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Maternal hemodynamics, fetal biometry and Dopplers in pregnancies followed up for suspected fetal growth restriction

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Abstract

Objectives: To assess whether in a cohort of patients with small for gestational age (SGA) foetuses with estimated fetal weight ≤10th percentile, maternal hemodynamics, fetal biometry and Dopplers at presentation, can predict the subsequent development of abnormal fetal Dopplers or delivery with birthweight <3rd percentile.

Methods: The study population comprised of 86 singleton pregnancies with SGA fetuses presenting at a median gestational age of 32 (range 26-35) weeks. We measured maternal cardiac function with a non-invasive transthoracic bioreactance monitor (NICOM, Cheetah), mean arterial pressure, fetal biometry, umbilical artery (UA), middle cerebral artery (MCA) and uterine artery (UT) pulsatility index (PI) and the deepest vertical pool (DVP) of amniotic fluid. Z-scores of these variables were calculated based on reported reference ranges and the values were compared between those with evidence of abnormal fetal Dopplers at presentation (group 1), those that developed abnormal Dopplers in subsequent visits (group 2) and those who did not develop abnormal Dopplers throughout pregnancy (group 3). Abnormal fetal Dopplers were defined as UAPI >95th percentile, or MCA PI <5th percentile. Differences in measured variables at presentation were also compared between pregnancies delivering a baby with birthweight <3rd and ≥3rd percentile. Multivariate logistic regression analysis was used to determine significant predictors of birthweight <3rd percentile and evolution from normal fetal Dopplers to abnormal fetal Dopplers in groups 2 and 3.

Results: In the study population 14 (16%) cases were in group 1, 19 (22%) in group 2 and 53 (62%) in group 3. The birthweight was <3rd percentile in 39 (45%) cases and ≥3rd percentile in 47 (55%). In the study groups, compared to normal populations, there was decreased cardiac output and stroke volume and increased peripheral vascular resistance and mean arterial pressure (MAP) and the deviations from normal were most marked in group 1. Pregnancies with a birthweight <3rd, compared to those ≥3rd percentile, had higher deviations from normal in fetal biometry, maternal cardiac output, stroke volume, heart rate and peripheral vascular resistance and UT-PI. Multivariate logistic regression analysis demonstrated that in the prediction of birth weight ≤3rd percentile, maternal hemodynamics provided significant improvement to the prediction provided by maternal demographics, fetal biometry and UT-PI, UA-PI and MCA-PI (difference between AUCs 0.18, 95% CI 0.06-0.29,

p=0.002). In contrast, there was no significant independent contribution from maternal hemodynamics in the prediction of subsequent abnormal fetal Dopplers.

Conclusions: In pregnancies with SGA fetuses there is decreased maternal cardiac output and stroke volume and increased peripheral vascular resistance and MAP and the deviations from normal are most marked in cases of redistribution in the fetal circulation and reduced amniotic fluid volume.

Introduction

Small for gestational age (SGA) fetuses with birthweight <10th percentile are at increased risk of perinatal death and long term handicap. [1 2] The risk of adverse outcome is particularly marked in the subgroup with the most severe impairment of growth reflected in birth weight <3rd percentile and in those with evidence of impaired placentation and fetal oxygentation reflected in redistribution in the fetal circulation with increased pulsatility index (PI) in the umbilical artery (UA), reduced PI in the fetal middle cerebral artery (MCA) and reduced amniotic fluid. [3-8]

Physiological adaptation in pregnancy includes a decrease in maternal peripheral vascular resistance (PVR), expansion in plasma volume, and increase in cardiac output (CO).[9] In pregnancies with SGA fetuses there is impairment in this physiological adaptation reflected as reduced CO and increased PVR;[10-15] these findings are more pronounced in fetal growth restriction (FGR) compared to SGA.[10] More recently, the knowledge that in pregnancies with impaired fetal growth there is abnormal maternal cardiac function has been utilised for screening for the risk of placental insufficiency at the routine first trimester scan in both low[16] and high-risk pregnancies[12] and also at a routine third trimester scan in low risk pregnancies[17] with promising results.

The aim of this study was to assess whether maternal hemodynamics, fetal biometry and Dopplers at presentation, in women referred to a specialist clinic for the management of pregnancies with SGA fetuses identified by routine ultrasound screening in the second and / or third trimesters, can predict the subsequent development of abnormal fetal Dopplers or birthweight <3rd percentile.

