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Hemodynamic findings in normotensive women with small for gestational age and growth restricted fetuses

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ABSTRACT

Introduction: Fetal growth restriction (FGR) in most instances results as a consequence of primary placental dysfunction due to inadequate trophoblastic invasion. Maternal cardiac maladaptation to pregnancy has been proposed as a possible determinant of placental insufficiency and impaired fetal growth. This study aimed to compare the maternal hemodynamic parameters between normotensive women with small-for-gestational age (SGA) and FGR fetuses and to evaluate their correlation with neonatal outcome.
Material and methods: observational cohort study including singleton pregnancies referred to our tertiary care center due to fetal smallness. At the time of diagnosis, fetuses were classified as SGA or FGR according to the Delphi consensus criteria and pregnant women underwent hemodynamic assessment by using cardiac output monitor (USCOM 1A Ltd). A group of women with singleton uncomplicated pregnancies ≥35 weeks of gestation were recruited as controls. Cardiac output, systemic vascular resistance, stroke volume and heart rate were measured and compared among the three groups (controls vs. FGR vs. SGA). The correlation between antenatal findings and neonatal outcome was also evaluated by multivariate logistic regression analysis.
Results: 51 women with fetal smallness were assessed at 34.8+2.6 weeks. SGA and FGR were diagnosed in 22 and 29 cases, respectively. The control group included 61 women assessed at 36.5±0.8 weeks of gestation. Women with FGR had a lower cardiac output -Z score (respectively, -1.3±1.2 vs. -0.4±0.8 vs. -0.2±1.0; p<.001) and a higher systemic vascular resistance Z-score compared with both SGA and controls (respectively, 1.2±1.2 vs.

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0.2±1.1 vs. -0.02±1.2; p<.001), while no difference in the hemodynamic parameters was found between women with SGA and controls. The incidence of NICU admission did not differ between SGA and FGR fetuses (18.2% vs 41.4%; p=0.13), however FGR had a longer hospitalization compared to SGA fetuses (14.2±17.7 vs. 4.5±1.6 days; p=0.02). Multivariate analysis showed that the cardiac output Z-score at diagnosis (p=0.012) and the birthweight Z-Score (p= 0.007) were independent predictors of the length of neonatal hospitalization.
Conclusions: Different maternal hemodynamic profiles characterize women with SGA or FGR fetuses. Furthermore, a negative correlation was found between the maternal cardiac output and the length of neonatal hospitalization.

Keywords:
maternal hemodynamics, growth restriction, small for gestational age, fetal growth restriction, cardiac output monitor, perinatal morbidity, neonatal hospitalization

Abbreviations:

SGA small-for-gestational age
FGR fetal growth restriction
PI pulsatility index
EFW estimated fetal weight
CO cardiac output
SV stroke volume
SVR systemic vascular resistance
USCOM Ultrasound Cardiac Output Monitor
AC abdominal circumference
UtA uterine arteries
UA umbilical artery

Key-message

Cardiac output, systemic vascular resistance and stroke volume are significantly different between mothers of small for gestational age and growth restricted fetuses. In case of fetal smallness, maternal hemodynamic assessment could help in identifying fetuses at higher risk of adverse neonatal outcome.

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INTRODUCTION

Small-for-gestational age (SGA) fetuses are at high risk of adverse outcome [1]. However, such risk is mostly confined to those fetuses that do not reach their growth potential[2]. This latter condition, which is commonly referred to as fetal growth restriction (FGR), has been defined by the association of reduced fetal size and abnormal indices of feto-placental function at ultrasound Doppler examination[3-6]. Recently, an international consensus using a Delphi procedure has produced new standards for the antenatal diagnosis of FGR which include biometric and Doppler analysis[7].

Fetal growth restriction has been traditionally considered the consequence of a primary placental dysfunction due to inadequate trophoblastic invasion, which leads to reduced fetal blood supply and chronic hypoxia[8-11]. More recently, maternal cardiac maladaptation to pregnancy has been proposed as a potential determinant of placental insufficiency leading to impaired fetal growth[12].

Some studies have documented a reduction in the maternal cardiac output (CO) and stroke volume (SV) and an increase in the systemic vascular resistances (SVR) among normotensive women carrying FGR fetuses[12,13]. Furthermore, an increased prevalence of maternal cardiac structural abnormalities has been found in women with high mid-trimester uterine artery Doppler resistance indices, thus suggesting that the maternal cardiac dysfunction could represent the primary event leading to defective placentation and reduced blood supply to the placental bed[13,15].

