Are maternal hemodynamic indices markers of fetal growth restriction in pregnancies with a small-for-gestational-age fetus?

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CONTRIBUTION

What does this work add to what is already known?

Pregnancies complicated by fetal growth restriction present with worse maternal hemodynamic function whilst pregnancies with a small for gestational age neonate, without evidence of fetal growth restriction, have normal maternal hemodynamic function.

What are the clinical implications of this work?

Maternal hemodynamic indices may be of value in distinguishing fetal growth restriction from small for gestational age pregnancies.

ABSTRACT

Objective: Pregnancies complicated by fetal growth restriction (FGR) have worse outcomes than pregnancies with a small for gestational age (SGA) fetus. There is increasing evidence of a maternal cardiovascular role in the pathophysiology. We aimed to compare the maternal hemodynamic indices (cardiac output and systemic vascular resistance) in pregnancies complicated by FGR and pregnancies with an SGA fetus using a non-invasive device (USCOM-1A®).

Methods: This was a prospective study of normotensive pregnancies complicated by FGR (defined as pregnancies with a birthweight <3rd centile or with Doppler evidence of impaired placental-fetal blood flow), pregnancies with an SGA fetus (defined as pregnancies with a birthweight <10th centile) and control pregnancies (defined as having an appropriately-grown fetus). Assessment of the maternal hemodynamics was performed using a non-invasive device (USCOM-1A®). Hemodynamic variables that are affected by gestational age and maternal characteristics were corrected for using device-specific reference ranges. Statistical analysis was performed using the Chi-square test and the Mann-Whitney test.

Results: A total of 102 FGR, 64 SGA and 401 control pregnancies at 28-41 weeks' gestation were included in the analysis. Women with pregnancies complicated by FGR and pregnancies with an SGA fetus were shorter and weighed less than controls. The FGR group had significantly lower median heart rate (80bpm vs 85bpm, p=0.001), lower cardiac output (0.91MoM vs 0.98MoM, p=0.003), higher

mean arterial pressure (90mmHg vs 87 mmHg, p= 0.040), higher systemic vascular resistance (1.2MoM vs 1.0MoM, p<0.001) and higher uterine artery pulsatility index (1.1MoM vs 0.96MoM, p<0.001) compared to controls, but there was no significant difference in stroke volume (p=0.647). The FGR group had a significantly lower median heart rate (80bpm vs 87bpm, p=0.022), higher mean arterial pressure (90mmHg vs 85 mmHg, p=0.025), higher systemic vascular resistance (1.2MoM vs 1.0MoM, p=0.002) and higher uterine artery pulsatility index (1.1MoM vs 0.98MoM, p=0.005) compared to the SGA group, but there was no significant difference in cardiac output (0.91MoM vs 0,96MoM, p=0.092) or stroke volume (1.0MoM vs 1.0MoM, p=0.806). There were no significant differences in maternal hemodynamic indices between the SGA and control groups.

Conclusion: Pregnancies complicated by FGR present with worse maternal hemodynamic function, as evidenced by lower heart rate and cardiac output as well as higher mean arterial pressure, systemic vascular resistance and uterine artery resistance. Pregnancies resulting in a SGA neonate, without evidence of FGR have normal maternal hemodynamic function. Maternal hemodynamic indices may be of value in distinguishing FGR from SGA pregnancies.

INTRODUCTION

Small for gestational age (SGA) pregnancies, and in particular those with fetal growth restriction (FGR), are associated with an increased risk of adverse fetal, neonatal and longer term childhood outcomes.[1–11] Fetal growth restriction is defined as a fetus with an estimated fetal weight less than the <3rd centile or a pregnancy with impaired placental-fetal blood flow, defined as a uterine or umbilical artery pulsatility index >95th centile or absent end-diastolic flow in the umbilical artery (<32 weeks gestation) or redistribution of cerebral blood flow, defined as a cerebral-placental ratio <5th centile (≥32 weeks gestation).[10,12] Conversely, many SGA neonates without these Doppler changes can be considered constitutionally small but healthy and likely to have reached their full growth potential. They are at a lower risk of adverse outcomes.[13] The cause of FGR is not fully understood but incomplete physiological transformation of the spiral arteries and the presence of placental bed vascular lesions, including thrombosis, infarction, villitis and atherosis, have been implicated.[14–22] Uterine artery pulsatility index is independently associated with

