling et al[21], who showed those who developed PE had larger BSAs than normotensive women. This difference seems driven by the greater weight of women who developed hypertension, since there was no height difference between the hypertensive and normotensive cohort. Therefore it seems the association between BSA and higher CO relates to the higher metabolic demands of larger individuals[18] and the association between BSA and higher MAP reflects the positive correlation between weight and blood pressure[22].

Findings in pregnancies with PE

This study highlights the different hemodynamic profile of hypertensive disorders of pregnancy with a predominantly maternal component (PIH, PE only, chronic hypertension) and PE with a predominantly fetal component (PE-FGR). At presentation, all five subgroups

from 'high risk' pregnancies demonstrated increased MAP and PVR compared to the normal pregnancy group, but only those who developed PE with FGR had a low CO.

The finding of a low CO in PE with FGR corresponds with studies that investigated FGR without PE. A study in 126 high-risk first-trimester pregnancies found a reduced CO in gestations with FGR.[7] Similarly, a screening study of 534 pregnancies reported decreased CO at 11-13 weeks in those delivering small babies.[23] Another study in 1345 normotensive mid-trimester women, concluded early and late PE constitute distinct entities, with the former primarily placental in origin and the latter linked to maternal metabolic factors; in the early PE group, with a high FGR rates, the CO was reduced, whereas in the late PE group, with lower FGR rates, CO was increased[10]. In our study, PE was divided by the presence or absence of FGR, not gestational age; nevertheless, in those with FGR delivery was earlier than in those without FGR.

The cause of low CO in FGR is uncertain. In normal pregnancy, there is an early rise in CO, peaking with a 40-50% increase around 32 weeks[24, 25]. The initial stimulus, a reduction in peripheral resistance, triggers tachycardia, upregulation of the renin-angiotensin system and erythropoietin production with a lowering of the osmotic threshold for anti-diuretic hormone secretion[26]. Plasma volume thereby increases giving an increased CO. The drop in peripheral resistance is potentially placental in origin, with apoptotic trophoblastic debris causing an inflammatory response in the maternal circulation[27]. In FGR, one could hypothesise either that this placental apoptosis and / or transfer to the maternal circulation may be impaired, or the maternal cardiovascular response to this stimulus is attenuated.

Which of these mechanisms, placental dysfunction or cardiovascular maladaptation, causes PE with FGR remains contested. That aspirin is less effective in obese or chronically hypertensive women may suggest it is a primary failure of cardiovascular adaptation rather than a failure of angiogenesis and trophoblast invasion (thought to be addressed by aspirin's

prophylactic mode of action in early pregnancy) which is the primary pathophysiological mechanism in some groups[28].

Iatrogenic mechanisms affecting CO also impact fetal growth. Easterling *et al* have shown growth is preserved by titrating antihypertensives to avoid suppressing CO[29], suggesting maternal haemodynamics are integral to growth not only during placentation, but throughout gestation. We do not believe, however, this mechanism affected our results, since only two patients from the PE-FGR group were taking antihypertensives at assessment.

Clinical and research implications

Clinicians treating women with PE and FGR should avoid compromising an already suppressed maternal CO by careful titration of antihypertensives. In research terms, this study shows diverse haemodynamic profiles of PE may be masked if study populations are analysed as a whole and not grouped by the presence or absence of FGR. Furthermore, identifying women with a suppressed CO may provide a way to triage patients at risk of FGR.

Study limitations

We examined haemodynamics in high-risk women. Consequently, we have not assessed those without *a priori* risk factors who developed PE. More work is needed to confirm FGR is associated with the same CO suppression in early pregnancy among low risk women with PE.

In addition, our high-risk cohort were disparate in terms of risk factors: some had chronic hypertension, others had previous pregnancy hypertension, and in terms of assessment timing. We note, however, this high-risk cohort reflects the likely composition of a high-risk

hypertension clinic, and in clinical practise a significant number present late. According to one study 31% of patients at a London hospital booked after 18 weeks[30]. We addressed late booking with z-scores, obviating haemodynamic differences accounted for by gestational age.

Conclusions

Our work highlights the distinct haemodynamic profile associated with PE and FGR, based on comparison against device-specific reference ranges. Women who develop PE with FGR, compared to those who develop PE only, have a significantly suppressed CO from early in pregnancy. This suggests these pregnancies are afflicted by a failure of cardiovascular adaptation, and the persistence of a low CO, high-resistance haemodynamic profile.