Methods

Patient selection

This was a prospective observational cohort study, conducted in a specialist clinic for the management of pregnancies with SGA fetuses at Kings College Hospital, London. The routine practice in this hospital is to offer three ultrasound examinations during pregnancy. A scan at 11-13 weeks' gestation for dating and estimation of the risk for fetal trisomies, an anomaly scan at 19-24 weeks and a third trimester growth scan at 35-37 weeks. Additional scans for assessment of fetal growth are carried out in first, suspicion of SGA based on symphysio-fundal height measurement, second, serum PAPPA ≤ 0.2 multiples of the median (MoM) at 11-13 weeks, third, UT-PI ≥1.6 at 19-24 weeks, fourth, single umbilical artery and fifth, medical conditions associated with FGR (such as lupus erythematosus, chronic hypertension, asthma, diabetes) or history of FGR or PE in a previous pregnancy.

When the EFW by sonographic fetal biometry is ≤10th percentile the patients are referred to a specialist clinic. This study reports on the maternal hemodynamic characteristics and their association with fetal biometry and Dopplers in 86 patients referred to the SGA clinic between April 2016 and October 2016. Gestational age was determined by fetal crown-rump length at 11-13 weeks[18] (81 patients) or fetal head circumference at 19-24 weeks (5 patients:

two in group 1, one in group 2 and two in group 3).[19] Pregnancies with chromosomal abnormalities or congenital infection were excluded.

Maternal demographics were recorded at the booking appointment and updated at their subsequent growth scans. Demographics recorded were age, height, weight, race (White, Black, South East-Asian or other) cigarette smoking (yes or no), medication (labetalol, nifedipine, methyldopa, steroids, beta mimetics) and medical history (asthma, chronic hypertension, diabetes), and Body Surface Area (BSA) at first presentation to the SGA clinic.

Maternal hemodynamic and fetal assessment

Maternal hemodynamic assessment was performed on initial presentation to the SGA clinic using a non-invasive bioreactance method (NICOM, Cheetah Medical Ltd, Maidenhead, Berkshire, UK).[20] This cardiac output monitor has been validated in pregnant and postpartum women by comparing it against trans-thoracic echocardiography with good correlation in the third trimester of pregnancy.[21] Four dual surface electrodes were placed on the posterior aspect of the thorax and after 15 minutes of rest in an upright sitting position (to remove the impact of aortocaval compression on maternal cardiac output) recordings were made over five minutes at one minute intervals. The average value of the five cycles was used for the estimation of each cardiac parameter. Cardiac parameters recorded were CO in L/min, stroke volume (SV) in ml, heart rate (HR) in bpm and PVR in dynes x s/cm^5. Stroke volume was calculated based on relative phase shift of electrical current between the input and output signal transmitted by the electrodes. Cardiac output (CO) is a product of SV and HR, mean arterial pressure (MAP) was defined as (2x Diastolic blood pressure + Systolic blood pressure)/3 and PVR was calculated by the equation PVR = 80 x MAP / CO. Blood pressure recordings were taken concurrently with maternal hemodynamic assessment, in accordance with British Hypertension Society guidance.[22]

In a SGA clinic where patients are referred at different points of pregnancy (from 20 to 42 weeks) it is impossible to recruit a control group in order to match all referred patients. We therefore, used previously established reference ranges across gestation for maternal hemodynamic[23] and fetal variables[19, 24, 25] and calculated their z-scores, controlling for the effects of gestational age on the examined parameters. The EFW percentile and z-score were derived from the sonographic measurements of fetal head circumference (HC), abdominal circumference (AC) and femur length (FL)[19, 26] and birthweight centile from Marsal *et al*.[27] Doppler assessment included the measurement of umbilical artery PI (UA-PI), middle cerebral artery PI (MCA-PI) and mean UT-PI. The measurement of the deepest vertical pool (DVP) was used to assess amniotic fluid volume.

