Article type : Main research article

Maternal hemodynamic function differs in preeclampsia when it is associated with a small for gestational age newborn: a prospective cohort study.

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Running Title: Maternal hemodynamic function in preeclampsia

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/1471-0528.16269

Abstract

Objective: To describe maternal hemodynamic differences in gestational hypertension with small for gestational age babies (HDP+SGA), gestational hypertension with appropriate for gestational age babies (HDP-only) and control pregnancies.

Design: Prospective cohort study.

Setting: Tertiary Hospital, UK.

Population: Women with gestational hypertension and healthy pregnant women.

Methods: Maternal hemodynamic indices were measured using a non-invasive Ultrasound Cardiac Output Monitor (USCOM-1A®) device and corrected for gestational age and maternal characteristics using device-specific reference ranges.

Main outcome measures: maternal cardiac output, stroke volume, systemic vascular resistance.

Results: We included 114 HDP+SGA, 202 HDP-only and 401 control pregnancies at 26-41 weeks' gestation. There was no significant difference in the mean arterial blood pressure (110mmHg vs 107mmHg, p=0.445) between the two HDP groups at presentation. Pregnancies complicated by HDP+SGA had significantly lower median heart rate (76bpm vs 85bpm vs 83bpm), lower cardiac output (0.85MoM vs 0.98MoM vs 0.97MoM) and higher systemic vascular resistance (1.4MoM vs 1.0MoM vs 1.2MoM) compared to control and HDP-only pregnancies, respectively (all p<0.001).

Conclusion: Women with HDP+SGA present with more severe hemodynamic dysfunction than HDP-only. Even HDP-only pregnancies exhibit impaired hemodynamic indices compared to normal pregnancies, supporting a role of the maternal cardiovascular system in gestational hypertension irrespective of fetal size. Central hemodynamics changes may play a role in the pathogenesis of preeclampsia and should be considered alongside placental aetiology.

Funding: HP is supported by a grant from the National Institute for Health Research (NIHR) Collaboration for Leadership in Applied Health Research and Care South London at King's College Hospital NHS Foundation Trust.

Keywords: cardiac output, heart rate, hypertension, maternal hemodynamics, non-invasive monitoring, preeclampsia, small for gestational age, systemic vascular resistance

Tweetable abstract: Hypertensive disorders of pregnancy are associated with worse maternal hemodynamic function when associated with small for gestational age birth

INTRODUCTION

There is increasing evidence for the role of the maternal cardiovascular system in the development of gestational hypertension and preeclampsia. Not only do hypertensive disorders of pregnancy (HDP) share the same risk factors as cardiovascular disease,[1–5] but there is also good echocardiographic evidence of structural and functional changes in pregnancies affected by preeclampsia. For example, in pregnancies complicated by preeclampsia at term, global diastolic dysfunction has been observed in 40% of cases compared to 14% of control pregnancies whilst in preterm preeclampsia biventricular systolic dysfunction was seen in 26% and severe left ventricular hypertrophy seen in 19% compared to 0% of controls.[6–8] Furthermore, women who develop preeclampsia and gestational hypertension are at an increased risk of developing postpartum hypertension and cardiovascular disease in later life, with the risk correlating to the severity of their hypertension disorder of pregnancy.[9–16]

Different classifications of hypertension in pregnancy have been proposed which are differentiated by the development of proteinuria, maternal organ dysfunction or fetal growth restriction in preeclampsia[17] as well as different variations on 'early' and 'late-onset' preeclampsia. These two conditions have typically been separated at 34 weeks of gestation and have been purported as different disease entities with different pathological mechanisms.[18–20] Early-onset preeclampsia is a placenta-mediated disease secondary to a failure of the physiological transformation of the spiral arteries into dilated, non-elastic vessels to allow for maximal maternal-placental blood flow. The resulting narrow vessels impede blood flow leading to placental ischaemia, which results in small for gestational age fetuses in addition to hypertension.[20–25] Late-onset disease is thought to be secondary to maternal cardio-metabolic dysfunction, which is less likely to be associated with small for gestational age babies.[18–20] An alternative explanation to the theory of two separate disease mechanisms, is that gestational hypertension and preeclampsia are a disease-continuum, with its severity related to the degree of underlying maternal hemodynamic dysfunction; notably a lack of increase in maternal cardiac output and decrease in systemic vascular resistance as would be expected in normal pregnancy.[26]

The objective of this study was to describe maternal hemodynamic differences (stroke volume, heart rate, cardiac output and systemic vascular resistance), using a non-invasive continuous-wave Doppler device,[27,28] in hypertensive disorders with and without small for gestational age babies and in control pregnancies. We hypothesised impaired maternal hemodynamic function would predispose to small for gestational age birth.