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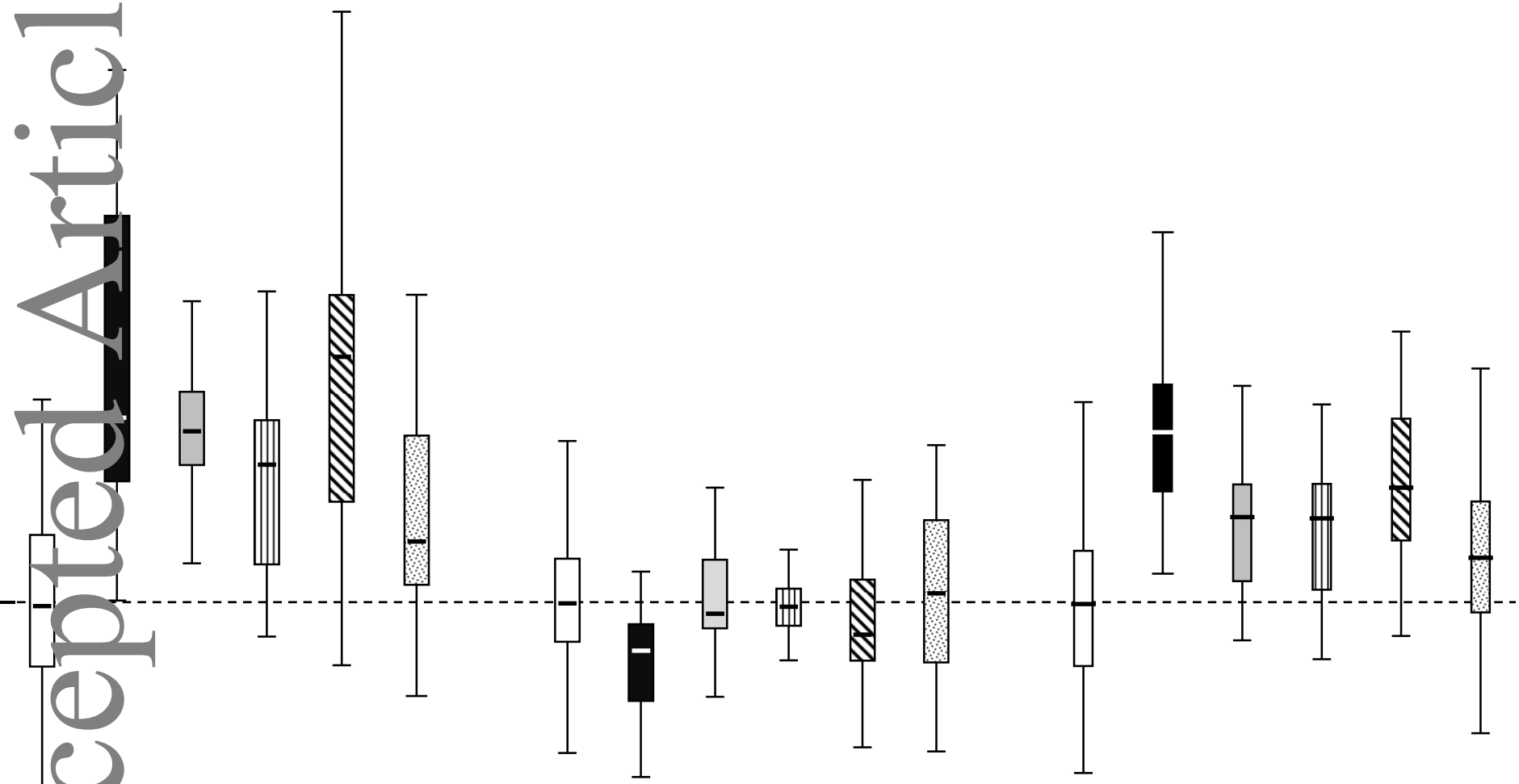
Figure Captions

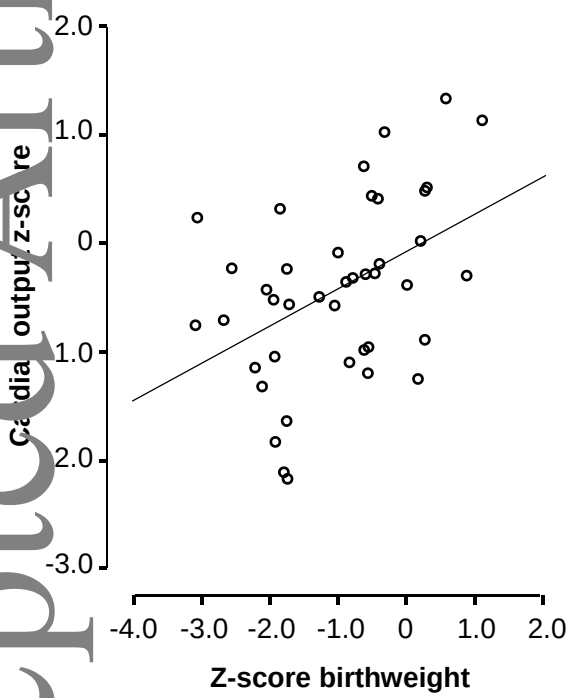
Figure 1: Box and whisker plots showing z-score values for mean arterial pressure (left), cardiac output (centre) and log-peripheral vascular resistance (right).
The normal group is indicated by white boxes, the PE-FGR group by black boxes, the PE-only group by grey boxes, the PIH group by boxes with a vertical cross-hatch, the chronic HTN with uncomplicated outcome by boxes with a diagonal cross-hatch and the history of HDP with normal outcome by boxes with a dotted fill.