Definitions and pregnancy management

Abnormal fetal Dopplers were defined as UA-PI >95th percentile and / or MCA-PI <5th percentile. [7]

The consensus definition of fetal growth restriction through a Delphi procedure was used to define FGR in subsequent visits.[28] Follow up ultrasound assessment was carried out every 1-2 weeks and timing of delivery was based on national guidelines[7] and randomised control trial evidence.[29, 30] More specifically, in FGR before 32 weeks with absent or reversed end-

diastolic flow (EDF) in the UA delivery would be recommended at 32 weeks or sooner if there were abnormal ductus venosus Dopplers or pathological computerised CTG. [29, 30] For FGR with abnormal UA Dopplers after 32 weeks' gestation delivery would be planned at 37 weeks if UAPI >95th but positive EDF and sooner if absent or reversed EDF.[7] Fetuses with EFW <10th percentile but normal Dopplers and amniotic fluid were offered delivery at term.[7]

Pregnancy outcomes were obtained from local hospital records or from the patient directly if they delivered in a hospital other than Kings College Hospital.

Ethics approval

Ethical approval for the study was obtained by the Hospital Ethics committee (REC reference:15/LO/1815) and written consent obtained from all patients recruited.

Statistical analysis

Due to the spread of gestational age at presentation we calculated z-scores for all examined variables. More specifically, z-scores (z) for maternal hemodynamic variables controlled for gestational age and maternal demographic characteristics (age, height, weight, BSA, ethnicity, parity, previous PE, smoking)[23] and those for fetal biometry and Doppler variables controlled for gestational age.[19, 24, 25]

Maternal demographics, fetal biometry, UA-PI, MCA-PI, mean UT-PI, amniotic fluid DVP and maternal hemodynamic variables were compared between women with abnormal fetal Dopplers at presentation (group 1), those that developed abnormal fetal Dopplers in subsequent visits (group 2) and those who did not develop abnormal fetal Dopplers throughout pregnancy (group 3). Comparisons were also made between the above parameters in women who delivered a neonate with a birth weight <3rd percentile and ≥3rd percentile (supplementary material).

The Kolmogorov-Smirnov test was used to assess the normality of the distribution of the data. For the comparison of groups 1, 2 and 3 the ANOVA or Kruskal-Wallis tests were used for normally and non-normally distributed data, respectively with the Bonferroni correction for the post-hoc tests. For the comparison of the two groups (birthweights ≥3rd or <3rd percentile) the unpaired t-test or Mann-Whitney U-test were used for normally and non-normally distributed data, respectively. Categorical variables were compared using the chi-square or Fisher's exact test, where appropriate.

Bivariate correlation was used to assess the relationship between maternal hemodynamic and fetal biometry and Doppler variables and the correlation coefficients were tabulated with corresponding significance levels. Multivariate logistic regression analysis was performed to assess the additional contribution of the z-scores of the maternal hemodynamic variables (SV, HR, MAP) for the prediction of a birthweight <3rd percentile compared to using solely maternal demographics, fetal biometry (z-scores of HC, AC and FL), fetal and placental Dopplers (z-scores of UA-PI, MCA-PI and UT-PI) and gestational age at presentation. The maternal demographic variables included age, height, weight, race (white, black, South-east Asian, other), medication (labetalol, methyldopa, nifedipine, beta-mimetics, steroids), medical comorbidities (chronic hypertension, diabetes, asthma).

The statistical software package SPSS (Version 22; SPSS Inc, Chicago, IL) and MedCalc Statistical Software version 17.9.7 (MedCalc Software bvba, Ostend, Belgium; http://www.medcalc.org; 2017) were used for data analysis.

Results

Comparisons between groups at presentation

The maternal demographic and hemodynamic characteristics and pregnancy outcomes of the total study population (N=86) and groups 1, 2 and 3 are presented in Table 1 and Figure 1. There was no significant difference in the maternal demographics of the women in Groups 1, 2 and 3, apart from a higher rate of women taking labetalol and methyldopa for blood pressure control in Group 1 versus Group 3. The gestational age at presentation to the SGA clinic was similar in all groups (around 32 weeks) but there was a significant difference in estimated fetal weight percentile at presentation to the SGA clinic between Groups 1 and 3 (Table 1). All three groups had a low-negative z-score in maternal CO (due to a lower SV) and high-positive z-score in PVR. CO z-score and SV z-score was lower in Group 1 versus Groups 2 and 3, but the difference did not reach statistical significance. Group 1 had higher MAP compared to Group 2 and higher PVR compared to Groups 2 and 3.