MATERIALS AND METHODS

Study population and recruitment

This was a prospective study of pregnancies complicated by hypertensive disorders and control normotensive pregnancies seen at a tertiary referral centre between January 2012 and May 2018. The inclusion criteria were singleton pregnancies with a viable fetus at 26 weeks' gestation or greater with gestational hypertension, defined according to the ISSHP 2014 revised criteria[17], or uncomplicated singleton pregnancies. The exclusion criteria were women with multiple pregnancies, a history of chronic hypertension or cardiac disease and pregnancies complicated by aneuploidy, genetic syndromes or major structural fetal abnormalities. A small for gestational age neonate was defined as having a birthweight below the 10th centile. Fetal growth restriction was defined as per the Delphi Consensus agreement.[29] At <32 weeks: abdominal circumference/estimated fetal weight <3rd centile *or* absent end-diastolic flow in the umbilical artery *or* abdominal circumference/estimated fetal weight <10th centile combined with uterine artery pulsatility index >95th centile *and/or* umbilical artery pulsatility index >95th centile. At ≥32 weeks: abdominal circumference/estimated fetal weight <3rd centile *or at least two out of the following:* 1. abdominal circumference/estimated fetal weight <10th centile, 2. abdominal circumference/estimated fetal weight crossing >two quartiles, 3. Cerebral placental ratio <5th centile *or* umbilical artery pulsatility index >95th centile. A centile calculation obtained from a study of 92,000 healthy neonates from a similar population to ours was used. This calculator was chosen over the Intergrowth-21st standard as it has been shown to detect a greater proportion of small for gestational age fetuses in our population.[30] Women with hypertensive disorders of pregnancy were divided into two groups: those that had a small for gestational age neonate (HDP+SGA) and those with an appropriately grown neonate (HDP-only). According to the modified ISSHP criteria, those in the HDP+SGA group had

preeclampsia whilst those in the HDP-only group had either gestational hypertension or preeclampsia. All women with hypertensive disorders of pregnancy were managed as per the hospital protocol, which is based on the National Institute for Clinical Excellence (NICE) guidance.[31] At less than 34 weeks' gestation, delivery was indicated after a course of steroids if the mother developed severe refractory hypertension or if there was evidence of severe maternal or fetal compromise (systolic blood pressure ≥160mmHg or diastolic blood pressure ≥110mmHg not controlled by first and second line treatment; pulmonary oedema or cyanosis, platelet count ≤100, transaminases >2 x the normal limit, evidence of cerebral disturbance, oliguria, fetal growth restriction with Dopplers indicating delivery or abnormal computerised cardiotocography. Between 34^{+0}–36^{+6} weeks' gestation, delivery was indicated after a course of steroids if the mother developed preeclampsia and there was evidence of maternal or fetal compromise. After 37 weeks' gestation, delivery was usually indicated within 24-48 hours if the mother developed preeclampsia. For women with gestational hypertension, delivery was planned on an individual basis by a senior clinician. The control group had no pre-existing cardiac or metabolic disease. Those control pregnancies that subsequently developed hypertension or resulted in the birth of a small for gestational age neonate were excluded from the analysis. Patients in the control group were recruited whilst attending an antenatal visit or a third trimester ultrasound assessment (placental localisation, presentation, measuring small or large for dates). Written consent was obtained from all study participants and research ethics committee approval (12/LO/0810) was obtained prior to performing the study investigations. There was no specific funding for this study, however, HP was supported by a grant from the National Institute for Health Research (NIHR) Collaboration for Leadership in Applied Health Research and Care South London at King's College Hospital NHS Foundation Trust.

