Ultrasound Obstet Gynecol 2024; **64**: 480–485
Published online in Wiley Online Library (wileyonlinelibrary.com). **DOI:** 10.1002/uog.27678

Maternal vascular indices at 36 weeks' gestation in pregnancy with small or growth-restricted fetus

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KEYWORDS: arterial stiffness; augmentation index; cardiac output; central blood pressure; heart rate; pulse-wave velocity; stroke volume; third-trimester screening; total peripheral resistance

CONTRIBUTION

What are the novel findings of this work?
At 36 weeks' gestation, pregnancies complicated by delivery of a growth-restricted (FGR) or small-for-gestational-age (SGA) neonate in the absence of hypertensive disorder have a distinct maternal hemodynamic profile compared with unaffected pregnancies, characterized by increased peripheral vascular resistance and reduced cardiac output. Central systolic and diastolic blood pressure are increased in FGR pregnancies compared with unaffected pregnancies, whereas aortic stiffness, assessed by pulse-wave velocity, and augmentation index do not differ between affected and unaffected pregnancies.

What are the clinical implications of this work?
SGA and FGR pregnancies exhibit deranged maternal hemodynamic responses compared with unaffected pregnancies. Pregnancies with FGR have increased central blood pressure and lower heart rate compared to those with SGA, but it remains unclear whether these differences are driven by the size of the fetus or pathological fetal growth.

ABSTRACT

Objective *To compare maternal vascular indices and hemodynamic parameters at 35–37 weeks' gestation in pregnancies complicated by delivery of a small-for-gestational-age (SGA) or growth-restricted (FGR) neonate.*

Methods *This was a prospective observational study of women with a singleton pregnancy attending for a routine hospital visit at 35 + 0 to 36 + 6 weeks' gestation. The visit included recording of maternal demographic characteristics, medical history, vascular indices and hemodynamic parameters, which were obtained using a non-invasive operator-independent device and included pulse-wave velocity, augmentation index, cardiac output, stroke volume, central systolic and diastolic blood pressure, total peripheral resistance and heart rate. Women with hypertensive disorders of pregnancy were excluded. SGA was diagnosed if birth weight was < 10th percentile. FGR was diagnosed if, in addition to birth weight < 10th percentile, at the 35–37-week scan, uterine artery or umbilical artery pulsatility index (PI) was > 95th percentile or fetal middle cerebral artery PI was < 5th percentile.*

Results *Among the 6413 women included in the study, there were 605 (9.4%) cases of SGA, 133 (2.1%) cases of FGR and 5675 (88.5%) cases that were unaffected by SGA or FGR. Women with SGA or FGR, compared to unaffected pregnancies, had increased peripheral vascular resistance and reduced cardiac output. Central systolic and diastolic blood pressure were increased in the FGR group compared with the unaffected group. Aortic stiffness, as assessed by pulse-wave velocity, and augmentation index did not differ between affected and unaffected pregnancies. In the FGR group, compared with the SGA group, central systolic and diastolic blood pressure were higher, whereas heart rate was lower.*

Conclusions *SGA and FGR pregnancies exhibit deranged maternal hemodynamic responses compared with unaffected pregnancies. Pregnancies with FGR have higher central blood pressure compared to those with SGA, but it remains unclear whether these differences are driven by the size of the fetus or pathological fetal growth.*

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Accepted: 23 April 2024

INTRODUCTION

Epidemiological studies have shown that women with pre-eclampsia (PE) have a 4-fold increased risk for hypertension and a 2-fold increased risk for adverse cardiovascular events within the first decade from the index pregnancy[1–3]. Pregnancies complicated by delivery of a small-for-gestational-age (SGA) neonate or those with fetal growth restriction (FGR), in the absence of hypertensive disorder, share similar features to pregnancies with PE, including impaired placentation and endothelial dysfunction. Women with these pregnancy complications are at increased risk of long-term development of cardiovascular disease[4–9].

