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Maternal cardiac function at 35–37 weeks' gestation: relationship with birth weight

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KEYWORDS: cardiac output; large-for-gestational-age neonates; maternal cardiovascular function; small-for-gestational-age neonates; third-trimester screening; total peripheral resistance

ABSTRACT

Objective *To evaluate the relationship between maternal cardiovascular parameters and neonatal birth weight and examine the potential value of these parameters in improving the prediction of small-for-gestational-age (SGA) and large-for-gestational-age (LGA) neonates provided by maternal characteristics and medical history.*

Methods *In 2835 singleton pregnancies maternal characteristics and medical history were recorded and maternal cardiovascular parameters were measured. The observed measurements of cardiovascular parameters were expressed as multiples of the normal median (MoM) values after adjustment for those characteristics found to provide a substantial contribution to their measurement. Regression analysis was used to determine the significance of association between the normalized values of the cardiovascular parameters with birth-weight Z-score. Multivariable logistic regression analysis was then used to determine if the maternal factors, fetal biometry and maternal cardiovascular parameters had a significant contribution to predicting SGA and LGA neonates. The performance of screening was determined by the area under receiver–operating characteristics curves (AUC).*

Results *In the study population there were significant positive associations between maternal cardiac output and heart rate with neonatal birth-weight Z-score, and significant negative associations between total peripheral resistance and mean arterial pressure (MAP) with neonatal birth-weight Z-score. In pregnancies delivering SGA neonates (n = 249 (8.8%)), cardiac output and heart rate were lower and total peripheral resistance and MAP were higher, whereas in pregnancies delivering LGA neonates (n = 292 (10.3%)) cardiac output and heart rate were higher and total peripheral resistance and MAP were lower. The performance of screening for delivery of SGA neonates achieved by maternal characteristics and fetal biometry was not improved by the measurement of maternal cardiovascular parameters. There was a small but significant improvement in the performance of screening for delivery of LGA neonates by maternal factors and fetal biometry with the addition of maternal heart rate (comparison of AUC, P = 0.0095).*

Conclusions *There are significant associations between maternal cardiac output, heart rate, total peripheral resistance and MAP and neonatal birth-weight Z-score; such findings reflect the close relationship between maternal cardiac function and fetal demands. However, assessment of these parameters at 35–37 weeks' gestation is unlikely to improve substantially the performance of screening for SGA or LGA neonates provided by a combination of maternal factors and fetal biometry. Copyright © 2016 ISUOG. Published by John Wiley & Sons Ltd.*

INTRODUCTION

The birth of a small-for-gestational-age (SGA) neonate is associated with impaired uteroplacental perfusion, reflected in increased uterine artery pulsatility index, but also impaired maternal cardiovascular function reflected in reduced cardiac output and increased peripheral resistance, and these changes in biomarkers are apparent from the first trimester of pregnancy[1–5]. In most of these studies on biomarkers, biomarker levels in pregnancies delivering SGA neonates were compared with those in pregnancies with appropriate-for-gestational-age (AGA) neonates, and it is therefore uncertain what the levels are in pregnancies with large-for-gestational-age (LGA) neonates.

The objective of this screening study at 35–37 weeks' gestation was to evaluate the relationship between maternal cardiovascular parameters and neonatal birth weight

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and to examine the potential value of these parameters in improving the prediction of SGA and LGA neonates provided by maternal characteristics and medical history.

METHODS

The data for this study were derived from prospective screening for adverse obstetric outcomes in women attending for their routine hospital visit in the third trimester of pregnancy at King's College Hospital, London, UK and Medway Maritime Hospital, Kent, UK, between March 2015 and December 2015. This visit, which is held at $35 + 0$ to $37 + 6$ weeks' gestation, included the recording of maternal characteristics and medical history, ultrasonographic estimation of fetal weight and measurement of maternal cardiovascular parameters[6]. Gestational age was determined by measurement of fetal crown–rump length at 11–13 weeks or fetal head circumference at 19–24 weeks[7,8]. Cardiovascular function was assessed using a non-invasive, bioreactance method (NICOM, Cheetah Medical Ltd, Maidenhead, Berkshire, UK); this operator-independent technology has been validated in both non-pregnant and pregnant populations[9–11]. We obtained measurements of cardiac output, stroke volume, heart rate, cardiac power, thoracic fluid capacity, ventricular ejection time, total peripheral resistance and mean arterial pressure (MAP)[6].