Research Investigations

Haemodynamic assessment was performed at diagnosis of gestational hypertension, and where possible, prior to the commencement of any antihypertensive medication. The proportion of patients on medication at the time of treatment and the kind of treatment was recorded. All hemodynamic assessments were performed in the same room, under

standardised conditions for the entire cohort. Maternal height (m), weight (kg) and brachial blood pressure (mmHg) were obtained prior to hemodynamic assessment. Blood pressure was obtained using an upper arm automatic blood pressure monitor (Microlife®, Microlife AG Swiss Corporation, Switzerland), in a semi-recumbent position and using an appropriately sized cuff. Mean arterial pressure was calculated as (2x diastolic blood pressure + systolic blood pressure)/3. Hemodynamic assessment was performed using the USCOM-1A® device (Figure S1) with the patient in a semi-recumbent position. The probe was placed at the patients' suprasternal notch and moved in three dimensions to obtain an optimal waveform, representing the velocity of blood at the left ventricular outflow tract. The Doppler profile was displayed on the device's computer screen in real-time and once a satisfactory profile was obtained, the recording was stopped, and the quality of the recording was reviewed. Each Doppler profile represents the velocity time integral which equates to the distance travelled by a column of blood during each cardiac cycle. The Doppler acquisitions used for analysis had a minimum of two consecutive Doppler profiles (cardiac cycles). Acquisitions with the least amount of interference and the best quality velocity time integrals, deemed by the study investigators to best represent transaortic blood flow, were used for measurements. USCOM 1A® uses an in-built anthropometric algorithm to calculate the diameter of the aortic root based on the patient's height. By multiplying the velocity of blood being ejected by the known cross-sectional area of the aortic valve, the volume of blood being ejected can be calculated, giving the stroke volume. By calculating the interval between successive ejections of blood, the heart rate can be calculated and by multiplying the stroke volume by the heart rate, the cardiac output can be obtained. By entering the patient's mean arterial pressure, the device will also calculate systemic vascular resistance (systemic vascular resistance = mean arterial pressure/cardiac output). We chose to measure cardiac output and systemic vascular resistance because of their direct influence on blood pressure. All measurements were performed by trained investigators. Repeatability and reproducibility studies of USCOM 1A® have shown excellent agreement between trained operators, including in pregnant women.[32–34] Cardiac output, stroke volume and systemic vascular resistance were converted into multiples of the median (MoM) to adjust for gestational age as well as maternal height, maternal weight and maternal age. These characteristics have been shown to influence maternal hemodynamic indices in a cohort of 600

pregnancies used to derive device-specific reference ranges using the USCOM 1A® device .[35]

Statistical Analysis

A sample size calculation was performed based on a study of a preterm preeclampsia pregnancies and control pregnancies using echocardiography which found a cardiac index difference of 0.6 L/min/m^2 (Preeclampsia group 2.6 L/min/m^2 (2-1-3.1), Control group 3.2 L/min/m^2 (2.7-3.7).[7] Standard deviation was calculated from the confidence intervals and a formula for difference in means was used to obtain sample size. We calculated that 94 patients would be required in the larger group to detect a difference between the groups at 90% power with a type 1 error of 0.05, based on a 2:1 ratio. Data distribution was assessed using the Shapiro-Wilk test as well as graphical methods. Categorical data were presented as number and percentage, while continuous data were presented as the median and interquartile range (IQR). Statistical analysis was performed using the Chi-square test, Mann-Whitney test or t-test. Spearman's rank correlation was used to explore the relationship between hemodynamic indices and birthweight. Sub-group analysis was performed according to whether the hypertensive women were receiving antihypertensive therapy or not in order to explore any potential confounding effect on the hemodynamic variables. A direct comparison between treated and untreated patients was also performed. A p value <0.05 was considered statistically significant. Statistical software (SPSS 25.0; SPSS Inc., Chicago, IL) was used to conduct the analysis.

Patient Involvement and Core Outcome Sets

Patients were not involved in the design or undertaking of this study. At the time of study inception, no core outcome set was in available for preeclampsia and this study does not evaluate a treatment or intervention.