Given the spreading use of non-invasive cardiovascular monitoring devices (i.e., Ultrasound Cardiac Output Monitor (USCOM), USCOM 1A Ltd, Sydney, NSW, Australia; NICOM Cheetah Medical, Inc. Wilmington, DE, USA; NICaS®, NI Medical, Petach Tikva, Israel), the assessment of maternal hemodynamics has been proposed for the antenatal workup of pregnancies with suspected placental insufficiency in order to identify the fetuses at risk of perinatal complications[16-19]. The aim of this study was to assess whether the maternal hemodynamic findings may predict perinatal outcome among normotensive women with small fetuses detected at 3rd trimester of pregnancy.

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MATERIAL AND METHODS

Study design and study population

This is a cohort study conducted between January 2018 and March 2019 and including a consecutive series of normotensive women referred to our tertiary care center in the third trimester due to suspected fetal smallness. In all the included cases an estimated fetal weight (EFW) [or an abdominal circumference (AC)] and a neonatal weight <10th percentile were confirmed respectively at antenatal ultrasound and at birth.

A non-consecutive group of healthy women with uncomplicated pregnancies attending at >35 weeks of gestation for antenatal care was selected as controls and used for comparison if an appropriate-for-gestational age neonate was confirmed at birth.

In both cases and controls the pregnancy had been dated by the crown-rump length measured at 11^{+0}-13^{+6} weeks of gestation.

Exclusion criteria were gestational age less than 24 weeks, multiple pregnancies, pre-existing chronic hypertension or kidney disease, established hypertensive disorders of pregnancy before or after birth, cardiac disease, chronic drug abuse, antenatal or postnatal diagnosis of congenital anomalies.

Demographic characteristics and clinical outcomes of the pregnancy were retrieved from hospital records.

Management

Upon referral, all women underwent sonographic assessment of the fetal biometry. The assessment of fetal biometry included the measurement of the f head circumference, the biparietal diameter, the AC and the femur length, and the EFW percentile was computed by means of the Hadlock 4 formula[20]. The EFW and the birthweight Z-score were calculated by using the Intergrowth-21 growth curves as reference[21].

Furthermore, the mean pulsatility index (PI) of the maternal uterine arteries (UtA)[22], the PI of the umbilical artery (UA) and the PI of the middle cerebral artery were recorded and converted into the corresponding percentile for the gestational week [23].

The Delphi consensus criteria based on the combined assessment of biometric and Doppler parameters was used to classify each case as FGR or SGA[7] as follows:

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- *<32 weeks:* AC/EFW<3rd centile or absent end-diastolic flow in UA or AC/EFW <10th centile combined with uterine arteries PI>95th centile and/or UA PI>95th percentile
- *≥32 weeks:* AC/EFW<3rd centile or at least two out of: AC/EFW <10th centile; AC/EFW crossing more than 2 quartiles; cerebral-placental ratio <5th centile or UA PI >95th centile.

All women underwent central hemodynamic assessment by means of the USCOM ultrasound cardiac output monitor (), a non-invasive device allowing the evaluation of the velocity time integrals (VTIs) of transaortic or transpulmonary blood flow by means of continuous wave-Doppler. Hemodynamic parameters including CO, the SV and the SVR can be indirectly obtained through the USCOM algorithm, which combines VTIs, anthropometric parameters (height and weight) and blood pressure values[17]. The normotensive controls were submitted to one single USCOM examination during their antenatal care.

The measurements were obtained under standardized conditions for the entire cohort. In details, the USCOM probe was placed in the suprasternal notch to obtain a minimum of 3 consecutive Doppler profiles with the woman lying in a semirecumbent position. Given that the CO and the SVR may vary based upon the gestational age and the maternal characteristics (age, height, weight, smoking status), they were expressed as Z-score by using previously published reference ranges of maternal central hemodynamic parameters during pregnancy[24]. The results of the hemodynamic investigation were collected for research purpose only and did not impact on the clinical management.