All three groups had low-negative z-scores in HC, AC and FL. Group 1 had lower HC compared to Group 2 and lower AC compared to both Groups 2 and 3. There was no difference in FL between the 3 groups. All three groups had high-positive z-scores in UA-PI with a gradual reduction from Group 1 to Group 3; Group 3 had lower UA-PI compared to both Groups 2 and 3. There was a gradual decline in MCA-PI from Group 3 to Group 1, with Group 3 having a statistically significant higher MCA-PI compared to Group 2. Group 1 had a higher prevalence of DVP $<5^{th}$ percentile compared to Group 3. 3 Mean UT-PI appeared higher in Group 1, compared to Groups 2 and 3, but the difference did not reach statistical significance.

The birthweight was <3rd centile, in 10 (71%) babies in Group 1, 11 (58%) in Group 2 and 18 (34%) in Group 3.

In group 1, four patients (28%) were treated with seven antihypertensive medications as follows: two patients took labetalol only and this was commenced in the third trimester. One patient took methyldopa only, which was commenced in the second trimester. Finally one patient was on a combination of three antihypertensives, methyldopa (commenced in the second trimester) and nifedipine and labetalol (both commenced in the third trimester). In group 2, no patient received antihypertensive medications. In group 3, three patients (5.6) were treated with four antihypertensive medications as follows: one patient was commenced on labetalol in the second trimester and one patient commenced on nifedipine in the third trimester. One patient was on a combination of labetalol and nifedipine, with treatment started in the second and third trimester respectively.

Correlations between maternal hemodynamics, fetal biometry and fetal and placental Dopplers.

There were modest correlations between maternal hemodynamic, fetal biometry and fetal and placental Doppler variables (Table 2). zCO was positively correlated with zMCA-PI and negatively with zUT-PI, zHR was positively correlated with zlogAC and zlogFL and negatively with zUT-PI. zMAP and zPVR were positively correlated with zUA-PI and zUT-PI and negatively with zlogHC, zlogAC and zMCA-PI.

Comparison between pregnancies with birthweight <3rd and ≥3rd percentile

Of the total study population 39 patients (45.3%) delivered a neonate with a birthweight <3rd centile and 47 patients (54.6%) delivered a neonate ≥3rd percentile (Supplementary Table 1).There was no significant difference in the maternal demographics between women delivering babies <3rd and ≥3rd percentile. Pregnancies that had babies with birthweights <3rd, compared to those ≥3rd percentile had lower estimated fetal weight centiles at presentation and delivered on average one week earlier. In pregnancies that had babies with birthweights <3rd, compared to those ≥3rd percentile, there were lower z-scores in maternal CO, SV, HR, AC, FL and higher LogPVR and UT-PI.

Multivariate logistic regression analysis for the prediction of delivery of a neonate <3rd percentile (Supplementary Table 2 and supplementary Figure 1) demonstrated that the addition of maternal hemodynamics produced a better prediction model compared to the one based solely on maternal demographics and fetal biometry and Dopplers (Difference between AUCs 0.18, 95% CI 0.06-0.29, p=0.002). On the contrary, in a multivariate logistic regression analysis for the prediction of subsequent FGR the maternal hemodynamics did not offer an improvement in the prediction model based on maternal demographics and fetal biometry and Dopplers (logitFGR=4.6-1.2 x zlogHC – 2.5 x zUA-PI, p<0.0001, R^2 Nagelkerke=0.32).

Discussion

Principal findings

The findings of this study demonstrate that pregnancies referred to a SGA clinic with EFW ≤10th percentile will comprise of three groups: those with abnormal fetal Dopplers at presentation (group 1), those that developed abnormal fetal Dopplers in subsequent visits (group 2) and those who did not develop abnormal fetal Dopplers throughout pregnancy (group 3). All three groups at presentation, compared with reference ranges based on women with normal pregnancy outcome, are characterised by lower maternal SV and CO and higher PVR. Women with abnormal fetal Dopplers at presentation demonstrated the lowest CO and SV, highest MAP and PVR, asymmetrical biometry, signs of redistribution

and the highest uterine artery PI. Pregnancies which subsequently demonstrated abnormal fetal Dopplers, compared to those which did not, had no significant differences in terms of maternal hemodynamics, fetal biometry and Dopplers, apart from a higher UA-PI. Consequently, the prediction model to screen for subsequent abnormal fetal Dopplers, was poor and without any contribution from the maternal hemodynamics. On the contrary, pregnancies with a birthweight <3rd had distinct differences compared to those ≥3rd percentile in terms of maternal hemodynamics and fetal Dopplers. Consequently, there was a significant improvement in the prediction of delivery with birthweight ≤3rd percentile by maternal demographics and fetal biometry and Dopplers with the addition of maternal hemodynamics.