Written informed consent was obtained from the women agreeing to participate in this study on adverse pregnancy outcome, which was approved by the ethics committee of each participating hospital. In this paper we present the results on the relationship between maternal cardiovascular parameters and neonatal birth weight. The patients included in the study all had pregnancies unaffected by pre-eclampsia (PE) or gestational hypertension (GH) resulting in the live birth of a phenotypically normal baby and were part of our previous publication on the relationship of maternal cardiovascular function and maternal characteristics[6].

Data on pregnancy outcome were collected from the hospital maternity records or the general medical practitioners of the women. The neonate was considered to be SGA, LGA or AGA when the birth weight corrected for gestational age at delivery was $< 10^{th}$ percentile, $> 90^{th}$ percentile or between the 10^{th} and 90^{th} percentiles, respectively[12]. The definition of PE was that of the International Society for the Study of Hypertension in Pregnancy[13]. The obstetric records of all women with pre-existing or pregnancy-associated hypertension were examined to confirm that the condition was chronic hypertension, PE or GH.

Statistical analysis

The observed measurements of maternal cardiovascular parameters were expressed as multiples of the median (MoM) values after adjustment for those characteristics found to provide a substantial contribution to their measurement[6]. Regression analysis was used to determine the significance of association between the normalized values of the maternal cardiovascular parameters and birth-weight *Z*-score. The Mann–Whitney *U*-test was used to compare the observed values and the normalized values of maternal cardiovascular parameters between the SGA, LGA and AGA groups. The *a-priori* risks for SGA and LGA were determined using the algorithms derived from the multivariable logistic regression analysis of maternal characteristics and ultrasonographic measurements of fetal biometry, as described previously[14,15]. Multivariable logistic regression analysis was then used to determine if the maternal factor and fetal biometry derived logit (*a-priori* risk) and maternal cardiovascular parameters had a significant contribution to predicting SGA and LGA. The performance of screening was determined by the area under receiver–operating characteristics curves (AUC).

The statistical software packages SPSS 22.0 (SPSS Inc., Chicago, IL, USA) and Medcalc (Medcalc Software, Mariakerke, Belgium) were used for all data analysis.

RESULTS

Regression analysis demonstrated significant associations between $\log_{10}$MoM values of cardiac output ($r = 0.117$, $P < 0.0001$), total peripheral resistance ($r = -0.133$, $P < 0.0001$) and MAP ($r = -0.067$, $P < 0.0001$) and MoM values of heart rate ($r = 0.141$, $P < 0.0001$) with neonatal birth-weight *Z*-score (Figure 1). Pearson correlation between $\log_{10}$MoM values of cardiac output, total peripheral resistance, MAP and MoM values of heart rate are shown in Table S1.

There were 2294 (80.9%) AGA neonates, 249 (8.8%) SGA and 292 (10.3%) LGA. Cardiac output and heart rate were lower and total peripheral resistance and MAP were higher in the SGA group than in the AGA group but stroke volume, cardiac power, thoracic fluid capacity and ventricular ejection time were not significantly different (Table 1; Figure 2). Cardiac output, heart rate and thoracic fluid capacity were higher and total peripheral resistance and MAP were lower in the LGA group than in the AGA group, but stroke volume, cardiac power and ventricular ejection time were not significantly different (Table 1; Figure 2).

Prediction of SGA and LGA neonates

The patient-specific risk for delivery of SGA and LGA neonates is calculated from the formula: risk = odds/(1 + odds), where odds = e^Y. Y for the prediction of delivery of SGA neonates was derived from backward stepwise multivariate regression analysis of the maternal factor and fetal biometry-derived logit (*a-priori* risk) and the normalized values of each of the maternal cardiovascular parameters. Multivariable logistic regression analysis for the prediction of delivery of a SGA neonate with maternal factors, fetal biometry and various maternal cardiovascular parameters is shown in Table S2. Maternal cardiac output was not a significant independent