Follow-up ultrasound assessment was carried out on a weekly/fortnightly basis, and obstetric care was based upon the national guidelines and the local protocol. In the case of early FGR (<32 weeks) with absent or reversed end-diastolic flow (EDF) in the UA, delivery was recommended at 32 weeks or earlier in case of abnormal ductus venosus Doppler indices or pathological computerized cardiotocography. Fetuses with late FGR (>32 weeks) were delivered between 36-38 weeks if the EFW was <3rd percentile or the UA-PI was above the 95th percentile with positive end-diastolic flow (EDF) while delivery was expedited at an earlier gestation in the case of absent or reversed UA EDF[3,24-26].

Outcome

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A comparison of the hemodynamic parameters and of the clinical outcomes between women with an EFW<10th percentile and controls was performed.

The primary outcome of the study was to compare the maternal hemodynamic parameters (CO, SVR, SV) between the women with SGA or FGR fetuses and controls.

The secondary outcome was to compare the following clinical outcomes between SGA and FGR fetuses and to analyze their relationship with the maternal hemodynamic findings:

- Composite adverse neonatal outcome, defined as the presence of at least one of the following: intrauterine fetal demise, UA pH <7.05 or vein pH <7.10, Apgar score at 5 min <7, grade 3 or 4 intracranial hemorrhage, encephalopathy, patent ductus arteriosus requiring treatment (pharmacological treatment or surgical closure), intravascular disseminated coagulation, respiratory support>1 week, necrotizing enterocolitis (NEC);
- Length of neonatal hospitalization (days).

Statistical Analyses

Statistical analysis was performed using Statistical Package for Social Sciences (SPSS) v. 22 (IBM Inc., Armonk, NY, USA). The sample size estimation was based on a previous echocardiographic study which reported a 10% lower maternal CO in normotensive women with FGR fetuses compared with appropriate-for-gestational age ones[27]. We calculated that the enrolment of 26 women either in the FGR and appropriate-for-gestational age group was needed to show a a 10% lower CO in the former group at 80% power and at a significance level of 0.05. The Kolmogorov–Smirnov test was used to assess the normality of the distribution of the data. Data were displayed as mean±standard deviation (SD) or as number (percentage). Categorical variables were compared using the Chi-square or Fisher exact test. Between-group comparison of continuous variables was undertaken using T-test and the Mann-Whitney nonparametric equivalent test. Comparisons between > 2 groups were performed using Kruskal-Wallis or ANOVA test as appropriate. Bivariate correlation was used to assess the relationship between maternal hemodynamic, fetal biometry and Doppler indices and postnatal outcome, and correlation coefficients were expressed with corresponding significance levels.

Stepwise multiple linear regression analysis was used to assess the independent predictors of length of neonatal hospitalization among neonates with a birthweight <10°

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percentile (SGA+FGR). After testing for collinearity, correlated variables (Variance Inflation Factor, VIF>3) were not used simultaneously in the same model (e.g. CO Z-Score and SVR Z-Score). Two-sided p-values were calculated and p-values <0.05 were considered as statistically significant. The study was performed following the STROBE guidelines[26].

Ethical approval

This study was approved by the local ethics committee of the University Hospital of Parma on 11-12-2018 (registration number 0001056).

RESULTS

Over the study period, 58 cases of normotensive pregnancies with EFW <10 percentile were confirmed at our ultrasound department and considered eligible for the study purposes; 3 of them were lost at follow-up, 3 cases were excluded because they developed hypertensive disorder of pregnancy and 1 was excluded because of postnatal diagnosis of metabolic disease. A total of 51 women with a mean gestational age at admission of 34.8±2.6 weeks were eventually included in the study group. Of these, 29 were classified as FGR and 22 as SGA in accordance with the Delphi classification[7]. In all these cases the birthweight was <10th centile for our reference neonatal charts.

Seventy-six normotensive women with uncomplicated pregnancies were considered as potential controls; 11 of them were subsequently removed as birthweight was found to be <10th percentile while 4 women were excluded as they developed hypertension within 3 days after delivery and 1 was lost at follow-up. Overall, a total of 61 women, who were submitted at USCOM assessment at a mean gestational age of 36.5±0.8 weeks, were used as controls (Figure 1).