In a previous screening study at 36 weeks' gestation, involving routine assessment of maternal vascular indices and hemodynamic parameters, we found that women who subsequently developed PE, compared to those who did not, had significantly higher central systolic and diastolic blood pressure, pulse-wave velocity (PWV), peripheral vascular resistance and augmentation index[10]. Other studies have also assessed maternal hemodynamics prior to development of PE and SGA, and have suggested that maternal uteroplacental malperfusion may precede placental dysfunction[11]. For instance, it was reported that pregnancies with PE and FGR are characterized by increased peripheral vascular resistance and reduced cardiac output, whereas, in pregnancies in which PE is not associated with FGR, there is pattern of hyperdynamic circulation with high cardiac output and low peripheral vascular resistance[12–15].

The objective of this study was to assess maternal vascular indices and hemodynamic parameters at 36 weeks' gestation in pregnancies complicated by SGA or FGR and those unaffected by either condition.

METHODS

Study design and participants

This was a prospective observational study of women attending for a routine hospital visit at 35 + 0 to 36 + 6 weeks' gestation at King's College Hospital, London, UK, between December 2021 and April 2022. In our hospital, all pregnant women undergo three routine ultrasound examinations during pregnancy, at around 12, 20 and 36 weeks' gestation. During the study period, the 36-week visit included: recording of maternal demographic characteristics and medical history; ultrasound examination for fetal anatomy and growth; color flow imaging of the left and right uterine arteries (UtA) by transabdominal ultrasound and measurement of mean pulsatility index (PI)[16]; color flow imaging of the umbilical artery (UA) and fetal middle cerebral artery (MCA) and measurement of UA-PI and MCA-PI, respectively[17]; and measurement of maternal vascular indices and hemodynamic parameters for the assessment of cardiac output, stroke volume, heart rate, total peripheral resistance, central systolic and diastolic blood pressure, mean PWV and augmentation index, using a non-invasive operator-independent device. Gestational age was determined by the measurement of fetal crown–rump length at 11–13 weeks or fetal head circumference at 19–24 weeks[18,19]. Women gave written informed consent to participate in the Advanced Cardiovascular Assessment in Pregnancy study (REC No. 18/NI/0013, IRAS ID: 237936), which was approved by the NHS Research Ethics Committee.

Patient characteristics that were recorded included maternal age, weight and height (measured at the time of screening), self-reported ethnicity (white, black, South Asian, East Asian or mixed), method of conception (natural or assisted by *in-vitro* fertilization or ovulation drugs), history of chronic hypertension, diabetes mellitus, systemic lupus erythematosus or antiphospholipid syndrome, family history of PE and obstetric history, including parity (parous or nulliparous if no previous pregnancy at ≥ 24 weeks).

The inclusion criteria for this study were singleton pregnancy delivering a non-malformed liveborn or stillborn infant. We excluded pregnancies with aneuploidy or major fetal abnormality and those that developed hypertensive disorders of pregnancy.

Maternal vascular indices and hemodynamic parameters

Participants were studied in the supine position after resting for approximately 5 min. Aortic stiffness was assessed by measuring carotid-to-femoral PWV. Measurements were performed using the Vicorder device (Skidmore Medical Ltd, Bristol, UK). This device measures simultaneous pressure waveforms by a volume displacement technique using blood-pressure cuffs placed around the neck to pick up the carotid pulse wave and the right upper thigh to measure the femoral pulse wave in real time over at least 10 heartbeats (Figure 1). Both cuffs are automatically inflated and the corresponding oscillometric signal is analyzed to accurately measure in real time the pulse time delay and consequent PWV. To calculate transit time, the Vicorder software automatically marks the steepest ascending part of the pulse wave (maximum systolic upstroke) and uses a definite timeframe to detect the nadir of the wave. The shift in time between the marked areas on the carotid and femoral pulse waves, which is the transit time, is detected by cross-correlation. The distance between the carotid and femoral pressure cuffs was measured using a tape. To account for differences in abdominal circumference associated with pregnancy and reduce variability and error in distance assessment, all measurements were performed from the suprasternal notch to the right shoulder and from there to the midpoint of the blood pressure cuff on the thigh. PWV was expressed in m/s.