RESULTS

We recruited 322 women with hypertensive disorders of pregnancy and 452 controls to the study. Six of the hypertensive cases were excluded due to loss to follow-up and fifty-one of the control cases were excluded because of an adverse pregnancy outcome. The

flow of participants is shown in Figure S2. The maternal demographic and pregnancy details are shown in Table 1. Women in both HDP groups were heavier and shorter than controls and also delivered smaller babies at an earlier gestation. There were significantly more women of Afro Caribbean and Asian ethnicity in the HDP+SGA group compared to the HDP-only and control groups. There was no significant difference in the proportion of patients taking antihypertensive medication in the HDP+SGA and HDP- only groups at the time of assessment [83/114 (31%) vs 163/202 (39%), p=0.105]. There was no difference in the haematocrit level between the HDP +SGA group and the HDP-only group (0.38 L/L(0.34-0.39) vs. 0.36L/L (0.35-0.38), p-0.632).

The hemodynamic differences between the two HDP groups and the control group are shown in Table 2 and Figure 1. Both HDP groups had a higher mean arterial pressure at the start of pregnancy and at recruitment compared to the control group. Women with HDP+SGA had significantly (all $p<0.001$) lower median heart rate (76bpm vs 85bpm), lower cardiac output (0.85MoM vs 0.98MoM), and higher systemic vascular resistance (1.4MoM vs 1.0MoM) and uterine artery pulsatility index (1.7MoM vs 1.0MoM) than controls. Women with HDP+SGA also had significantly (all $p<0.01$) lower heart rate (76bpm vs 83bpm) and cardiac output (0.85MoM vs 0.97MoM), and higher systemic vascular resistance (1.4MoM vs 1.2MoM) and uterine artery pulsatility index (1.7MoM vs 1.1MoM) compared to women with HDP-only. Women with HDP-only had significantly lower median heart rate (83bpm vs 85bpm, $p=0.028$) and higher systemic vascular resistance (1.2MoM vs 1.0MoM, $p<0.001$) and uterine artery pulsatility index (1.1MoM vs 1.0MoM, $p<0.001$) than controls. There was no significant difference in mean arterial pressure (110 mmHg vs 107 mmHg, $p=0.445$) or stroke volume (1.0MoM vs 0.99MoM, $p=0.411$) between the two HDP groups at presentation. Birthweight centile was positively correlated with cardiac output MoM ($R_s=0.287$, $p<0.001$) and heart rate ($R_s=0.256$, $p<0.001$) and negatively correlated with systemic vascular resistance MoM ($R_s=0.313$, $p<0.001$).

Differences in maternal hemodynamic indices between the HDP+SGA and HDP-only groups persisted, even after excluding women taking antihypertensive treatment (Table 3). Women with HDP+SGA had significantly (all $p<0.001$) lower median heart rate

(77bpm vs 85bpm), lower cardiac output (0.84MoM vs 0.98MoM), and higher systemic vascular resistance (1.4MoM vs 1.0MoM) and uterine artery pulsatility index (1.7MoM vs 1.0MoM) than controls. Women with HDP+SGA also had significantly (all $p<0.05$) lower heart rate (77bpm vs 83bpm) and cardiac output (0.84MoM vs 0.99MoM), and higher systemic vascular resistance (1.4MoM vs 1.2MoM) and uterine artery pulsatility index (1.7MoM vs 1.1MoM) compared to women with HDP-only. When comparing women who were taking antihypertensive medication to those who were not, there were no significant differences in the maternal hemodynamic indices in the HDP+SGA group. In the HDP-only group, women who were on antihypertensive medication had significantly lower cardiac output MoM [0.90 (0.77-1.0) vs. 0.99 (0.87-1.1), $p=0.026$] and significantly higher systemic vascular resistance MoM [1.3 (1.1-1.6) vs. 1.2 (1.1-1.4), $p=0.036$] compared to women not on antihypertensive therapy (Table S1). On further analysis of the HDP+SGA group, there were no significant differences in the maternal hemodynamics of those women with fetuses with fetal growth restriction compared to those with small for gestational age alone (Table S2).

DISCUSSION

Main findings

Our study demonstrates that women with HDP+SGA present with lower cardiac output and higher systemic vascular resistance than women with HDP-only. Even HDP-only women exhibit lower heart rate and higher systemic vascular resistance compared to normal pregnancies. Stroke volume and mean arterial blood pressure were not significantly different between the two HDP groups indicating that maternal heart rate is the main determinant of lower cardiac output and higher systemic vascular resistance in HDP+SGA.