The demographic, pregnancy and hemodynamic characteristics of the study population are presented in Table 1, while a comparison of the antenatal findings and the clinical outcomes of the two groups is shown in Table 2. Compared to SGA fetuses, those with FGR showed a lower EFW Z-Score (-1.5±0.2 vs. -2.0±0.4; p<.001) and CPR Z-Score (-0.8±0.1 vs. -1.7±1.6; p=0.03), a higher UA-PI Z-Score (0.5±0.9 vs. 1.5±1.4; p<.001) and UtA-PI Z-Score (-0.3±1.2 vs. 0.9±1.8; p=0.01) (Table 2). The incidence of composite adverse

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neonatal outcome and NICU admission did not differ between the two groups, while FGR had a longer hospitalization compared to SGA fetuses (14.2±17.7 vs 4.5±1.6 days, p=0.02) (Table 2)

Maternal cardiac findings were similar between SGA fetuses and controls. In the FGR group compared with both the SGA and the control group the CO and SV Z score was lower and SVR Z-Score was greater (Table 3).

UtA-PI Z-Score and UA-PI Z-Score were negatively correlated with CO Z-Score and positively correlated with SVR Z-Score, while UtA-PI Z-Score was negatively correlated to SV percentile. CO Z-Score was negatively correlated with the length of neonatal hospitalization while SVR Z-Score, UtA-PI Z-Score and UA-PI Z-Score were positively correlated with this outcome (Table 4). At stepwise multiple linear regression analysis the CO Z-Score (p=0.012) and the birthweight Z-Score (p=0.007) were shown to be the strongest independent predictors of the length of hospitalization of neonates <10th percentile (Table 5) (Supporting Information Figure S1).

DISCUSSION

Our study confirmed that normotensive women carrying a growth restricted fetus show an impaired cardiac adaptation to pregnancy, characterized by reduced CO and SV and increased SVR. On the other hand, women with SGA fetuses have a hemodynamic profile similar to that of women with uneventful gestations. Furthermore, the pulsatility of uterine and UA appeared negatively correlated with maternal CO and positively with SVR. Finally, the maternal CO at diagnosis and the birthweight were found to be independent predictors of the length of neonatal hospitalization.

There are two main pathways explaining the association between reduced maternal cardiac performance and fetal hypoxia. In a first scenario, a shallow placentation could represent the main cause of higher impedance to blood flow directed to the tertiary villi causing an increased maternal uterine artery resistance[10,30]. This would lead to a reduction of maternal CO in order to provide placental supply without increasing the systemic blood pressure. In a second scenario, supported by more recent observations, primary maternal cardiac impairment, characterized by low CO, may cause an insufficient increase of the

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uterine blood supply in the early gestation and this is responsible for reduced trophoblastic invasion and ultimately for placental hypoxia[31].

Indeed, a similar mechanism has been recently advocated in the pathophysiology of early onset preeclampsia associated to FGR[32,33].

In our study the maternal hemodynamic assessment was performed following the diagnosis of FGR, therefore we are unable to determine whether the reduced CO is the cause or the consequence of the placental insufficiency.

Consistently with our findings, seminal studies based on maternal echocardiographic evaluation previously reported that normotensive pregnant women with FGR are characterized by a low output, high resistance circulatory state as well as a higher prevalence of asymptomatic global diastolic dysfunction[34-36]. Furthermore, an association between inadequate cardiac adaptation to pregnancy during the first weeks of gestation and subsequent occurrence of FGR has been reported[37-39].

In the very early gestation Duvekot et al.[38] had noted a smaller left atrium in women who eventually developed FGR, and this seemed related to a reduced cardiac preload This observation suggests that the insufficient increase of maternal cardiac performance precedes the occurrence of FGR, supporting the theory of a primary maternal cardiac dysfunction in the pathophysiology of FGR. In a cross-sectional study including 52 normotensive women with SGA fetuses (26 IUGR and 26 non-IUGR) at 20-36 weeks' gestation, Bamfo et al.[34] found that maternal CO was lower and total vascular resistance (TVR) was higher in the FGR compared to the non-FGR group. Stott et al.[39] recently demonstrated that a reduced cardiac output at booking in women at risk of placental insufficiency may predict the later development of FGR with a 100% sensitivity.