adverse perinatal outcome, regardless of fetal size or fetal umbilical and middle cerebral artery Doppler abnormalities.[23] Darcy's Law describes the relationship between pressure, flow and resistance; when uterine artery resistance is increased, flow will be decreased, resulting in reduced blood flow to the placenta. This reduction in flow (and perfusion) may result in FGR. We, and others, have demonstrated that uterine artery pulsatility index correlates positively with maternal systemic vascular resistance (SVR) and negatively with maternal cardiac output (CO).[24,25] This suggests that localised resistance at the placenta (and subsequent FGR) may be related to underlying differences in maternal hemodynamic function. Previous studies have described lower CO and higher SVR in pregnancies affected by both SGA and FGR, using both echocardiography and non-invasive cardiac output monitors.[26–31] However, inconsistencies in the methodology and definitions used, as well as the inclusion of patients with hypertension, have made the results harder to interpret.

The aim of this study was to investigate maternal hemodynamic indices (CO, stroke volume (SV) and SVR) in normotensive pregnancies complicated by FGR or SGA without evidence of FGR and in a cohort of control pregnancies.

MATERIALS AND METHODS

Study population and recruitment

This was a prospective case control study including pregnancies with SGA fetuses and uncomplicated pregnancies with a normally-grown fetus presenting to a tertiary referral hospital between January 2012 and May 2018. The inclusion criteria were singleton pregnancies with a viable fetus at 20 weeks' gestation or greater with SGA detected on antenatal ultrasound assessment and a birthweight below the 10th centile. The exclusion criteria were multiple pregnancies, pregnancies complicated by aneuploidy, genetic syndromes or major structural fetal abnormalities and women with a history of chronic hypertension, gestational hypertension or preeclampsia. The following definitions were used, as per the ISSHP 2014 criteria:[32]

- Chronic Hypertension: 'hypertension (≥140/90mmHg) that predates pregnancy or is present prior to 20 weeks' gestation.'
- Gestational Hypertension: 'de novo hypertension (≥140/90 mmHg) after 20 weeks' gestation.'
- Preeclampsia: ''de novo hypertension (≥140/90 mmHg) after 20 weeks' gestation with the coexistence of proteinuria, other maternal organ dysfunction or fetal growth restriction.'

Those SGA pregnancies that subsequently developed hypertension or resulted in the birth of an appropriate for gestational age neonate were excluded from the analysis. The SGA group were divided into those with and those without evidence of

FGR. Small for gestational age was defined antenatally as an estimated fetal weight below the 10th centile and at birth as a neonate with a birthweight below the 10th centile. We used a centile calculator derived from a study of 92,000 healthy neonates from a similar population to ours.[33] Fetal growth restriction was defined as per the Delphi Consensus agreement:[12]

- <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.
- ≥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.

The control group consisted of women with no evidence of an SGA fetus antenatally and who gave birth to an appropriately-grown neonate. They had no pre-existing cardiac or metabolic disease and were recruited whilst attending an antenatal visit or an 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.

Research investigations

Patients underwent a single hemodynamic investigation at the time of first diagnosis of SGA during the pregnancy. Control participants were recruited at any timepoint beyond 20 weeks of gestation in the pregnancy. Ultrasound assessment was performed on the same day. All hemodynamic assessments were performed in the same room, under standardised conditions for the entire cohort. Maternal height, weight and brachial blood pressure 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 (MAP) was calculated as 2 x diastolic blood pressure + systolic blood pressure /3. Maternal hemodynamics were assessed using the USCOM 1A® non-invasive device (Figure 1), while the uterine artery mean pulsatility index was recorded using trans-abdominal ultrasound. USCOM 1A® utilises continuous-wave Doppler, with a non-imaging probe in the suprasternal notch to obtain velocity time integrals of transaortic blood flow at the left ventricular outflow tract. Using an internal anthropometric algorithm, which correlates the outflow tract diameter with the patient's height, USCOM 1A® multiplies the velocity time integral by the aortic root diameter to calculate SV. By measuring the time interval between each Doppler

profile, the heart rate (HR) can be calculated. Cardiac Output (CO = SV x HR) and SVR (SVR = MAP/CO) were calculated after inclusion of the maternal MAP.