Strengths and limitations

The main strengths of our study are the prospective assessment of a large cohort of pregnancies with preeclampsia or gestational hypertension as well as control pregnancies. Furthermore, for the hemodynamic variables that could be affected by gestational age and maternal factors, we corrected using device-specific reference

ranges. One limitation of our study is that it is cross-sectional in nature, and whilst we can observe the trend of measurements across different gestational ages, we cannot report true longitudinal changes for each variable. Secondly, a minority of patients in this study were taking antihypertensive medication at the time of assessment. However, there was no difference in the proportion of patients between the two groups and sub-group analysis revealed that the reported findings persisted when patients taking antihypertensive medication were excluded. Finally, we cannot exclude the possibility of residual confounding affecting the study findings, but the inclusion of a relatively large number of patients and well-defined groups partially mitigate the magnitude of such effects.

Interpretation (in light of other evidence)

Previous studies of hemodynamic changes in preeclampsia have yielded conflicting results, with some authors describing preeclampsia as a high-output hyperdynamic state,[36–38] whilst others have described lower cardiac output with higher systemic vascular resistance.[7,39–41] These contrasting findings may be due to the heterogeneity of the population studied (with and without SGA) as well as the stage of the clinical disease at which the measurements were taken. This study shows that preeclampsia exhibits differences in haemodynamic profile depending on whether it is associated with a small fetus. Rang *et al.* undertook a longitudinal study of maternal hemodynamic indices and described lower cardiac output and higher systemic vascular resistance from preconception up to 32 weeks' gestation in women with HDP+SGA compared to HDP-only.[42] Our study confirms the latter findings and additionally shows that they persist until term. Ferrazzi *et al.* compared the same HDP groups (with and without SGA) and reported lower cardiac output and higher systemic vascular resistance in HDP+SGA. However, they found no significant difference in heart rate or stroke volume, presumably because their study was limited by smaller numbers and by not correcting hemodynamic indices for gestational age or maternal factors.[43] Tay *et al.* reported similar findings of a lower cardiac output and higher systemic vascular resistance in women with preeclampsia with fetal growth restriction, but higher cardiac output and lower systemic vascular resistance in women with preeclampsia alone compared to controls. This contrasting difference may be due to use of hemodynamic devices unvalidated in

pregnancy, lack of device-specific pregnancy reference ranges and because their HDP-only group consisted of just 13 patients, four of whom were taking antihypertensive medication.[38,44] The vast majority of hemodynamic studies have reported higher systemic vascular resistance in HDP consistent with a diagnosis of hypertension.

Our findings, along with those described by the studies above, support the theory that gestational hypertension and preeclampsia are a disease-continuum, with those women with a more severe clinical picture (HDP+SGA) having the lowest cardiac output and highest systemic vascular resistance. Those with less severe disease (HDP-only) have less impaired maternal hemodynamic function, but still demonstrate lower heart rate and systemic vascular resistance compared to controls. This pattern of relative maternal cardiac dysfunction occurs regardless of gestational age at onset, making it less conceivable that there are two different causes of preeclampsia. As in previous studies, we found that uterine artery pulsatility index is positively correlated with systemic vascular resistance and negatively correlated with cardiac output.[45,46] This measure of impendence at the uteroplacental interface has always been considered to reflect the failure of the physiological transformation of the spiral arteries[47,48] but it is perhaps more appropriate to consider the uteroplacental circulation and central maternal hemodynamics together. Spaanderman *et al.* found higher pre-pregnancy uterine artery pulsatility index in normotensive women with a history of preeclampsia who developed small for gestational age fetuses in the subsequent pregnancy.[49] This suggests that uterine and perhaps systemic impedance can be raised prior to the development of the placenta and may be a reflection of the underlying maternal cardiovascular health itself. Preconception studies of haemodynamics have also demonstrated lower cardiac output and higher systemic vascular resistance in pregnancies subsequently complicated by preeclampsia.[42,50]