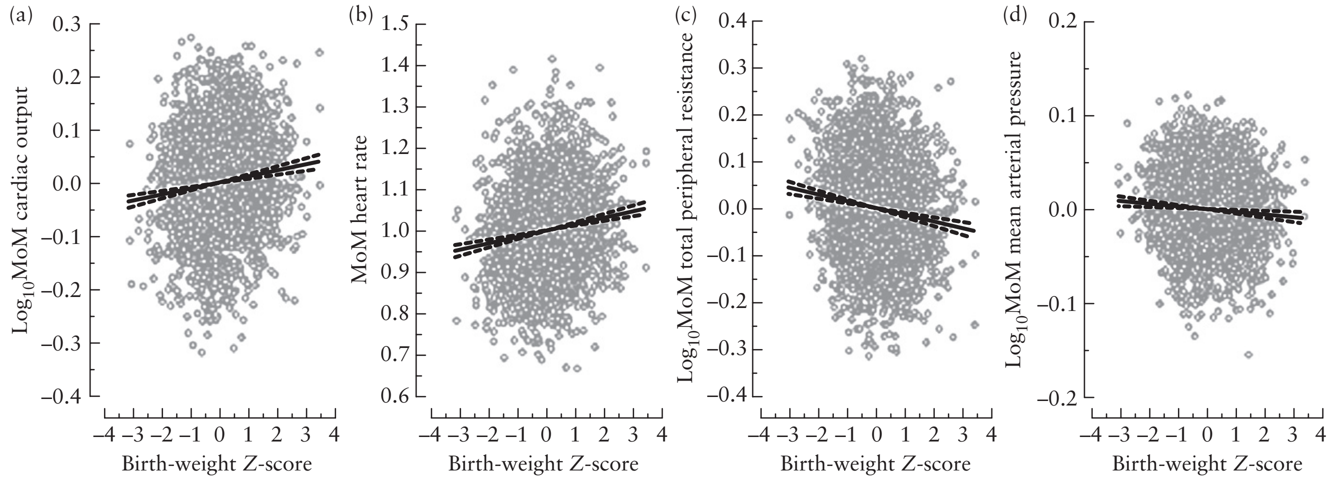

Figure 1 Association between cardiac output (a), heart rate (b), total peripheral resistance (c) and mean arterial pressure (d) and birth-weight *Z*-scores.

Table 1 Maternal cardiovascular parameters in pregnancies with delivery of appropriate-, small- and large-for-gestational-age neonates

	Appropriate-for-gestational age (n = 2294)		*Small-for-gestational age (n = 249)*		*Large-for-gestational age (n = 292)*	
Parameter	*Observed value*	*$Log_{10}MoM$*	*Observed value*	*$Log_{10}MoM$*	*Observed value*	*$Log_{10}MoM$*
CO (L/min)	6.820 (5.830 to 7.993)	0.002 (−0.059 to 0.062)	6.294 (5.313 to 7.694)*	−0.010 (−0.084 to 0.056)*	7.285 (6.385 to 8.735)*	0.196 (−0.039 to 0.075)*
SV (mL/beat)	76.095 (64.434 to 89.225)	0.003 (−0.063 to 0.067)	72.085 (60.213 to 85.806)*	−0.003 (−0.076 to 0.062)	80.249 (67.725 to 93.138)*	0.010 (−0.055 to 0.074)
HR (bpm)	90 (83 to 97)	0.000 (−0.032 to 0.028)	88 (81 to 94)*	−0.011 (−0.046 to 0.014)*	92 (86 to 99)*	0.013 (−0.017 to 0.040)*
TPR (dynes × s/cm^5)	1063.4 (896.3 to 1266.1)	−0.002 (−0.066 to 0.067)	1162.0 (956.7 to 1420.7)*	0.036 (−0.053 to 0.102)*	980.3 (832.4 to 1175.6)*	−0.025 (−0.093 to 0.047)*
MAP (mmHg)	89.7 (84.0 to 95.5)	0.000 (−0.026 to 0.026)	90.7 (85.4 to 96.0)	0.007 (−0.014 to 0.035)*	90.3 (84.5 to 96.5)	−0.003 (−0.029 to 0.025)*
CP (L/min)	1.350 (1.133 to 1.600)	0.004 (−0.069 to 0.068)	1.250 (1.042 to 1.550)*	−0.008 (−0.082 to 0.061)	1.450 (1.200 to 1.750)*	0.015 (−0.054 to 0.083)
TFC	64.200 (54.674 to 78.223)	−0.010 (−0.076 to 0.071)	64.544 (55.268 to 80.579)	−0.018 (−0.076 to 0.076)	65.328 (54.154 to 80.050)	0.008 (−0.059 to 0.098)*
VET (ms)	249.155 (225.000 to 270.777)	0.005 (−0.031 to 0.037)	250.375 (230.300 to 270.000)	0.008 (−0.028 to 0.036)	244.708 (219.778 to 264.775)*	0.008 (−0.030 to 0.032)