Roberts et al.[40] compared maternal hemodynamics among fetuses <10th percentile with different fetal Doppler findings (evidence of an abnormal fetal Doppler index at presentation vs. subsequent development of abnormal Doppler index vs. stable normal fetal Doppler). This study could not demonstrate a role of maternal hemodynamics in anticipating the subsequent development of abnormal fetal Doppler. However, the maternal hemodynamic profile was shown to improve the prediction of birthweight <3rd percentile. Of note, in their study Roberts et al. did not exclude women with hypertensive disorders of the pregnancy, among whom an increased prevalence of birthweight <3rd percentile was reported.

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In another recent study the USCOM technique was used to assess a large cohort of normotensive women[41]. The Authors showed that the cases of FGR were characterized by a lower CO and a higher SVR compared to the SGA and the appropriate-for-gestational age groups. Importantly, the low CO appeared to be related to a decreased maternal heart rate rather than to a low SV. Such findings are in contrast with previous studies and also with the findings from our study which suggest a lower SV in mothers with FGR compared to controls with no difference in the maternal heart rate. Our study has a similar methodology and smaller numbers in respect of the work by Perry, but we have additionally evaluated the correlation between maternal cardiac findings and both fetal Doppler and perinatal outcome.

The distinction between FGR and constitutionally small fetuses is of crucial importance for the clinical management of cases diagnosed with EFW <10th percentile in the third trimester[8,9]. Our data suggest that maternal cardiac assessment might support in identifying those cases where fetal smallness is due to a placental insufficiency, i.e. "true" growth restricted fetuses. Although our study was not powered to demonstrate a difference in the neonatal morbidity between SGA and FGR fetuses, we speculate that a reduced maternal CO might anticipate a more severe perinatal outcome of antenatally detected small fetuses, as witnessed by the longer neonatal hospitalization which was found to be associated with an abnormal maternal hemodynamic profile.

Recently, the use of angiogenic factors (e.g. Sflt-1/PIGF) has been widely proposed to anticipate the need for imminent delivery in women with early onset FGR[42-44]. A recent study[45] conducted on a large cohort of unselected pregnancies between 35 and 37 weeks demonstrated a significant association between maternal hemodynamic profile (CO and SVR) and biochemical markers of placental function (PLGF and s-FLT-1). Moreover, the EFW appeared to be associated with maternal CO and peripheral vascular resistance, thus confirming the strong relationship between maternal hemodynamics and placental function also among uncomplicated gestations.

The main strength of our study is its prospective design and the exclusion of pregnancies complicated by hypertensive disorders. Furthermore, we obtained Z-Score for all the hemodynamic measurements (CO, SVR) by means of a calculator which adjusts for demographic (i.e. maternal age, height, weight) and anthropometric characteristics influencing cardiovascular parameters.

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A limitation of our study is the small number of subjects included, even though such number is comparable to that of the majority of the previous studies on the same subject, and sample size calculation was performed prior to enrollment of the study participants. Furthermore, the decision to include in the control group neonates weighting >10th centile for the given gestation may have led to the inappropriate inclusion of cases of FGR characterized by a reduced intrauterine growth velocity (i.e. decrease of the longitudinal growth of more than 2 quartiles on the charts) but a normal weight at birth. Moreover, the selection bias due to the study setting (tertiary referral hospital) may justify the high fraction of fetuses with an EFW classified as FGR rather than SGA.

Finally, maternal hemodynamic parameters were only investigated on admission, therefore we cannot comment on the longitudinal changes of the hemodynamic function.

CONCLUSION

Maternal cardiac dysfunction might play a pivotal role in the pathophysiology of FGR in normotensive pregnant women. The degree of impairment of the maternal hemodynamic function seems to correlate with the perinatal outcomes of the neonates with a birthweight <10th percentile.

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Legend

Figure 1. Flow chart (according to STROBE guidelines) for inclusion of cases.

Supporting Information legend

Figure S1. Correlation and estimated marginal means between cardiac output (CO) Z-score and the length of neonatal hospitalizatio among neonates with a birthweight <10° percentile.

Accepted Article

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Table 1. Maternal demographic and pregnancy characteristics among control women and women with small for gestational age (SGA) or growth restricted fetuses (FGR).