The waveform of the brachial artery pulse was also obtained oscillometrically and analyzed. By applying a brachial-to-aortic generalized transfer function, the aortic waveform was generated. Analysis of the aortic waveform enables the calculation of parameters that describe characteristics of the arterial system, including central aortic

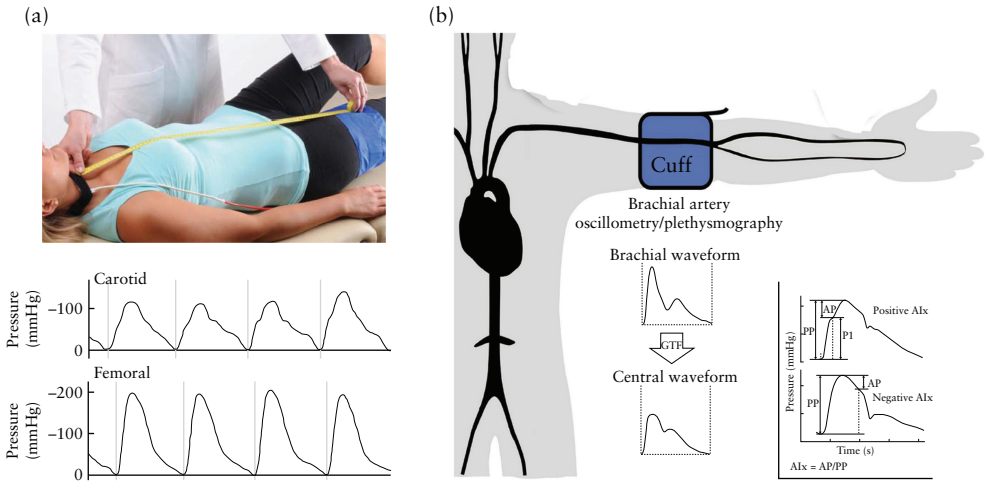

Figure 1 Schematic depiction of maternal vascular assessment. (a) Measurement of carotid-to-femoral pulse-wave velocity using oscillometric technique. (b) Aortic waveform was derived from brachial artery waveform using oscillometric technique by applying generalized transfer function (GTF). Augmentation index (AIx) was calculated as ratio of augmentation pressure (AP) to pulse pressure (PP) and expressed as percentage. AP was calculated as difference between first (P1) and second systolic pressure waveform.

systolic and diastolic blood pressure, cardiac output, stroke volume and total peripheral vascular resistance. Augmentation pressure was obtained and augmentation index was expressed as a percentage of central pulse pressure and adjusted for a heart rate of 75 bpm.

Outcome measures

Data on pregnancy outcome were collected from the hospital maternity records or the general medical practitioners of the women. Outcome measures were delivery with SGA or FGR. Diagnosis of SGA was made if the birth weight was $< 10^{th}$ percentile according to the Fetal Medicine Foundation (FMF) fetal and neonatal population weight charts[20] in the presence of UtA-PI $\leq 95^{th}$ percentile, UA-PI $\leq 95^{th}$ percentile and MCA-PI $\geq 5^{th}$ percentile at the 36-week scan. The diagnosis of FGR was made if the birth weight was $< 10^{th}$ percentile according to the FMF charts in the presence of UtA-PI $> 95^{th}$ percentile, UA-PI $> 95^{th}$ percentile and/or MCA-PI $< 5^{th}$ percentile at the 36-week scan.