Participants remained in a semi-recumbent position and a small amount of conducting gel was applied to their skin at the level of the suprasternal notch. The Doppler probe was applied and moved through three-dimensions to ensure that the velocity of blood was being measured at the left ventricular outflow tract and not in the more distal aorta. Each Doppler acquisition used for analysis had a minimum of two consecutive Doppler profiles (cardiac cycles) and these were assessed for quality by the study investigators. All hemodynamic measurements were performed by trained operators. USCOM 1A® has been in clinical use since 2001. The repeatability and reproducibility have been assessed in adult, paediatric and pregnant populations, demonstrating excellent agreement between operators with sufficient training.[34–36] USCOM 1A® has been validated against pulmonary artery catheterisation for measurement of cardiac output in adult populations demonstrating good agreement,[37,38] however it has not been validated against invasive methods during pregnancy. Comparison to echocardiography demonstrated good agreement in the third trimester however it is clear that measurements from different devices are not interchangeable.[36] Our group has therefore previously published device-specific (USCOM 1A®) reference ranges of the maternal hemodynamic indices in pregnancy, using a cohort of 600 uncomplicated pregnancies.[39] Once measured, CO (L/min), SV (ml) and SVR (dynes-sec-cm^5) measurements were converted into multiples of

the median (MoM) based on the expected values of this reference range. This calculation adjusted for gestational age as well as maternal height, maternal weight, maternal age and maternal smoking status because these characteristics were found to have significant correlation with maternal hemodynamic indices.[39]

Ultrasound examination was performed by experienced practitioners. Fetal biometry and Doppler measurements were undertaken and estimated fetal weight was calculated by the Hadlock formula.[40] Uterine artery pulsatility index was recorded using a standardised technique; the left and right uterine arteries were identified at the level of the cross-over of the external iliac artery using colour Doppler. Pulsed-wave Doppler was used to measure pulsatility index over three consecutive waveforms. The mean of the left and right pulsatility index was calculated and subsequently converted into MoM to adjust for gestational age in weeks.[41]

Outcomes

The primary outcomes were maternal hemodynamic indices [HR (bpm), MAP (mmHg), SV (mls), CO (L/min), SVR (dynes-sec-cm^5) and uterine artery pulsatility index]. Data on the characteristics of participants, gestational age at delivery and birthweight were also collected.

Statistical Analysis

The sample size estimation was based on echocardiographic measurements of cardiac output in women with pregnancies complicated by fetal growth restriction and

those resulting in small for gestational age fetuses, which demonstrated a difference of 1.4L/min (Fetal growth restriction group = 4.7L/min (4.4-5.1), Small for gestational age group = 6.1L/min (5.6-6.7).[27] The standard deviation was calculated from the confidence intervals and a formula for difference in means was used to acquire the sample size. We calculated that the enrolment of 62 patients into each group would show a difference of half a standard deviation at 80% power and at a significance level of 0.05. 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 and Mann-Whitney tests. Spearman's rank correlation was used to explore the relationship between hemodynamic indices and birthweight. A p value <0.05 was considered statistically significant. Statistical software (SPSS 25.0; SPSS Inc., Chicago, IL) was used to conduct the analysis.