				Between groups p-value		
	Control n=61	**SGA n=22**	**FGR n=29**	**Control *vs* SGA**	**Control *vs* FGR**	**SGA *vs* FGR**
Maternal age	32.0±5.0	32.3±5.8	33.0±5.9	0.92	0.29	0.43
Pre-pregnant BMI (Kg/m^2)	26.9±4.6	26.4±4.4	26.3±4.8	0.92	0.41	0.68
Parity	0.6±0.6	0.5±1.0	0.6±0.9	0.37	0.70	0.74
Caucasian	53(86.9)	17(77.3)	21(72.4)	0.30	0.09	0.69
Smoking during pregnancy	5(8.2)	2(9.1)	3(10.3)	0.80	0.95	0.74
Cesarean Section	13(21.3)	5(22.7)	11(37.9)	0.89	0.10	0.25
Gestational Age at examination (weeks)	36.5±0.8	35.2±1.9	34.5±3.1	<.01	<.01	0.39
Gestational Age at delivery (weeks)	39.7±1.1	38.1±1.1	37.2±2.2	<.001	<.001	0.08
Birthweight (g)	3532.4±468.7	2504.1±285.3	2089.8±463.9	<.001	<.001	<.001
Birthweight Z-Score	0.50±0.9	-1.5±0.4	-2.1±0.6	<.001	<.001	<.001

BMI= Body Mass Index; Number are expressed as Mean±SD or n (%)

Table 2. Antenatal ultrasound findings at admission and neonatal outcome between small for gestational age (SGA) and growth restricted fetuses (FGR)

	SGA n=22	**FGR n=29**	**p-value**
Estimated fetal weight Z-score	-1.5±0.2	-2.0±0.4	<.001
Umbilical Artery-PI Z-score	0.5±0.9	1.5±1.4	<.001
Middle Cerebral Artery-PI Z-Score	-0.2±-0.9	-0.5±0.8	0.28
Cerebro-Placental Ratio Z-Score	-0.8±0.9	-1.7±1.6	0.03
Uterine Arteries'-PI Z-score	-0.3±1.2	0.9±1.8	0.01
Birthweight <3° percentile	2(9.1)	6(20.7)	0.001
Composite neonatal outcome [a]	2(9.1)	3(10.3)	0.88
NICU/SCBU admission	4(18.2)	12(41.4)	0.13
Length of neonatal hospitalization (days)	4.5±1.6	14.2±17.7	0.02

PI=Pulsatility Index; NICU=Neonatal Intensive Care Unit; SCBU=special care baby unit; Number are expressed as Mean±SD or n(%).

[a] defined in presence of at least one of the following outcomes: intrauterine fetal demise, umbilical artery pH <7.05 or vein pH <7.10, Apgar score at 5 min <7, stillborn, intracranial hemorrhage grade 3-4, encephalopathy, ductus art treatment, Intravascular disseminated coagulation, respiratory support>1 week, Necrotizing enterocolitis (NEC).

Table 3. Maternal hemodynamic findings among control women and women with small for gestational age (SGA) or growth restricted fetuses (FGR).

				Between groups p-value		
	Control n=61	**SGA n=22**	**FGR n=29**	**Control *vs* SGA**	**Control *vs* FGR**	**SGA *vs* FGR**
CO Z-score	-0.2±1.0	-0.4±0.8	-1.3±1.2	0.15	<.001	0.01
SVR Z-Score	-0.02±1.2	0.2±1.1	1.2±1.2	0.46	<.001	0.01
Stroke Volume (mL)	82.0±40.6	76.2±14.6	67.3±17.7	0.78	<.01	0.04
Stroke Volume percentile	45.1±29.4	48.7±32.1	34.1±28.2	0.63	0.07	0.12
Heart Rate (bpm)	85.4±15.2	81.1±12.6	79.0±12.8	0.19	0.09	0.85

Number are expressed as Mean±SD.

CO=Cardiac Output; SVR=Systemic Vascular Resistance.

Table 4. Correlation matrix for maternal hemodynamic parameters and fetal Doppler findings in 51 fetuses with estimated birthweight <10° percentile