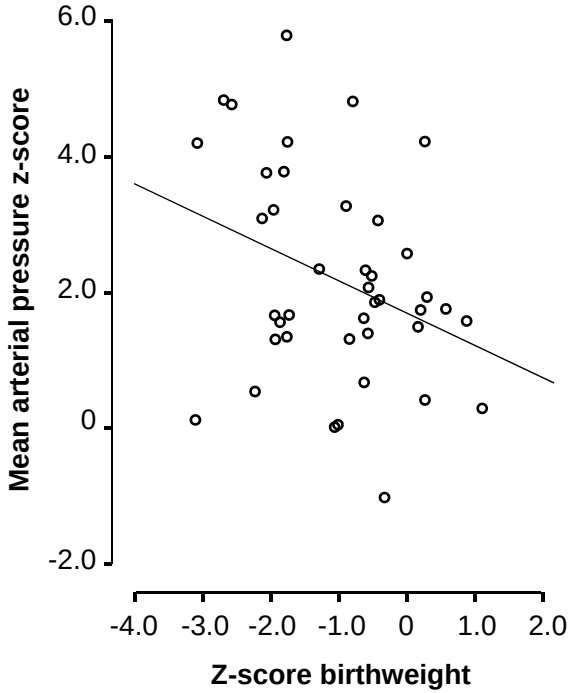
Key: HDP = history of hypertensive disorder of pregnancy

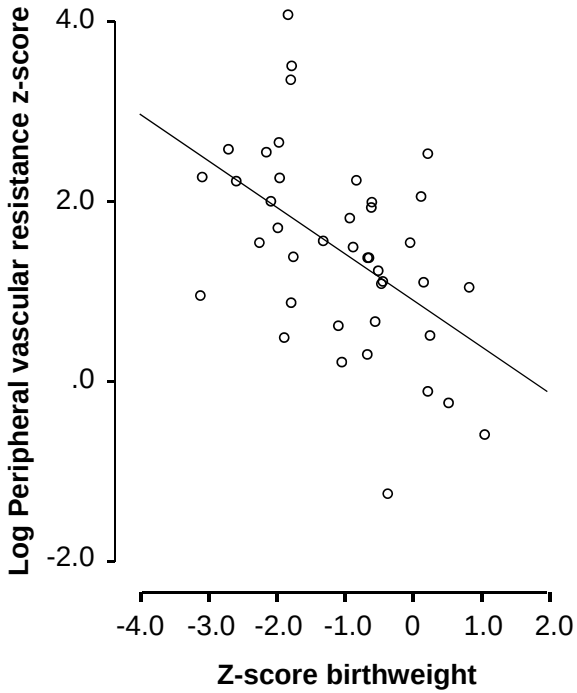
Figure 2: Scatterplots between maternal haemodynamics and z-score birthweight for all women with PE (N=41).