RESULTS

Demographic and Pregnancy Characteristics

We recruited 208 women with suspected SGA fetuses to this study. Thirty-two were excluded from the analysis (31 had a birthweight above the 10th centile and 11 developed preeclampsia) leaving 102 with a final diagnosis of FGR and 64 with a diagnosis of SGA. The control group included 401 women. The demographic and pregnancy details are displayed in Table 1. Women with FGR were significantly shorter (161cm vs 165cm, p<0.001) and lighter (71.9kg vs 75.7kg, p=0.002) than the control group. Women with SGA were also significantly shorter (161cm vs 165cm, p=0.002) and lighter (69.4kg vs 75.7kg, p=0.001) than the control group. There were no significant differences in the maternal height or weight between the FGR and SGA groups. The FGR group had a significantly (all p<0.001) lower median birthweight centile (2 vs 7) and gave birth at an earlier median gestation (38.3 weeks vs 39.9 weeks) than the SGA group. There was a greater proportion of women of Asian ethnicity in both the FGR group (38.2%) and the SGA group (31.3%) compared to the control group (17.2%) (p<0.001 and p=0.008, respectively).

Hemodynamic and Ultrasound Investigations

The FGR group had a significantly lower median HR (80bpm vs 85bpm, p=0.001), a lower CO (0.91MoM vs 0.98MoM, p=0.003), a higher MAP (90mmHg vs 87 mmHg, p=0.040) a higher SVR (1.2MoM vs 1.0MoM, p<0.001) and a higher uterine artery

pulsatility index (1.1MoM vs 0.96MoM, p<0.001) compared to the control group (Table 2 and Figure 2). There was no significant difference in SV (1.0MoM vs 0.98MoM, p=0.647) between the FGR and control pregnancy groups. The FGR group had a significantly lower median HR (80bpm vs 87bpm, p=0.022), a higher MAP (90mmHg vs 85 mmHg, p=0.025), a higher SVR (1.2MoM vs 1.0MoM, p=0.002) and a higher uterine artery pulsatility index (1.1MoM vs 0.98MoM, p=0.005) compared to the SGA group. There was no significant difference in CO (0.91MoM vs 0.96MoM, p=0.092) or SV (1.0MoM vs 1.0MoM, p=0.806) between the FGR and SGA groups. There were no significant differences in the maternal hemodynamic indices between the SGA and control groups (CO = 0.96MoM vs 0.98MoM, p=0.512, SVR = 1.0MoM vs 1.0MoM, p= 0.814).

Birthweight centile was positively correlated with CO MoM (R_s=0.159, p=0.041) and negatively correlated with SVR MoM (R_s=-0.223, p=0.004) and uterine artery pulsatility index (R_s=-0.246, p=0.002). The correlation between birthweight centile and HR (R_s=0.144, p=0.065), SV (R_s=0.041, p=0.602) and MAP (R_s=-0.146, p=0.063) was not statistically significant.

DISCUSSION

Summary of the main study findings

Pregnancies complicated by FGR present with worse maternal hemodynamic function, as evidenced by lower HR and CO as well as higher MAP, SVR and uterine artery resistance, when compared to pregnancies with an SGA fetus or healthy control pregnancies. Stroke volume is similar in the pregnancies complicated by FGR to the pregnancies with an SGA fetus or healthy control pregnancies, suggesting that the observed difference in maternal CO is a consequence of lower maternal HR. There were no significant differences in the maternal hemodynamic indices in the pregnancies with an SGA fetus compared to the healthy control pregnancies.

Interpretation of study findings and comparison with the existing literature

To date, this is one of the largest studies of normotensive pregnancies complicated by FGR and pregnancies with an SGA fetus to describe maternal hemodynamic function using a non-invasive cardiovascular device. Roberts *et al.* compared maternal hemodynamic function in 14 patients with FGR at presentation, 53 patients with SGA only and 19 SGA pregnancies that subsequently developed FGR. They did not find any significant differences in maternal HR, SV or CO between the groups. Consistent with our findings, they reported significantly higher MAP and SVR in the FGR group at presentation. When they compared the pregnancies complicated by