Statistical analysis

Data were expressed as median (interquartile range (IQR)) for continuous variables and *n* (%) for categorical variables. Continuous variables were compared using the Mann–Whitney *U*-test, while the chi-square test or Fisher's exact test were used for categorical variables. Box-and-whiskers plots were produced to visually depict cardiovascular indices in unaffected, SGA and FGR pregnancies. The statistical software package R was used for statistical analysis[21].

RESULTS

We examined 6746 women, of whom 333 were excluded because they developed PE or gestational hypertension. Among the 6413 women included in the study, there were 605 (9.4%) cases of SGA, 133 (2.1%) cases of FGR and 5675 (88.5%) cases that were unaffected by SGA or FGR. Baseline demographic and clinical characteristics of the participants are shown in Table 1. The median maternal weight was lower in the SGA and FGR groups compared with the unaffected group, while the incidence of black ethnicity, chronic hypertension, smoking and nulliparity was higher in affected pregnancies.

The distributions of the maternal vascular indices and hemodynamic parameters in the SGA, FGR and unaffected groups are shown in Table 2. Women with SGA or FGR, compared to unaffected pregnancies, had increased peripheral vascular resistance and reduced cardiac output (Figure 2). Central systolic and diastolic blood pressure were increased in the FGR group compared with the unaffected group (Figure 2), whereas aortic stiffness, as assessed by PWV, and augmentation index did not differ between affected and unaffected pregnancies. In the FGR group, compared to the SGA group, central systolic and diastolic blood pressure were higher, whereas heart rate was lower (Figure 2).

DISCUSSION

Main findings

There are four main findings in this prospective non-interventional study of pregnancies attending for a routine assessment at 36 weeks' gestation. First, in non-hypertensive pregnancies delivering a SGA or FGR neonate, compared to unaffected pregnancies, peripheral vascular resistance was increased and cardiac output was reduced. Second, in FGR pregnancies, systolic and diastolic blood pressure were increased compared with unaffected pregnancies. Third, aortic stiffness assessed by PWV and augmentation index did not differ between groups. Fourth, in FGR pregnancies, compared with

Table 1 Maternal and pregnancy characteristics of study population ($n = 6413$)

Characteristic	*No SGA or FGR* (n = *5675*)	*SGA* (n = *605*)	*FGR* (n = *133*)
Maternal age (years)	33.9 (30.7–36.9)	33.1 (29.6–36.5)*	34.0 (30.4–36.7)
Maternal weight (kg)	78.8 (71.0–89.0)	74.2 (65.8–83.9)*	73.6 (66.0–82.5)*
Maternal height (cm)	166 (161–170)	163 (160–168)*	164 (158–168)*
Maternal BMI (kg/m^2)	28.7 (26.0–32.3)	27.8 (24.8–31.5)*	27.7 (25.3–30.8)*
GA at screening (weeks)	35.6 (35.3–35.9)	35.6 (35.3–35.9)	35.6 (35.3–35.9)
Ethnicity			
White	4079 (71.9)	352 (58.2)*	81 (60.9)*
Black	848 (14.9)	121 (20.0)*	28 (21.1)
South Asian	399 (7.0)	82 (13.6)*	17 (12.8)
East Asian	119 (2.1)	23 (3.8)*	5 (3.8)
Mixed	230 (4.1)	27 (4.5)	2 (1.5)
Medical history			
Chronic hypertension	42 (0.7)	16 (2.6)*	5 (3.8)*
Diabetes mellitus Type 1	24 (0.4)	3 (0.5)	0 (0)
Diabetes mellitus Type 2	70 (1.2)	8 (1.3)	3 (2.3)
SLE/APS	17 (0.3)	4 (0.7)	0 (0)
Smoker	68 (1.2)	19 (3.1)*	5 (3.8)
Method of conception			
Natural	5224 (92.1)	570 (94.2)	124 (93.2)
In-vitro fertilization	418 (7.4)	34 (5.6)	9 (6.8)
Ovulation drugs	33 (0.6)	1 (0.2)	0 (0)
Parity			
Nulliparous	2713 (47.8)	361 (59.7)*	74 (55.6)
Parous, no previous PE or FGR	2682 (47.3)	183 (30.2)*	39 (29.3)*
Parous, previous FGR	195 (3.4)	56 (9.3)*	19 (14.3)*
Parous, previous PE	106 (1.9)	10 (1.7)	4 (3.0)
Interpregnancy interval (years)	2.5 (1.6–4.4)	2.6 (1.6–4.7)	3.4 (1.7–6.5)
GA at delivery (weeks)	39.7 (39.0–40.6)	39.3 (38.3–40.3)*	38.9 (37.4–39.9)*†
Birth weight (g)	3460 (3206–3730)	2730 (2530–2860)*	2655 (2420–2826)*†
Birth-weight percentile	53.9 (32.1–75.9)	4.9 (2.2–7.4)*	4.3 (1.6–7.3)*