Clinical and research implications

One limitation of the placental-cause theory of preeclampsia is that vascular and villous abnormalities are not seen in the majority of preeclampsia or gestational hypertension cases.[21,22,25,51,52] We have shown a spectrum of hemodynamic dysfunction across more severe to less severe preeclampsia and our results support the need for further work into

understanding maternal hemodynamic changes in pregnancy as well as the interaction between placental and central haemodynamics. Maintenance of a normal blood pressure is dependent on the balance between cardiac output and systemic vascular resistance.[53] In preeclampsia and gestational hypertension, systemic vascular resistance is increased with a relative deficiency in cardiac output, which appears, from our findings, to be due to a lower heart rate, rather than stroke volume. These changes may be caused by increased utero-placental resistance contributing to systemic vascular resistance and afterload. A lack of sympathetic response may contribute by failed elevation in heart rate and/or contractility to overcome afterload. Alternatively, if there is a pre-existing lower cardiac output and higher systemic vascular resistance, the maternal circulation will be working maximally in order to maintain uteroplacental perfusion. Where this is not sufficient, our study suggests that this will predispose to SGA and perhaps fetal growth restriction.

In normal pregnancy, heart rate should increase throughout gestation but in preeclampsia and gestational hypertension this does not happen to the same extent. Alternatively, it may be that the heart rate is decreased in preeclampsia and gestational hypertension in order to increase ventricular filling time, and subsequently maintain stroke volume. Monitoring changes in cardiac output and systemic vascular resistance after the initiation of antihypertensive therapy, could help optimise blood pressure control without impacting on uteroplacental perfusion and placental function.

Conclusion

The clinical severity of gestational hypertension and preeclampsia is reflected in underlying maternal hemodynamic function, with lower heart rate, cardiac output and higher systemic vascular resistance in more severe HDP+SGA. Central hemodynamic changes may play an important role in the pathogenesis of preeclampsia irrespective of the finding of fetal growth restriction.

ACKNOWLEDGMENTS

We would like to thank all doctors, midwives and sonographers who helped with patient recruitment. We would like to thank USCOM for the loan of the USCOM 1A® device for research purposes.

CONFLICT OF INTERESTS

The authors report no conflicts of interest. Completed disclosure of interest forms are available to view online as supporting information.

CONTRIBUTION TO AUTHORSHIP

AK and BT conceived the study. HP, JB and JG undertook patient recruitment, study investigations and data analysis. HP prepared the initial manuscript. All authors contributed to the writing of the manuscript and approved the final manuscript.

FUNDING

HP is supported by a grant from the National Institute for Health Research (NIHR) Collaboration for Leadership in Applied Health Research and Care South London at King's College Hospital NHS Foundation Trust. The views expressed are those of the author(s) and not necessarily those of the NHS, the NIHR or the Department of Health.

DETAILS OF ETHICS APPROVAL

Research ethics committee approval (12/LO/0810) was obtained from NRES Committee London-Stanmore on 25/7/2012.

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Table 1. Demographic and pregnancy characteristics of pregnant women with hypertension and small for gestational age, hypertension-only and normotensive control pregnancies. Data presented as median (inter-quartile range) or number (%).