FGR (defined as a birthweight <3rd centile) to those with a birthweight >3rd centile, they reported significantly lower maternal HR, SV, CO and higher SVR in the FGR pregnancies.[31] Stott *et al*. described longitudinal hemodynamic indices in pregnant women with, or at high-risk of hypertension and reported significantly lower CO and SV with higher SVR in early pregnancy, predating the development of SGA (n=16).[30] They also noted that women in the SGA group had a higher HR in early pregnancy, but that this did not increase with advancing gestation, as seen in healthy controls. In a small study using echocardiography, Vasapollo *et al.* described significantly lower cardiac output and higher systemic vascular resistance in normotensive pregnancies that were subsequently complicated by FGR compared to those complicated by SGA. In their study, the lower cardiac output was a result of both a lower heart rate and lower stroke volume. They did not include a control group, so it is unclear if the SGA cohort had similar hemodynamic measurements to healthy pregnant women, as found in our current study.[42] Other echocardiographic findings that have been described in FGR include impaired myocardial relaxation and diastolic dysfunction.[43]

Clinical and research implications

Our findings demonstrate a high resistance maternal circulation in the pregnancies complicated by FGR, even in the absence of maternal hypertension. The hemodynamic balance between CO and SVR is dependent on Darcy's Law of flow, pressure and resistance and Bernoulli's theory of the circulation. Flow (CO) is dependent on the pressure difference between two points (MAP – central venous

pressure) divided by resistance (SVR). Bernoulli added that pressure, gravitational and kinetic energy also influence flow. The resistance of the systemic circulation is located mainly in terminal arteries and arterioles where the pressure difference is greatest. The addition of the utero-placental vascular bed during pregnancy contributes to the systemic resistance. If this occurs where SVR is already higher, the effect will be compounded because resistance in series (end-to-end) is summative. Furthermore, vessels with resistance regulate local blood flow and if resistance is doubled, conductance will be halved, reducing the blood flow. This theory of hydraulics equates to the finding of raised uterine artery resistance in FGR (likely secondary to reduced placental flow). The fact that SVR is also raised is reflective of the entire circulation and helps to explain the association between hypertension and FGR. Furthermore, the fact that these differences are evident pre-conception and in early pregnancy also supports this theory.[44–46] Maternal cardiovascular dysfunction has also been reported post-natally following pregnancies that were complicated by FGR indicating an underlying contribution of the cardiovascular system to the development of FGR, rather than a purely placental aetiology.[47]

A lower maternal HR with no difference in SV in those pregnancies complicated by FGR suggests that a relative tachycardia may be a physiological response to the increasing metabolic demands of pregnancy. An increased heart rate helps to maintain CO against SVR thus ensuring adequate placental blood flow. When this

fails to happen, FGR occurs. In SGA pregnancies without FGR, there were no differences in maternal hemodynamic indices compared to healthy control pregnancies, supporting the hypothesis that these may be 'normal small' neonates that have met their growth potential, hence the absence of fetal redistribution. Assessment of both the maternal and fetal circulations could become a better way of understanding, monitoring and managing SGA pregnancies. For example, iatrogenic prematurity of 'normal small' fetuses may be reduced or conversely, earlier intervention before maternal of fetal compromise ensues may be possible. The fact that differences in maternal hemodynamic indices can be demonstrated using a non-invasive device, which has reference ranges for pregnancy,[39] is likely to be important in terms of increasing research and clinical applicability.

Study limitations and strengths

The main strengths of our study are that it was prospective in nature and involved a large cohort compared to similar published studies. Secondly, no participants were hypertensive or taking antihypertensive medication at the time of assessment, excluding the effect of such medications on the maternal hemodynamic profile and of hypertension as a cause for differences in the hemodynamic function. Finally, we corrected the maternal hemodynamic indices for both the gestational age and for maternal factors using a device-specific reference range. One limitation of our study is that it is cross-sectional in nature and we did not observe longitudinal changes in

these pregnancies. We also cannot detect from these results if the differences seen pre-dated the pregnancy or not.

Conclusion

Pregnancies complicated by FGR present with a worse maternal hemodynamic profile, as evidenced by lower HR and CO as well as higher SVR and uterine artery resistance compared to pregnancies with an SGA fetus and to control pregnancies. Pregnancies with an SGA fetus, without evidence of FGR have normal hemodynamic function. Maternal HR and other hemodynamic indices may be of value in distinguishing SGA pregnancies with and without evidence of FGR.

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CONFLICT OF INTERESTS

The authors report no conflicts of interest.