Data are given as median (interquartile range) or *n* (%). Comparisons between outcome groups were by chi-square or Fisher's exact test for categorical variables and Mann–Whitney *U*-test for continuous variables. *P*-values were adjusted for multiple comparisons by Bonferroni correction. *Significant difference *vs* unaffected group. †Significant difference *vs* small-for-gestational-age (SGA) group. APS, anti-phospholipid syndrome; BMI, body mass index; FGR, fetal growth restriction; GA, gestational age; PE, pre-eclampsia; SLE, systemic lupus erythematosus.

Table 2 Maternal vascular indices and hemodynamic parameters in pregnancies delivering a small-for-gestational-age (SGA) neonate, those delivering a growth-restricted (FGR) neonate and unaffected pregnancies

Measurement	*No SGA or FGR* (n = *5675*)	*SGA* (n = *605*)	*FGR* (n = *133*)
Cardiac output (L/min)	6.9 (6.1–7.9)	6.8 (5.8–7.7)*	6.7 (5.9–7.5)
Stroke volume (mL/beat)	78 (68–88)	78 (67–90)	80 (72–92)*
Total peripheral resistance (mmHg/mL/min)	0.75 (0.66–0.86)	0.79 (0.68–0.90)*	0.79 (0.71–0.96)*
Central systolic blood pressure (mmHg)	114 (107–121)	114 (107–122)	117 (109–125)*†
Central diastolic blood pressure (mmHg)	63 (59–68)	64 (60–68)	66 (61–70)*†
Pulse-wave velocity (m/s)	8.2 (7.5–9.1)	8.3 (7.6–9.1)	8.4 (7.4–9.1)
AIx@75 (%)	24.7 (14.6–34.7)	24.8 (13.6–36.2)	22.7 (12.9–32.4)
Heart rate (bpm)	90 (81–99)	88 (77–97)*	80 (74–90)*†

Data are given as median (interquartile range). Comparison between outcome groups was by Mann–Whitney *U*-test. *P*-values were adjusted for multiple comparisons by Bonferroni correction. *Significant difference *vs* unaffected group. †Significant difference *vs* SGA group. AIx@75, augmentation index adjusted for heart rate of 75 bpm.

SGA pregnancies, there was an accentuated maternal hemodynamic response, with higher central blood pressure and lower heart rate. However, it remains unclear whether these differences are driven by the size of the fetus or pathological fetal growth.