Comparisons between outcome groups were by Mann–Whitney *U*-test, with *post-hoc* Bonferroni correction (*$P < 0.025$). CO, cardiac output; CP, cardiac power; HR, heart rate; MAP, mean arterial pressure; MoM, multiples of the median; SV, stroke volume; TFC, thoracic fluid capacity; TPR, total peripheral resistance; VET, ventricular ejection time.

predictor of SGA ($P = 0.293$). Y for the prediction of delivery of a LGA neonate was derived from backward stepwise multivariate regression analysis of the maternal factor and fetal biometry-derived logit (*a-priori* risk) and the normalized values of each of the maternal cardiovascular parameters. Multivariable logistic regression analysis for the prediction of delivery of a LGA neonate with maternal factors, fetal biometry and maternal heart rate is shown in Table S3. Maternal cardiac output ($P = 0.173$), total peripheral resistance ($P = 0.073$), MAP ($P = 0.077$) and thoracic fluid capacity ($P = 0.156$) were not significant independent predictors of LGA.

The performance of screening for delivery of SGA and LGA neonates is shown in Table 2 and Figure 3. The performance of screening for delivery of SGA neonates achieved by maternal characteristics and fetal biometry was not improved by inclusion of maternal cardiovascular parameters. There was a small but significant improvement in the performance of screening for delivery of LGA neonates by maternal factors and fetal biometry with the addition of maternal heart rate (comparison of AUCs, $P = 0.0095$).

DISCUSSION

Principal findings of the study

This screening study at 35–37 weeks' gestation demonstrates significant associations between maternal cardiac output, heart rate, total peripheral resistance and MAP and neonatal birth-weight *Z*-score; such findings reflect the close relationship between maternal cardiac function and fetal demands. In pregnancies delivering SGA neonates, cardiac output and heart rate were lower and total peripheral resistance and MAP were higher, whereas

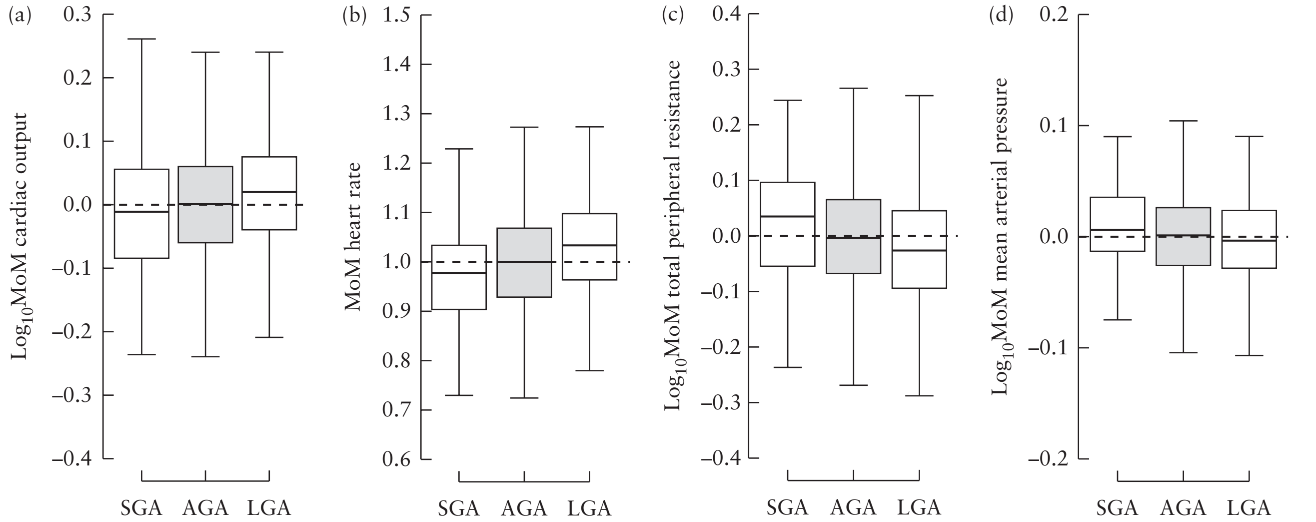

Figure 2 Box-and-whisker plots of cardiac output (a), heart rate (b), total peripheral resistance (c) and mean arterial pressure (d) in pregnancies delivering small- (SGA), appropriate- (AGA) and large-for-gestational-age (LGA) neonates. Boxes with internal lines represent median and interquartile range and whiskers are range.