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FIGURE LEGENDS

Figure 1: The USCOM 1A® Device

Figure 2: Differences in a) cardiac output multiple of median (MoM), b) heart rate (bpm) and c) systemic vascular resistance multiple of median (MoM) between the fetal growth restriction group, the small for gestational age group and the control group. The P-value represents the comparison to the control group.

Table 1. Demographic and pregnancy characteristics of the groups with fetal growth restriction, small for gestational age and control pregnancies.

	Group			P Value		
	Fetal Growth Restriction (n=102)	**Small for Gestational Age (n=64)**	**Control (n=401)**	**Fetal Growth Restriction vs Control**	**Small for Gestational Age vs Control**	**Fetal Growth Restriction vs Small for Gestational Age**
Maternal age (years)	31 (25-35)	31 (26-35)	32 (28-36)	**0.030**	**0.047**	0.964
Gestation at assessment (weeks)	35.3 (32.0-36.5)	36.0 (32.4-37.0)	36.0 (31.4-36.4)	0.796	0.321	0.314
Maternal weight (kg)	71.9 (63.0-82.2)	69.4 (62.5-79.4)	75.7 (68.1-74.1)	**0.002**	**0.001**	0.900
Maternal height (cm)	161 (156-165)	161 (156-167)	165 (160-169)	**<0.001**	**0.002**	0.893
Smoker in pregnancy*	5 (4.5)	5 (7.6)	22 (5.5)	0.815	0.460	0.443
Taking Aspirin in pregnancy for prevention of preeclampsia†	6 (5.9)	2 (3.1)	1 (0.2)	**<0.001**	**0.008**	0.419
Nulliparous	65 (59.1)	45 (68.2)	207 (51.6)	0.193	**0.011**	0.198
Ethnicity						
Caucasian	44 (42.2)	33 (51.6)	260 (64.8)	**<0.001**	**0.041**	0.289
Afro Caribbean	19 (18.6)	9 (14.1)	48 (12.0)	0.077	0.636	0.445
Asian	38 (38.2)	20 (31.3)	69 (17.2)	**<0.001**	**0.008**	0.430
Mixed/other	1 (1.0)	2 (3.1)	24 (6.0)	**0.038**	0.355	0.313
Cerebroplacental Ratio MoM	0.86 (0.66-1.0)	0.99 (0.82-1.2)	1.0 (0.87-1.2)	**<0.001**	0.917	**<0.001**
Birthweight centile	2 (0.6-3)	7 (5-9)	50 (25-74)	**<0.001**	**<0.001**	**<0.001**

Gestation at delivery (weeks)	38.3 (36.9-39.5)	39.9 (38.7-41.0)	40.0 (39.0-40.9)	**<0.001**	0.793	**<0.001**

*Smoking in pregnancy was defined as any active tobacco intake documented at the booking visit in the first trimester. †Aspirin use was defined as any dose commenced during the first or second trimester for the prevention of preeclampsia.

Data presented as median (interquartile range) or number (%).

Table 2. Maternal hemodynamic indices of the groups with fetal growth restriction, small for gestational age and control pregnancies.

Cardiovascular Indices	Group			P value		
	Fetal Growth Restriction (n=102)	Small for Gestational Age (n=64)	Control (n=401)	Fetal Growth Restriction vs Control	Small for Gestational Age vs Control	Fetal Growth Restriction vs Small for Gestational Age
Booking Mean Arterial Pressure (mmHg)	81 (73-88)	81 (75-89)	82 (76-88)	0.409	0.779	0.720
Examination Mean Arterial Pressure (mmHg)	90 (79-97)	85 (79-89)	87 (81-92)	**0.040**	0.112	**0.025**
Heart Rate (bpm)	80 (72-88)	87 (76-92)	85 (76-95)	**0.001**	0.900	**0.022**
Cardiac Output (L/min)	5.9 (5.1-6.8)	6.2 (5.5-7.0)	6.6 (5.8-7.5)	**<0.001**	**0.027**	0.139
Stroke Volume (ml)	76.9 (64.5-86.7)	72.4 (63.5-85.7)	78.7 (67.4-89.2)	0.099	0.083	0.700
Systemic Vascular Resistance (dynes-sec-cm^{-5})	1199 (1061-1402)	1048 (972-1278)	1061 (918-1210)	**<0.001**	0.377	**0.004**
Cardiac Output (MoM)	0.91 (0.79-1.1)	0.96 (0.87-1.1)	0.98 (0.87-1.1)	**0.003**	0.512	0.092
Stroke Volume MoM	1.0 (0.87-1.1)	1.0 (0.90-1.1)	0.98 (0.87-1.1)	0.647	0.502	0.806
Systemic Vascular Resistance MoM	1.2 (0.96-1.3)	1.0 (0.91-1.2)	1.0 (0.89-1.2)	**<0.001**	0.874	**0.002**