Interpretation of findings and comparison with literature

During normal pregnancy, there is a close interaction between placental development and maternal systemic adaptation. Maternal cardiac output increases to accommodate the increase in volume loading, whereas systemic vascular resistance drops[22]. Our group has demonstrated previously in uncomplicated pregnancies that there is a linear relationship between birth weight, cardiac output and peripheral vascular resistance, such that the lower the birth weight, the lower the cardiac output and the higher the peripheral vascular resistance[23]. However, in the presence of pregnancy complications, this response can be exaggerated. For instance, FGR and SGA in normotensive pregnancy have been associated

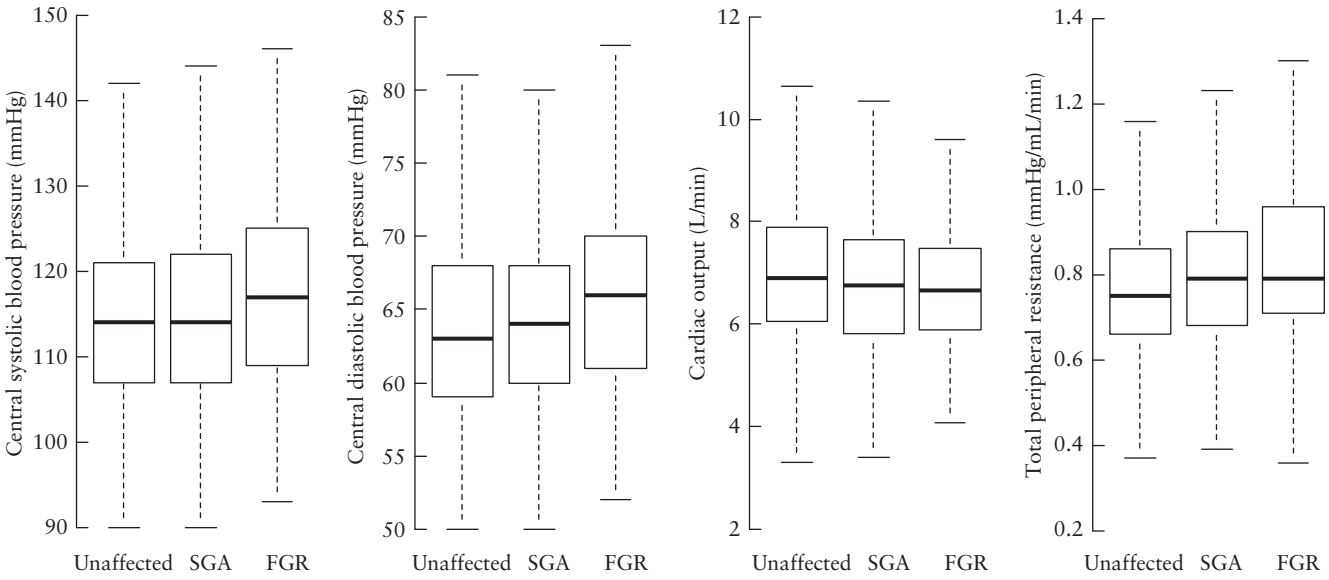

Figure 2 Box-and-whiskers plots showing maternal cardiovascular indices measured at 36 weeks' gestation in unaffected pregnancies, pregnancies delivering a small-for-gestational-age (SGA) neonate and those delivering a growth-restricted (FGR) neonate. Boxes show median and interquartile range and whiskers are range.

with lower cardiac output and higher mean arterial blood pressure and systemic vascular resistance[24,25]. This finding was also confirmed in pregnancies complicated by PE. More than a decade ago, Valensise *et al.*[15] reported two different phenotypes in women developing PE: low cardiac output and high peripheral vascular resistance or high cardiac output and low peripheral vascular resistance. This was later shown to be attributable not purely to gestational age at development of PE, but to the presence or absence of FGR. In this large prospective cohort in the third trimester, we confirmed that maternal hemodynamics differ in FGR and SGA pregnancies compared with unaffected cases; peripheral vascular resistance was increased, whereas cardiac output was reduced. In the FGR group, central blood pressure was higher compared with the SGA group, but it remains unclear whether deranged maternal hemodynamics are the cause or the consequence of reduced fetal size.