	CO Z-Score	**SVR Z-Score**	**SV (percentile)**	**Mean UTA-PI Z-Score**	**UA- PI Z-Score**	**CPR Z-Score**	**Birthweight Z-Score**	**Gestational Age at delivery**	**Length of neonatal hospitalization**
CO Z-Score	-	-0.87 ***	0.59***	-0.36**	-0.36*	0.22	0.16	0.25	-0.42**
SVR Z-Score		-	-0.69***	0.46***	0.38***	-0.29	-0.16	-0.32*	0.42**
SV (percentile)		-	-	-0.37**	-0.19	0.12	-0.03	0.09	-0.19
Mean UtA-PI Z-Score	-	-	-	-	0.37**	-0.22	-0.44**	-0.40**	0.52***
UA- PI Z-Score	-	-	-	-	-	-0.80***	-0.28	-0.36*	0.33*
CPR Z-Score	-	-	-	-	-	-	0.38**	0.39**	-0.30*
Birthweight Z-Score	-	-	-	-	-	-	-	0.24	-0.43**
Gestational Age at delivery	-	-	-	-	-	-	-	-	-0.67***

* p < .05, ** p < .01, *** p < .001.

CO=Cardiac Output; SVR=Systemic Vascular Resistance; PI=Pulsatility Index; UtA-PI=Uterine Arteries; UA=Umbilical Arteries; CPR=Cerebro-Placental Ratio

Table 5. Predictors of length of neonatal hospitalization in neonates with a birthweight <10th percentile by using stepwise multiple regression

Predictors	**Estimate**	**SE**	**t**	**p-value**
Cardiac output (Z-score)	-3.5	1.4	-2.7	0.012
Birthweight (Z-Score)	-7.0	2.5	-2.8	0.007
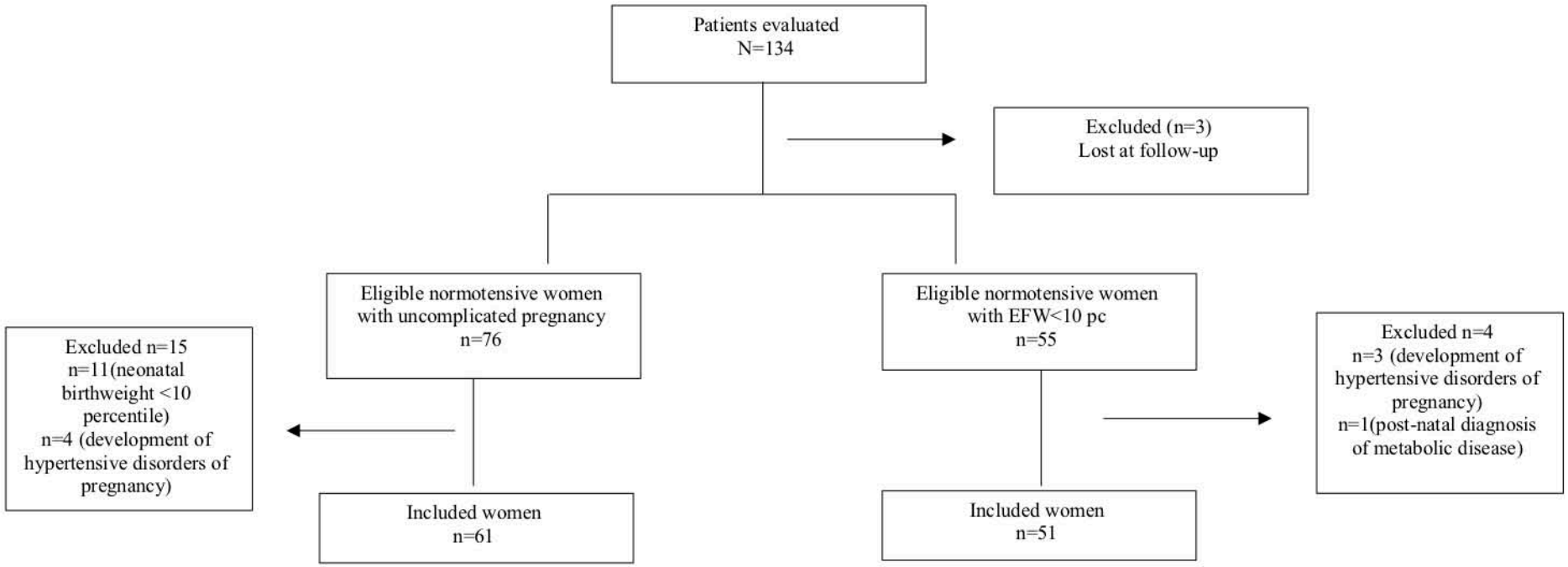
Figure 1. Flow chart (according to STROBE guidelines) for inclusion of cases