Uterine Artery Mean Pulsatility Index MoM	1.1 (0.95-1.4)	0.98 (0.83-1.2)	0.96 (0.82-1.1)	**<0.001**	0.523	**0.005**

Data presented as median (interquartile range)

Figure 1: The USCOM 1A® Device

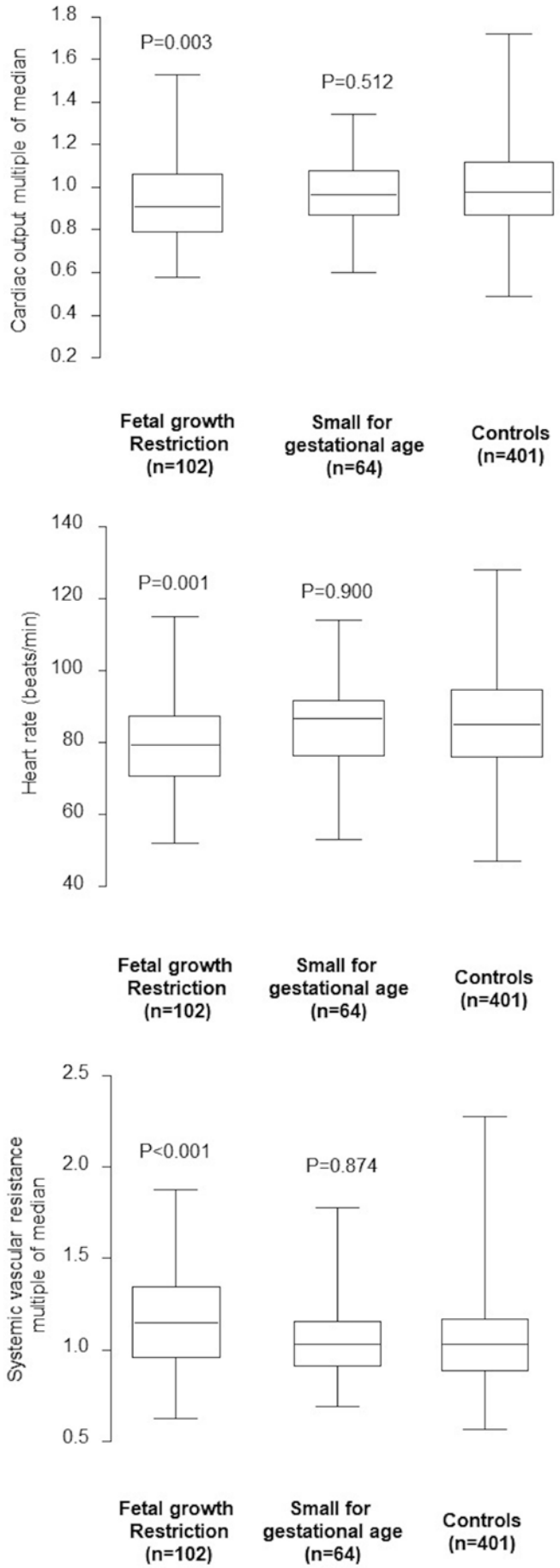

Figure 2: Differences in a) cardiac output multiple of median (MoM), b) heart rate (bpm) and c) systemic vascular resistance multiple of median (MoM) between the fetal growth restriction group, the small for gestational age group and the control group. The P-value represents the comparison to the control group.