It is therefore possible that placental dysfunction could be the primary cause of maternal hemodynamic changes, considering that increased UtA-PI contributes to higher maternal peripheral vascular resistance and the increase in afterload reduces maternal cardiac output[20]. Alternatively, low maternal cardiac output/high peripheral vascular resistance could be responsible for reduced placental perfusion[26]. This enigma is difficult to resolve. First, histopathological studies in late FGR demonstrate failure of the physiological transformation of maternal spiral arteries as well as delayed villous maturation[27], which supports some degree of placental dysfunction. On the other hand, maternal hemodynamic responses in SGA pregnancies follow the same pattern as those in FGR pregnancies, and in the former case, there is no placental dysfunction. This suggests that the status of low cardiac output/high peripheral vascular resistance is less likely to be responsible for placental dysfunction in FGR.

Peripheral vascular resistance represents the resistance to blood flow that occurs in blood vessels. This may involve structural changes in the vessels or aortic remodeling, as well as hemodynamic adaptations with peripheral vasoconstriction or autonomic dysregulation[28]. In the current study, we used well-established techniques which have been used to assess aortic stiffness and, outside pregnancy, are considered as useful markers to predict cardiovascular risk. We demonstrated that both aortic PWV and augmentation index were comparable between affected and unaffected pregnancies. These findings would argue against significant vascular structural dysfunction in these women.

However, before structural lesions develop, impaired endothelial responses can be observed in the early course of atherosclerosis[29]. For instance, it is well established that placental dysfunction is associated with endothelial dysfunction and that this can affect the extent to which the autonomic nervous system regulates vascular tone by vasoactive factors[30]. In the current study, consistent with previous reports, we demonstrated that maternal heart rate is lower in SGA and FGR pregnancies, and this mostly accounts for the reduction in cardiac output[31]. Whether this represents a dysregulation of the sympathetic nervous system in these women remains to be established.

Implications for clinical practice and research

The findings of this large screening study confirm the close interrelationship between maternal hemodynamic responses and placental disorders. In addition, they demonstrate that women with late FGR and SGA have preserved aortic structure, as assessed by aortic PWV and augmentation index. It is therefore possible that unmeasured vasoactive factors produced in the circulation can influence the extent to which the autonomic nervous

system affects vascular tone and modifies maternal peripheral vascular resistance and cardiac output. In addition, it remains unclear whether the maternal hemodynamic changes observed are physiological responses to reduced fetal size.

Strengths and limitations

This study documented central hemodynamics and aortic stiffness in the largest reported cohort of unselected pregnant women of diverse ethnic background at 35–37 weeks' gestation. We used established non-invasive and reproducible techniques to assess maternal vascular indices, which have been shown to offer insight into future cardiovascular risk in the general population, and assessed their value in pregnancies complicated by SGA or FGR in the absence of hypertensive disorders of pregnancy.

A limitation of the study is that our methodology does not allow for conclusions to be drawn as to whether there is pre-existing vasculopathy or maladaptive vascular changes during pregnancy in women who deliver a SGA or FGR neonate. Moreover, although oscillometric methods have been validated against invasive measurements in adults, different elastic properties of the arterial tree during pregnancy may influence the calculation of the transfer function, and this requires further validation.

Conclusions

At 35–37 weeks' gestation, women who subsequently deliver a FGR neonate, compared with unaffected pregnancies, have increased central systolic and diastolic blood pressure and dysregulated hemodynamic responses. Pregnancies with SGA or FGR exhibit increased peripheral vascular resistance and reduced cardiac output, which is mostly driven by a reduction in heart rate. In addition, aortic stiffness is comparable between affected and unaffected pregnancies. Pregnancies with FGR have increased central blood pressure and lower heart rate compared to those with SGA, but it remains unclear whether these differences are driven by the size of the fetus or pathological fetal growth.

ACKNOWLEDGMENT

This study was supported by a grant from the Fetal Medicine Foundation (charity no.: 1037116). This body had no involvement in the study design, in the collection, analysis and interpretation of data, in the writing of the report or in the decision to submit the article for publication.

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