	Group			**P value**		
	HDP+SGA (n=114)	**HDP-only (n=202)**	**Controls (n=401)**	**HDP+SGA vs Control**	**HDP-only vs Control**	**HDP+SGA vs HDP-only**
Maternal age (years)	31 (28-35)	33 (29-36)	32 (28-36)	0.185	0.473	0.085
Gestation at assessment (weeks)	34.0 (29.8-36.0)	36.4 (34.4-38.1)	36.0 (31.4-36.4)	**<0.001**	**<0.001**	**<0.001**
Maternal weight (kg)	78.8 (69.2-92.9)	88.2 (78.4-99.9)	75.7 (68.1-85.0)	**0.016**	**<0.001**	**<0.001**
Maternal height (cm)	160 (157-166)	165 (160-170)	165 (160-169)	**<0.001**	0.363	**<0.001**
Body mass index (kg/m^2)	30.5 (27.2-35.1)	32.0 (28.9-35.8)	28.1 (25.3-31.2)	**<0.001**	**<0.001**	0.054
Body Surface Area (m^2)	1.9 (1.8-2.0)	2.0 (1.9-2.2)	1.9 (1.8-2.0)	0.193	**<0.001**	**<0.001**
Smoking in pregnancy	4 (3.5)	4 (2.0)	22 (5.5)	0.395	**0.045**	0.406
Nulliparous	75 (65.8)	108 (53.5)	207 (51.6)	**0.007**	0.669	**0.033**
Ethnicity						
Caucasian	48 (42.1)	140 (69.3)	260 (64.8)		**<0.001**	
Afro Caribbean	26 (22.8)	25 (12.4)	48 (12.0)		**<0.010**	
Asian	35 (30.7)	28 (13.9)	69 (17.2)		**<0.001**	
Mixed/other	5 (4.4)	9 (4.5)	24 (6.0)		0.653	
Antihypertensive treatment at assessment	31 (27.2)	39 (19.3)	0 (0.0)	**-**	-	0.105
Haematocrit (L/L)	0.38 (0.34-0.39)	0.36 (0.35-0.38)	-	**-**	-	0.632
Birthweight centile	3 (1-6)	43 (23-74)	50 (25-74)	**<0.001**	0.353	**<0.001**
Gestation at delivery (weeks)	36.1 (32.8-38.0)	39.0 (37.6-39.9)	40.0 (39.0-40.9)	**<0.001**	**<0.001**	**<0.001**

Table 2. Hemodynamic indices of pregnant women with hypertension and small for gestational age, hypertension-only and normotensive control pregnancies. Data presented as median (interquartile range).

	Group			P Value		
	HDP+SGA (n=114)	**HDP-only (n=202)**	**Controls (n=401)**	**HDP+SGA vs Control**	**HDP-only vs Control**	**HDP+SGA vs HDP-only**
Booking Mean Arterial Pressure (mmHg)	87 (83-96)	92 (87-98)	82 (76-88)	**<0.001**	**<0.001**	**0.001**
Exam Mean Arterial Pressure (mmHg)	110 (101-115)	107 (101-113)	87 (81-92)	**<0.001**	**<0.001**	0.445
Heart Rate (bpm)	76 (70-85)	83 (72-91)	85 (76-95)	**<0.001**	**0.022**	**0.003**
Cardiac Output (L/min)	5.7 (4.9-6.8)	6.5 (5.6-7.5)	6.6 (5.8-7.5)	**<0.001**	0.374	**<0.001**
Stroke Volume (ml)	76.9 (61.0-88.6)	78.7 (66.2-92.5)	78.7 (67.4-89.2)	0.147	0.475	0.075
Systemic Vascular Resistance (dynes-sec-cm^5)	1519 (1288-1741)	1329 (1123-1550)	1061 (918-1210)	**<0.001**	**0.001**	**<0.001**
Cardiac Output MoM	0.85 (0.76-1.0)	0.97 (0.83-1.1)	0.98 (0.87-1.1)	**<0.001**	0.206	**<0.001**
Stroke Volume MoM	1.0 (0.85-1.1)	0.99 (0.87-1.2)	0.98 (0.87-1.1)	0.984	0.250	0.411
Systemic Vascular Resistance MoM	1.4 (1.2-1.6)	1.2 (1.1-1.5)	1.0 (0.89-1.2)	**<0.001**	**<0.001**	**<0.001**
Uterine Artery Mean Pulsatility Index MoM	1.7 (1.2-2.1)	1.1 (0.91-1.4)	1.0 (0.82-1.1)	**<0.001**	**<0.001**	**<0.001**

Table 3. Hemodynamic indices of pregnant women with hypertension and small for gestational age, hypertension-only and normotensive control pregnancies with women on antihypertensive medication excluded. Data presented as median (interquartile range).

