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

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

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30 **Conflicts of Interest**

31 None

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43 **ABSTRACT**

44

45 **Introduction:** Fetal growth restriction (FGR) in most instances results as a consequence of  
46 primary placental dysfunction due to inadequate trophoblastic invasion. Maternal cardiac  
47 maladaptation to pregnancy has been proposed as a possible determinant of placental  
48 insufficiency and impaired fetal growth. This study aimed to compare the maternal  
49 hemodynamic parameters between normotensive women with small-for-gestational age  
50 (SGA) and FGR fetuses and to evaluate their correlation with neonatal outcome.

51 **Material and methods:** observational cohort study including singleton pregnancies referred to  
52 our tertiary care center due to fetal smallness. At the time of diagnosis, fetuses were classified as  
53 SGA or FGR according to the Delphi consensus criteria and pregnant women underwent  
54 hemodynamic assessment by using cardiac output monitor (USCOM 1A Ltd). A group of women  
55 with singleton uncomplicated pregnancies  $\geq 35$  weeks of gestation were recruited as controls.

56 Cardiac output, systemic vascular resistance, stroke volume and heart rate were measured and  
57 compared among the three groups (controls vs. FGR vs. SGA). The correlation between antenatal  
58 findings and neonatal outcome was also evaluated by multivariate logistic regression analysis.

59 **Results:** 51 women with fetal smallness were assessed at  $34.8 \pm 2.6$  weeks. SGA and FGR  
60 were diagnosed in 22 and 29 cases, respectively. The control group included 61 women  
61 assessed at  $36.5 \pm 0.8$  weeks of gestation. Women with FGR had a lower cardiac output -Z  
62 score (respectively,  $-1.3 \pm 1.2$  vs.  $-0.4 \pm 0.8$  vs.  $-0.2 \pm 1.0$ ;  $p < .001$ ) and a higher systemic  
63 vascular resistance Z-score compared with both SGA and controls (respectively,  $1.2 \pm 1.2$  vs.

64 0.2±1.1 vs. -0.02±1.2; p<.001), while no difference in the hemodynamic parameters was  
65 found between women with SGA and controls. The incidence of NICU admission did not  
66 differ between SGA and FGR fetuses (18.2% vs 41.4%; p=0.13), however FGR had a longer  
67 hospitalization compared to SGA fetuses (14.2±17.7 vs. 4.5±1.6 days; p=0.02). Multivariate  
68 analysis showed that the cardiac output Z-score at diagnosis (p=0.012) and the birthweight  
69 Z-Score (p= 0.007) were independent predictors of the length of neonatal hospitalization.

70 **Conclusions:** Different maternal hemodynamic profiles characterize women with SGA or  
71 FGR fetuses. Furthermore, a negative correlation was found between the maternal cardiac  
72 output and the length of neonatal hospitalization.

73  
74 **Keywords:**  
75 maternal hemodynamics, growth restriction, small for gestational age, fetal growth  
76 restriction, cardiac output monitor, perinatal morbidity, neonatal hospitalization

77  
78 **Abbreviations:**

79 SGA small-for-gestational age  
80 FGR fetal growth restriction  
81 PI pulsatility index  
82 EFW estimated fetal weight  
83 CO cardiac output  
84 SV stroke volume  
85 SVR systemic vascular resistance  
86 USCOM Ultrasound Cardiac Output Monitor  
87 AC abdominal circumference  
88 UtA uterine arteries  
89 UA umbilical artery

90  
91 **Key-message**

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

111

## 112 INTRODUCTION

113

114 Small-for-gestational age (SGA) fetuses are at high risk of adverse outcome<sup>1</sup>.

115 However, such risk is mostly confined to those fetuses that do not reach their growth  
116 potential<sup>2</sup>. This latter condition, which is commonly referred to as fetal growth restriction

117 (FGR), has been defined by the association of reduced fetal size and abnormal indices of  
118 fetoplacental function at ultrasound Doppler examination<sup>3-6</sup>. Recently, an international  
119 consensus using a Delphi procedure has produced new standards for the antenatal diagnosis  
120 of FGR which include biometric and Doppler analysis<sup>7</sup>.

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

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

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

## 141 MATERIAL AND METHODS

142

### 143 Study design and study population

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

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

152 In both cases and controls the pregnancy had been dated by the crown-rump length  
153 measured at 11<sup>+0</sup>-13<sup>+6</sup> weeks of gestation.

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

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

160

### 161 Management

162 Upon referral, all women underwent sonographic assessment of the fetal biometry.  
163 The assessment of fetal biometry included the measurement of the fetal head circumference, the  
164 biparietal diameter, the AC and the femur length, and the EFW percentile was computed by  
165 means of the Hadlock 4 formula<sup>20</sup>. The EFW and the birthweight Z-score were calculated by  
166 using the Intergrowth-21 growth curves as reference<sup>21</sup>.

167 Furthermore, the mean pulsatility index (PI) of the maternal uterine arteries (UtA)<sup>22</sup>,  
168 the PI of the umbilical artery (UA) and the PI of the middle cerebral artery were recorded  
169 and converted into the corresponding percentile for the gestational week<sup>23</sup>.