Table 2 Performance of screening for delivery of small- and large-for-gestational-age neonates with maternal factors, fetal biometry and various combinations of maternal cardiovascular parameters at 35–37 weeks' gestation

	Small-for-gestational age			*Large-for-gestational age*		
		Detection rate (%)			*Detection rate (%)*	
Parameter	*AUC*	*5% FPR*	*10% FPR*	*AUC*	*5% FPR*	*10% FPR*
History	0.721 (0.691–0.750)	13.3 (9.6–18.6)	24.1 (18.9–29.9)	0.745 (0.714–0.777)	27.4 (22.4–32.5)	41.8 (36.1–47.7)
History with fetal biometry	0.859 (0.836–0.882)	40.6 (34.4–46.9)	55.8 (49.4–62.1)	0.859 (0.839–0.879)	41.8 (36.1–47.7)	55.8 (49.9–61.6)
History with fetal biometry plus:						
HR	0.861 (0.838–0.883)	41.4 (35.2–47.8)	57.8 (51.4–64.0)	0.865 (0.845–0.884)	43.5 (37.7–49.4)	57.2 (51.3–62.9)
TPR	0.860 (0.837–0.882)	41.0 (34.8–47.4)	55.8 (49.4–62.1)	—	—	—
MAP	0.860 (0.837–0.882)	42.6 (36.3–49.0)	56.6 (50.2–62.9)	—	—	—
HR, TPR	0.861 (0.839–0.884)	40.6 (34.4–36.9)	57.8 (51.4–64.0)	—	—	—
HR, MAP	0.862 (0.710–0.767)	44.6 (38.3–51.0)	57.0 (50.6–63.3)	—	—	—

Data in parentheses are 95% CI. AUC, area under receiver–operating characteristics curve; FPR, false-positive rate; HR, heart rate; MAP, mean arterial pressure; TPR, total peripheral resistance.

in pregnancies delivering LGA neonates cardiac output and heart rate were higher and total peripheral resistance and MAP were lower.

The performance of screening for delivery of SGA neonates achieved by maternal characteristics and fetal biometry was not improved by the inclusion of maternal cardiovascular parameters, but there was a small improvement in the performance of screening for delivery of LGA neonates by the addition of maternal heart rate to maternal factors and fetal biometry.

Strengths and limitations of the study

The strengths of this late third-trimester screening study for delivery of SGA and LGA neonates are first, examination of pregnant women attending routine assessment of fetal growth and wellbeing; second, recording of data on maternal characteristics and medical history and fetal biometry to define the prior risk; third, use of an automated non-invasive cardiac monitor to provide accurate measurements of cardiovascular function, and expression of values as MoMs after adjustment for factors that affect the measurements; and fourth, use of multivariable logistic regression to combine the prior risk with biomarkers to estimate patient-specific posterior risks and the performance of screening for delivery of SGA and LGA neonates.

A limitation of the study is that it was a cross-sectional one and it was not possible to determine whether the