The correlations between maternal hemodynamics, fetal biometry and fetal and placental Doppler variables were statistically significant but of modest power. The fact that higher zCO is associated with higher zMCA-PI and lower zUt-PI whilst higher zMAP and zPVR were associated with higher zUA-PI and zUt-PI and lower zMCA-PI, zHC and zAC are surrogate markers that a volume deplete and high resistance maternal cardiovascular system is associated with increased placental resistance and fetal growth impairment. However, the correleations are modest and explain only a small part of the variability of the fetal biometry and Doppler variables.

The fact that 28% of women in group 1 were on antihypertensive medication, could partly explain the low CO seen in this group. However, none of the women in group 2, whose fetuses subsequently developed abnormal Dopplers were on antihypertensive treatment and therefore, their impaired hemodynamic profile cannot be attributed to the maternal medication.

Comparison with previous studies and clinical implications

Our work is in agreement with the pre-mentioned studies both in high and low-risk populations that portrayed in pregnancies with SGA or FGR fetuses impaired maternal cardiovascular adaptation with reduced CO and increased MAP and PVR.[10-16, 23] Furthermore, the lower SV and CO and higher PVR in Group 1 compared to Group 3 were also found in two echocardiography studies comparing maternal hemodynamic function between FGR and SGA pregnancies in the third trimester.[10, 14] What was unexpected in our study was that the maternal hemodynamics, fetal biometry and Dopplers were similar between Groups 2 and 3, despite the fact that abnormal fetal Dopplers were evident in Group 2 and led to their delivery within five weeks from presentation. This finding raises two questions. Firstly, is Group 2 at an earlier stage of the FGR process and eventually they would also transition to an even more volume deplete and vasoconstricted state similar to Group 1 or are they a better group from the maternal hemodynamic point of view and a further insult, such as hypertension with subsequent antihypertensive treatment worsened the maternal and fetal homeostasis. The latter does not appear to be the case as none of the pregnancies in Group 2 were complicated by a hypertensive disorder and they did not have a higher prevalence of a pre-existing medical condition. The second question concerns Group 3, that both the maternal hemodynamic and the fetal biometry and Dopplers are abnormal in a similar pattern to Group 2.

One possible explanation for the impaired maternal hemodynamic profile of Group 3 could be the fact that 33% of babies had birthweights <3rd percentile, albeit with normal fetal

Dopplers. However, one would have expected Group 3, which did not exhibit Doppler deterioration in the next few weeks and with a 3-times lower emergency cesarean section rate compared to Group 2, to have at presentation a better maternal hemodynamic profile. This is potentially a concerning finding and it warrants further investigation as to whether mothers with SGA pregnancies and normal fetal Dopplers have a significantly impaired cardiovascular adaptation, similar to that of those who subsequently had abnormal fetal Dopplers. These concerns are in keeping with findings from studies that demonstrated in SGA babies antenatal fetal brain MRI findings suggestive of brain reorganization[31], abnormal cardiovascular programming at five years of age[32], worse education performance at 12 and 18 years of age[33] and higher risk of insulin resistance and the metabolic syndrome in later life[34]. Further work is needed in this matter as traditional policies of planning later gestations of delivery in SGA versus FGR fetuses at term may not be entirely justified if it exposes them to longer periods of relative hypoxia and worse outcomes in adult life.[35]

There is evidence that a birthweight <3rd percentile is an antepartum predictor of adverse outcome, independent of Doppler evidence of FGR.[36] Neonates born with a birthweight <3rd percentile, compared to appropriate for gestational age pregnancies carry an 11-fold, 17-fold and 4-fold increased risk of stillbirth, neonatal hypoglycemia and neonatal death, respectively.[4, 5] Their risk of neonatal encephalopathy is increased 38-fold and the development of cerebral palsy, even in the absence of neonatal encephalopathy is increased 2.8-fold.[3, 6] Therefore, in its own right, birthweight <3rd percentile should be considered as a target for any screening program aiming at reducing perinatal mortality and morbidity from FGR. It is positive therefore, that the addition of maternal hemodynamic function added significantly to the power of a model based on fetal biometry and Dopplers and maternal demographic variables for the prediction of babies born below the <3rd percentile. More work could assess whether earlier delivery in pregnancies with a combination of impaired maternal cardiovascular adaptation and evidence of placental insufficiency would lead to improved outcomes in such a high risk group.