170 The Delphi consensus criteria based on the combined assessment of biometric and  
171 Doppler parameters was used to classify each case as FGR or SGA<sup>7</sup> as follows:

- 172 - <32 weeks: AC/EFW<3<sup>rd</sup> centile or absent end-diastolic flow in UA or AC/EFW  
173 <10<sup>th</sup> centile combined with uterine arteries PI>95<sup>th</sup> centile and/or UA PI>95<sup>th</sup>  
174 percentile
- 175 - ≥32 weeks: AC/EFW<3<sup>rd</sup> centile or at least two out of: AC/EFW <10<sup>th</sup> centile;  
176 AC/EFW crossing more than 2 quartiles; cerebral-placental ratio <5<sup>th</sup> centile or UA  
177 PI >95<sup>th</sup> centile.

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

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

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

202  
203 **Outcome**

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

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

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

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

216 • Length of neonatal hospitalization (days).

217

## 218 **Statistical Analyses**

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

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



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

240

#### 241 **Ethical approval**

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

244

#### 245 **RESULTS**

246

247 Over the study period, 58 cases of normotensive pregnancies with EFW  $< 10$  percentile  
248 were confirmed at our ultrasound department and considered eligible for the study purposes;  
249 3 of them were lost at follow-up, 3 cases were excluded because they developed  
250 hypertensive disorder of pregnancy and 1 was excluded because of postnatal diagnosis of  
251 metabolic disease. A total of 51 women with a mean gestational age at admission of  
252  $34.8 \pm 2.6$  weeks were eventually included in the study group. Of these, 29 were classified as  
253 FGR and 22 as SGA in accordance with the Delphi classification<sup>7</sup>. In all these cases the  
254 birthweight was  $< 10^{\text{th}}$  centile for our reference neonatal charts.

255 Seventy-six normotensive women with uncomplicated pregnancies were considered as  
256 potential controls; 11 of them were subsequently removed as birthweight was found to be  
257  $< 10^{\text{th}}$  percentile while 4 women were excluded as they developed hypertension within 3  
258 days after delivery and 1 was lost at follow-up. Overall, a total of 61 women, who were  
259 submitted at USCOM assessment at a mean gestational age of  $36.5 \pm 0.8$  weeks, were used as  
260 controls (Figure 1).

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

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

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

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

281

## 282 **DISCUSSION**

283

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

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

298 uterine blood supply in the early gestation and this is responsible for reduced trophoblastic  
299 invasion and ultimately for placental hypoxia<sup>31</sup>.

300 Indeed, a similar mechanism has been recently advocated in the pathophysiology of  
301 early onset preeclampsia associated to FGR<sup>32,33</sup>.

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

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

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

321 Roberts et al.<sup>40</sup> compared maternal hemodynamics among fetuses <10<sup>th</sup> percentile with  
322 different fetal Doppler findings (evidence of an abnormal fetal Doppler index at presentation  
323 vs. subsequent development of abnormal Doppler index vs. stable normal fetal Doppler).

324 This study could not demonstrate a role of maternal hemodynamics in anticipating the  
325 subsequent development of abnormal fetal Doppler. However, the maternal hemodynamic  
326 profile was shown to improve the prediction of birthweight <3<sup>rd</sup> percentile. Of note, in their  
327 study Roberts et al. did not exclude women with hypertensive disorders of the pregnancy,  
328 among whom an increased prevalence of birthweight <3<sup>rd</sup> percentile was reported.

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

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

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

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

360 A limitation of our study is the small number of subjects included, even though such  
361 number is comparable to that of the majority of the previous studies on the same subject, and  
362 sample size calculation was performed prior to enrollment of the study participants.

363 Furthermore, the decision to include in the control group neonates weighting >10<sup>th</sup> centile  
364 for the given gestation may have led to the inappropriate inclusion of cases of FGR  
365 characterized by a reduced intrauterine growth velocity (i.e. decrease of the longitudinal  
366 growth of more than 2 quartiles on the charts) but a normal weight at birth. Moreover, the  
367 selection bias due to the study setting (tertiary referral hospital) may justify the high fraction  
368 of fetuses with an EFW classified as FGR rather than SGA.

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

371

## 372 CONCLUSION

373

374 Maternal cardiac dysfunction might play a pivotal role in the pathophysiology of FGR  
375 in normotensive pregnant women. The degree of impairment of the maternal hemodynamic  
376 function seems to correlate with the perinatal outcomes of the neonates with a birthweight  
377 <10<sup>th</sup> percentile.

378

379

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520 **Legend**

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

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525 **Supporting Information legend**

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527 Figure S1. Correlation and estimated marginal means between cardiac output (CO) Z-score and  
528 the length of neonatal hospitalization among neonates with a birthweight <10<sup>th</sup> percentile.

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

	Control n=61	SGA n=22	FGR n=29	Between groups p-value		
				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 <sup>2</sup> )	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)

	<b>SGA n=22</b>	<b>FGR n=29</b>	<b>p-value</b>
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 <sup>o</sup> percentile	2(9.1)	6(20.7)	0.001
Composite neonatal outcome <sup>a</sup>	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(%).

<sup>a</sup> 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).

	<b>Control n=61</b>	<b>SGA n=22</b>	<b>FGR n=29</b>	Between groups p-value		
				<b>Control vs SGA</b>	<b>Control vs FGR</b>	<b>SGA vs FGR</b>
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<sup>o</sup> 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 <10<sup>th</sup> percentile by using stepwise multiple regression

<b>Predictors</b>	<b>Estimate</b>	<b>SE</b>	<b>t</b>	<b>p-value</b>
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