Mean arterial pressure Cardiac output Peripheral vascular resistance







	Normal pregnancies (n=300)	PE FGR (n=22)	PE Only (n=19)	PIH (n=17)	Chronic HTN (No PE) (n=39)	Previous pregnancy HTN (n=39)
Age (years)	32.0 (29-36) †	34.0 (28.7-40.0)	37.0 (33.0-39.0)	34.0 (30.0-37.0)	34.0 (31.0-37.0)	33.0 (31.0-36.0)
Weight (kg)	64.95 (58.6-73.6) *	74.0 (64.2-91.7) #	71.0 (67.0-93.0)	75.0 (70.0-89.0)	89.0 (79.0 -105.0) ♣	70.0 (65.0-107.0)
Height (cm)	164.5 (160.0-169.0) § #	159.5 (152.0-166.0) #	162.0 (158.0-169.0) #	164.0 (159.0-167.0) #	164.0 (159.0-171.0) ♣	166.0 (161.0-169.0)
Body surface area (m^2)	1.7 (0.1) # ♣	1.8 (0.2)	1.8 (0.2)	1.8 (0.2)	1.9 (0.2) ♣	1.8 (0.2)
Primiparous, n (%)	207 (69) *	7 (32) ∞ ♣	3 (16) ♣	0 (0)	7 (18) ♣	0 (0)
Chronic HTN, n (%)	0 (0) § † #	18 (82) ∞ # ♣	12 (63) ∞ # ♣	0 (0) #	39 (100) ♣	0 (0)
Anti-hypertensives, n (%)	0 (0) § † #	2 (9) ∞	6 (32) ♣	0 (0)	6 (15) ♣	0 (0)
Ethnicity, n(%)						
White	188 (63) † #	11 (50)	7 (37)	7 (41)	10 (26) ♣	22 (56)
Black	77 (26) § † #	10 (45)	11 (58)	7 (41)	26 (67) ♣	14 (36)
South Asian	16 (5)	1 (5) #	1 (5)	0 (0)	2 (5)	3 (8)
East Asian	7 (2)	0 (0)	1 (5)	2 (12)	0 (0)	0 (0)
Mixed	13 (4)	0 (0)	0 (0)	1 (6)	1 (2)	0 (0)
Gestation Age at Presentation	-	13.8 (11.0 – 17.7)	12.5 (11.9-13.9)	14.1 (12.6 16.9)	13.0 (11.3-15.0)	13.3 (12.3-14.4)
Outcomes						
Birthweight (grams)	3443 (3215-3801) † ♣	2207 (1592-2538) *	3030 (2725-3320) # ♣	3290 (3065-3627)	3294 (3025-3650)	3285 (2830 – 3650)

Gestational Age at Delivery	40.3 (39.5-41.0) † # ♣	37.1 (34.0-38.6) *	38.0 (37.3-39.1)	39.0 (38.6-40.4)	39.3 (38.4-40.1)	39.1 (38.0-39.7)
Birthweight z-score	0.091 (0.9)	-1.7 (0.9) *	- 0.26 (0.5)	0.20 (1.16)	0.33 (1.09)	0.05 (0.95)
Birthweight Centile	48.9 (29.2-75.3)	3.2 (1.5-10.6) *	32.7 (26.4-59.5) #	51.5 (25.6-76.4)	59.49 (30.9-86.6)	49.3 (23.1-72.7)

Table 1: Maternal demographic and outcome variables at presentation compared between the cohorts. Data are represented as mean (standard deviation) if normally distributed and as median (interquartile range) if non-normally distributed.

Symbol key:

* Statistically significant compared to all other five groups

§ Statistically significant from PE-FGR

† Statistically significant from PE-Only

∞ Statistically significant from PIH

Statistically significant from women with chronic HTN and no PE

♣ Statistically significant from women with previous pregnancy HTN

Table 2: Mutivariate regression for women with normal pregnancies. Significant predictors are presented for cardiac output, mean arterial pressure and peripheral vascular resistance (Log10).

GA = gestational age; BSA = body surface area

	Cardiac output			Mean arterial pressure			Peripheral vascular resistance (log10)		
	Parameter	Standard error	p-value	Parameter	Standard error	p-value	Parameter	Standard error	p-value
Intercept	-1.7	0.90	0.08	61.55	6.67	<0.001	3.42	0.074	<0.001
GA	0.13	0.04	0.006	-0.59	0.316	0.061	-0.010	0.003	0.005
GA^2	-0.002	0.0009	0.006	0.012	0.006	0.040	0.0002	<0.001	0.003
BSA	4.05	0.44	<0.001	13.75	2.991	<0.001	-0.188	0.033	<0.001
Ethnicity									
Black	0.39	0.15	0.01	-	-	-	-0.027	0.011	0.017
Mixed	0.83	0.32	0.01	-	-	-	-0.053	0.024	0.029
ANOVA p-value	<0.001			<0.001			<0.001		
Adjusted R^2	0.26			0.078			0.14		

Table 3: Maternal z-scores for haemodynamic variables compared between the cohorts. Data are represented as mean (standard deviation).

	Normal pregnancies	PE with FGR	PE Only	PIH	Chronic HTN	Previous pregnancy HTN
z-score CO	0.001 (0.85)	-0.75 (0.80) *	-0.04 (0.70)	-0.11 (0.78)	-0.22 (1.00)	0.25 (1.89)
z-score MAP	0.01 (0.96) *	2.55 (1.76) *	1.77 (1.19)	1.35 (1.11) #	2.46 (1.65) ♣	0.86 (1.08)
z-score Log PVR	0.16 (0.93) *	1.75 (1.08) †♣	0.59 (0.91)	0.79 (0.91)	1.30 (0.92) ♣	0.43 (1.29)

Symbol key:

* Statistically significant compared to all other five groups
† Statistically significant from PE-Only
# Statistically significant from chronic HTN and no PE
♣ Statistically significant from previous pregnancy HTN

CO = cardiac output; MAP = mean arterial pressure; PVR = peripheral vascular resistance