Strengths and limitations of the study

The strength of this study is that it allowed concomitant comparison in maternal cardiac function as well as fetal biometry, fetal and placental Doppler studies and amniotic fluid volume between pregnancies with a common referral criterion to a dedicated SGA clinic but distinct outcomes in terms of ensuing and timing of FGR.

A limitation of the study is that due to the nature of a referral SGA clinic, the entry point in the study could not be standardised as it followed the needs of everyday practise. However, using reference ranges from normal outcome pregnancies, we controlled for the changes with gestational age and, in terms of hemodynamic variables, for maternal ethnicity and somatometric parameters, providing z-scores for all variables. Furthermore, this was a cross sectional study and therefore it was not possible to determine whether there was an increase or fall in hemodynamic parameters proceeding the time of assessment in the SGA clinic. This, together with the relatively small sample size, necessitates larger longitudinal studies to ascertain longitudinal hemodynamic changes in these pregnancies.

Conclusions

Pregnancies referred to a dedicated SGA clinic with an EFW ≤10th percentile have reduced maternal SV and CO with increased MAP and PVR. Prediction of birthweight <3rd percentile at first visit, but not of subsequent Doppler deterioration, is improved by the assessment of maternal hemodynamic function along with maternal history and demographics, fetal biometry, Dopplers and amniotic fluid.

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Figure Legend:

Figure 1. z-scores of maternal hemodynamics and fetal biometry and Dopplers in pregnancies with FGR at presentation (black box and whiskers), FGR in subsequent visits (shaded box and whiskers) and those with no evidence of FGR throughout pregnancy (white box and whiskers).

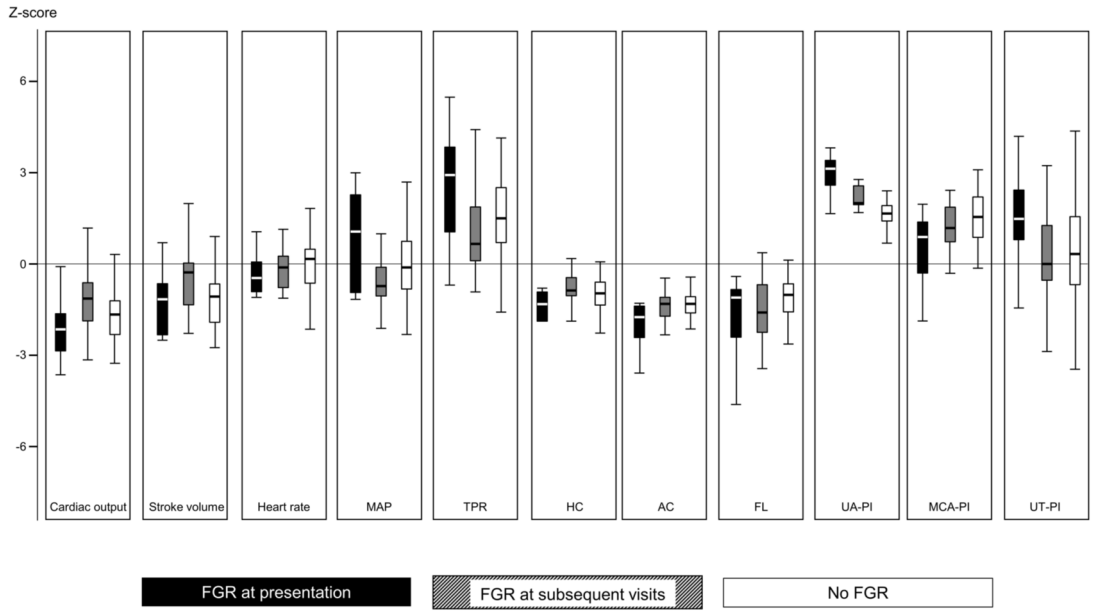

Figure 1.TIF

Table 1: Maternal demographic and hemodynamic characteristics at time of presentation and pregnancy outcome. The p-values correspond to the overall p-value of the ANOVA or Kruskal-Wallis. The post-hoc test results are represented with symbols within the table.