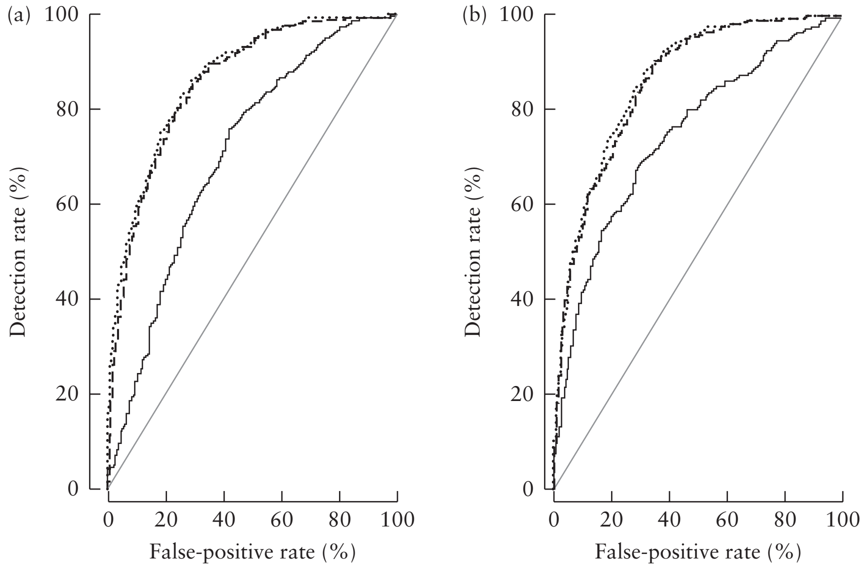

Figure 3 Receiver–operating characteristics (ROC) curves of maternal factors (——), maternal factors with fetal biometry (- - -), and maternal factors with fetal biometry, mean arterial pressure and heart rate (······) at 35–37 weeks' gestation, in the prediction of delivery of small-for-gestational-age neonates (a) and large-for-gestational-age neonates (b).

observed alterations in cardiac output and peripheral resistance in the few weeks before delivery of SGA or LGA neonates were preceded by a different pattern of values in the first or second trimester; this can be answered only by longitudinal studies. An additional limitation relates to the exclusion of the most severe cases of SGA, which would have been delivered before the gestational window investigated in this study.

Comparison with previous studies

The finding of our late third-trimester study that low maternal cardiac output and high peripheral resistance precede the birth of SGA neonates is compatible with the results of a previous study that demonstrated that these changes are apparent from as early as 11–13 weeks' gestation[5]. Normal pregnancy is associated with a more than 40% expansion in plasma volume, which starts from before 10 weeks' gestation and peaks at 32 weeks[16]. Normal pregnancy is also characterized by generalized vasodilatation, possibly triggered by placental angiogenic growth factors, with a secondary compensatory increase in cardiac output[17–19]. In pregnancies with SGA fetuses, the physiological expansion in plasma volume is substantially reduced[17], with a consequent reduction in preload and therefore cardiac output[4,5]. The increased peripheral resistance observed in SGA pregnancies may be the consequence of first, impaired placentation and reduced production of angiogenic growth factors[1] and second, increased viscosity due to impaired plasma volume expansion[20,21].

Previous studies have not directly assessed maternal cardiovascular function in pregnancies delivering LGA neonates. Our findings that in such pregnancies there is increased cardiac output and reduced peripheral resistance could be the consequence of increased plasma volume expansion and reduced vascular tone and viscosity, compared with pregnancies delivering AGA neonates. Previous studies have reported that in women delivering LGA neonates, compared to those with AGA neonates, the serum concentration of placental growth factor is increased and uterine artery pulsatility index is decreased in the first, second and third trimesters of pregnancy[15]. A previous first-trimester screening study reported a linear association between maternal cardiac output and birth-weight percentile, and by implication cardiac output was lower in pregnancies delivering SGA neonates and higher in those with LGA neonates, compared to those with AGA neonates[5].

In our pregnancies with LGA neonates, the increase in cardiac output was primarily due to an increase in heart rate rather than stroke volume. The heart in a normal non-pregnant individual operates in the ascending part of the Frank–Starling curve, with a substantial increase in stroke volume in response to increased preload[22]. However, in a normal pregnancy with its expanded blood volume and venous return, the heart is likely to operate in the upper flat part of the Frank–Starling curve, with an increase in preload being accompanied by only a small increase in stroke volume.

Clinical implications of the study

This study has demonstrated alterations in maternal cardiovascular parameters in pregnancies delivering SGA and LGA neonates. However, assessment of these parameters at 35–37 weeks' gestation is unlikely to provide a substantial improvement in the performance of screening for SGA or LGA neonates provided by a combination of maternal factors and fetal biometry.

ACKNOWLEDGMENT

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SUPPORTING INFORMATION ON THE INTERNET

The following supporting information may be found in the online version of this article:

Table S1 Pearson correlation between $\log_{10}$MoM values of cardiac output, total peripheral resistance, mean arterial pressure and MoM values of heart rate

Table S2 Fitted regression models with maternal factors and fetal biometry (*a-priori* risk), and maternal cardiovascular parameters at 35–37 weeks' gestation for the prediction of delivery of small-for-gestational-age neonates

Table S3 Fitted regression models with maternal factors and fetal biometry (*a-priori* risk) and maternal heart rate at 35–37 weeks' gestation for the prediction of delivery of large-for-gestational-age neonates