	Group			P Value		
	HDP+SGA (n=83)	**HDP-only (n=163)**	**Controls (n=401)**	**HDP+SGA vs Control**	**HDP-only vs Control**	**HDP+SGA vs HDP-only**
Booking Mean Arterial Pressure (mmHg)	87 (81-95)	91 (87-98)	82 (76-88)	**<0.001**	**<0.001**	**<0.001**
Exam Mean Arterial Pressure (mmHg)	109 (100-113)	107 (102-113)	87 (81-92)	**<0.001**	**<0.001**	0.820
Heart Rate (bpm)	77 (70-87)	83 (71-94)	85 (76-95)	**<0.001**	**0.046**	**0.011**
Cardiac Output (L/min)	5.7 (5.0-6.6)	6.5 (5.7-7.6)	6.6 (5.8-7.5)	**<0.001**	0.589	**0.003**
Stroke Volume (ml)	76.9 (63.4-88.0)	79.0 (65.8-92.5)	78.7 (67.4-89.2)	0.189	0.303	0.076
Systemic Vascular Resistance (dynes-sec-cm^5)	1512 (1276-1741)	1325 (1098-1528)	1061 (918-1210)	**<0.001**	**<0.001**	**<0.001**
Cardiac Output MoM	0.84 (0.77-0.98)	0.99 (0.87-1.1)	0.98 (0.87-1.1)	**<0.001**	0.636	**<0.001**
Stroke Volume MoM	0.97 (0.84-1.1)	1.0 (0.87-1.2)	0.98 (0.87-1.1)	0.711	0.084	0.150
Systemic Vascular Resistance MoM	1.4 (1.2-1.6)	1.2 (1.1-1.4)	1.0 (0.89-1.2)	**<0.001**	**<0.001**	**<0.001**
Uterine Artery Mean Pulsatility Index MoM	1.7 (1.2-2.1)	1.1 (0.91-1.3)	1.0 (0.82-1.1)	**<0.001**	**0.001**	**<0.001**

Figure and table list

Figure 1. Differences in a) cardiac output multiple of the median (MoM), b) heart rate (bpm) and c) systemic vascular resistance MoM between the Hypertension with small for gestational age and Hypertension-only groups.

Table 1. Demographic and pregnancy characteristics of pregnant women with hypertension and small for gestational age, hypertension-only and normotensive control pregnancies.

Table 2. Hemodynamic indices of pregnant women with hypertension and small for gestational age, hypertension-only and normotensive control pregnancies.

Table 3. Hemodynamic indices of pregnant women with hypertension and small for gestational age compared to hypertension-only after excluding those who were receiving antihypertensive therapy. Data presented as median (inter-quartile range).

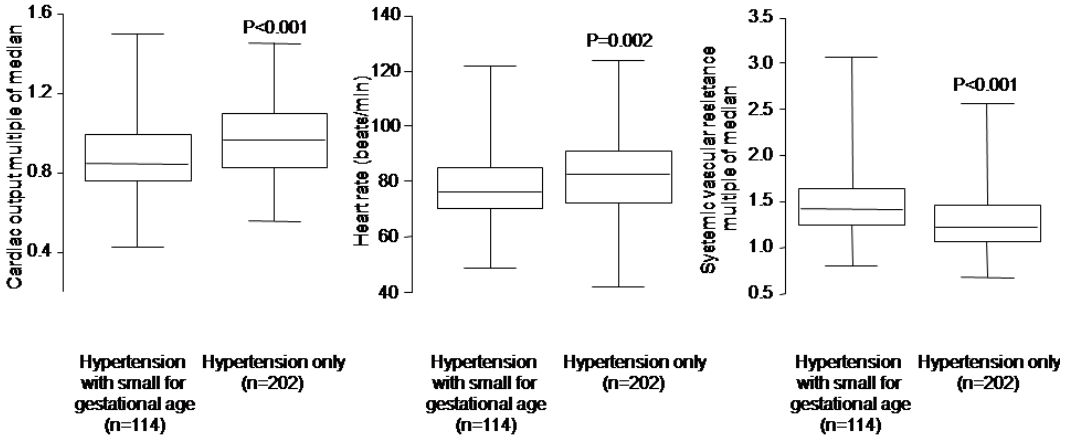
Online Supporting Material

Figure S1. The USCOM 1A® Machine

Figure S2. Study flow chart.

Table S1. Comparison of hemodynamic indices in pregnant women in the Hypertension with small for gestational age group and the Hypertension-only group, according to whether they were receiving antihypertensive therapy or not.

Table S2. Comparison of maternal hemodynamic indices in the Hypertension with small for gestational age group depending on whether there was prenatal evidence of fetal growth restriction or small for gestational age.



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