Maternal characteristics	Total population (n=86)	EFW <10th centile and abnormal Dopplers		EFW <10th centile and normal Dopplers (Group 3, n=53)	P value
		At presentation (Group 1, n=14)	At subsequent visits (Group 2, n=19)		
Age in years, mean (SD)	31.9 (5.8)	33.9 (3.6)	30.2 (6.1)	31.9 (5.9)	0.2
Height in cm, mean (SD)	162.8 (6.6)	159.4 (7.6)	163.1 (6.0)	163.6 (6.3)	0.1
Weight at presentation in kg, median (IQR)	70.7 (63 to 77.5)	71.0 (60.4 to 81.2)	69.4 (63 to 76)	71 (64 to 79.5)	0.2
Body Surface Area in m^2, mean (SD)	1.8 (0.2)	1.7 (0.2)	1.7 (0.1)	1.8 (0.2)	0.2
Race					
White, n (%)	46 (53.4)	7 (50)	10 (52.6)	29 (54.7)	
Black, n (%)	25 (29.1)	4 (28.6)	5 (26.3)	16 (30.2)	
South East Asian, n (%)	11 (12.8)	3 (21.4)	2 (10.5)	6 (11.3)	
Other, n (%)	4 (4.7)	0 (0)	2 (10.5)	2 (3.8)	
Smoking, n (%)	6 (7.0)	1 (7.1)	2 (10.5)	3 (5.7)	
Medication					
Labetalol, n (%)	5 (5.8)	3 (21.4)	0 (0)	2 (3.8) †	
Nifedipine, n (%)	3 (3.5)	1 (7.1)	0 (0)	2 (3.8)	
Methyldopa, n (%)	2 (2.3)	2 (14.2)	0 (0)	0 (0) †	
Steroids, n (%)	1 (8.6)	0 (0)	0 (0)	1 (1.9)	
Beta mimetics, n (%)	7 (8.1)	0 (0)	3 (15.8)	4 (7.5)	
Past medical history					
Asthma, n (%)	11 (12.8)	0 (0)	4 (21.1)	7 (13.2)	
Chronic hypertension, n (%)	2 (2.3)	0 (0)	0 (0)	2 (3.8)	
Diabetes, n (%)	6 (7.0)	2 (14.3)	0 (0)	4 (7.5)	
Gestational age in weeks, median (IQR)	32.4 (30.4 to 34.2)	31.9 (26.7 to 34.1)	32.4 (31.4 to 35.3)	32.4 (30.7 to 34.3)	0.5
Estimated fetal weight percentile, median (IQR)	4.0 (2.0 to 7.0)	1.5 (1.0 to 3.2)	5.0 (1.0 to 8.0)	5.0 (3.0 to 7.0) ††	0.009
Maternal hemodynamics in z scores, mean (SD)					
Cardiac output in L/min	-1.07 (1.1)	-1.6 (1.04)	-0.7 (1.2)	-1.1 (1.0)	0.06
Stroke volume in mL	-0.96 (1.0)	-1.2 (0.99)	-0.5 (1.1)	-1.0 (0.9)	0.07
Heart rate in beats per minute	-0.02(0.8)	-0.3 (0.6)	-0.1 (0.7)	0.09 (0.9)	0.2
Mean arterial pressure in mmHg	-0.2 (-0.9 to 1.0)	1.1 (-0.9 to 2.3) *	-0.7 (-1.1 to 0.1)	-0.09 (-0.8 to 0.8)	0.01
Peripheral vascular resistance in dynes x s/cm^5	1.6 (1.5)	2.6 (1.8) **	1.1 (1.4)	1.5 (1.3) †	0.007
Fetal biometry in z scores, mean (SD)					

Log10 Head circumference	-0.96 (-1.3 to -0.6)	-1.3 (-2.3 to -0.9) **	-0.8 (-1.0 to -0.4)	-0.9 (-1.3 to -0.5)	0.006
Log10 Abdominal circumference	-1.3 (-1.7 to -1.1)	-1.7 (-2.6 to-1.3) *	-1.3 (-1.8 to -0.4)	-1.3 (-1.6 to -1.0) ††	0.007
Femur length $^{0.5}$	-1.1 (-1.9 to -0.7)	-1.1 (-2.8 to -0.8)	-1.6 (-2.3 to -0.6)	-1.1 (-1.6 to 0.7)	0.4
Dopplers and amniotic fluid in z scores, median (IQR)					
Umbilical artery pulsatility index	1.8 (1.5 to 2.3)	3.1 (2.5 to 3.7)	1.9 (1.8 to 2.5) §§§	1.6 (1.4 to 1.9) †††	<0.0001
Middle cerebral artery pulsatility index	1.3 (0.92)	0.5 (1.1)	1.2 (0.8)	1.5 (0.8) ††	0.001
Mean uterine artery pulsatility index	0.4 (-0.6 to 1.8)	1.5 (0.7 to 2.5)	0.06 (-0.6 to 1.4)	0.3 (-0.7 to 1.6)	0.06
Amniotic fluid deepest pool <5th centile, n (%)	5 (5.8)	3 (21.4)	1 (5.3)	1 (1.9) ††	
Induction of labour, n (%)	53 (61.6)	6 (42.9)	10 (52.6)	37 (69.8)	
Vaginal delivery, n (%)	58 (67.4)	5 (35.7)	10 (52.6) §§	43 (81.1) †††	
Emergency cesarean section, n (%)	24 (27.9)	9 (64.2)	9 (47.3) §§	7 (13.2) †††	
Gestational age at delivery in weeks, median (IQR)	38.2 (36.8 to 39.2)	35.2 (28.4 to 37.2)	37.3 (36.0 to 38.6)	38.4 (37.6 to 39.6) †††	<0.0001
Birth weight centile, median (IQR)	3.4 (1.5 to 8.9)	0.9 (0.1 to 3.3)	2.3 (1.4 to 4.6) §	5.5 (2.4 to 13.9)†††	<0.0001
Birth weight z score, median (IQR)	-1.8 (-2.2 to -1.3)	-2.3 (-3.0 to -1.8)	-2.0 (-2.2 to -1.7)§	-1.6 (-1.9 to -1.1)†††	<0.0001
Birth weight below the 3rd centile, n (%)	39 (44.8)	10 (71.4)	11 (57.9)	18 (33.3) †	
Admission to neonatal unit, n (%)	23 (26.7)	10 (71.4) *	6 (31.6)	7 (13.2) †††	
Preeclampsia, n (%)	3 (3.5)	2 (14.2)	0 (0)	1 (1.9) †	
Pregnancy induced hypertension, n (%)	2 (2.3)	1 (7.1)	0 (0)	1 (1.9)	

EFW = estimated fetal weight; IQR = interquartile range; SD = standard deviation

Statistically significant difference between Group 1 and Group 2 = * p<0.05; ** p<0.01; *** p<0.0001
Statistically significant difference between Group 1 and Group 3 = † p<0.05; †† p<0.01; ††† p<0.0001
§ Statistically significant difference between 2 and Group 3 = § p<0.05; §§ p<0.01; §§§ p<0.0001

Table 2: Correlation matrix between maternal hemodynamic and fetal biometry and Doppler variables

	CO	HR	MAP	log10 PVR	SV	Log10 HC	Log10 AC	Log 10 FL	Umbilcal artery PI	Uterine artery mean PI
HR	0.19									
MAP	-0.32**	0.008								
log10 PVR	-0.86**	-0.17	0.60*							
SV	0.89*	-0.24*	-0.35**	-0.78**						
Log10 HC	0.2	0.09	-0.35**	-0.29**	0.16					
Log10 AC	0.09	0.23*	-0.38**	-0.24*	0.01	0.68**				
Log 10 FL	0.06	0.22*	-0.17	-0.17	-0.05	0.42**	0.52**			
Umbilcal artery PI	-0.11	-0.12	0.31*	0.23*	-0.07	-0.39**	-0.38**	-0.12		
MCA PI	0.24*	0.15	-0.31**	-0.32**	0.15	0.26*	0.19	0.17	-0.35**	
Uterine artery mean PI	-0.32**	-0.31**	0.17	0.28**	-0.16	-0.31**	-0.29*	-0.29**	0.14	-0.31**

CO = cardiac output; HR = heart rate; MAP = mean arterial pressure; PVL = peripheral vascular resistance; SC = xxx; FL = femur length; PI = pulsatility index.

* Correlation is significant at the 0.05 level; ** Correlation is significant at the 0.01 level