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Accuracy of the fetal cerebroplacental ratio for the detection of intrapartum compromise in non-small fetuses

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ABSTRACT

Objective

To study the accuracy of the cerebroplacental ratio (CPR) for the detection of intrapartum fetal compromise (IFC) in fetuses growing over the 10^{th} centile.

Methods

This was a prospective study of 569 non-small fetuses attending the day hospital unit of a tertiary hospital that underwent an ultrasound examination at 36-40 weeks, and were delivered within 4 weeks of examination. IFC was defined as a composite of: abnormal intrapartum fetal heart rate or intrapartum fetal scalp pH<7.20 requiring cesarean section, neonatal umbilical cord pH<7.20, 5’ Apgar score <7 and postpartum admission to neonatal or pediatric intensive care units. The accuracy of CPR for the prediction of IFC was calculated alone and in combination with other perinatal parameters using univariate and multivariate logistic regression models, which alternatively included the onset of labor to evaluate the influence of induction of labor (IOL) on IFC and a brief composite adverse outcome of two parameters to prove the strength of the approach.

Results

The incidence of IFC was 17.9%. CPR sensitivity was 30.4% for a false positive rate (FFR) of 10% and 14.7% for a FPP of 5% (AUC=0.62, p<0.001. The multivariate analysis showed that only fetal gender and parity increased the predictive accuracy of CPR alone, although the improvement was poor (AUC=0.67, p<0.001). No differences were observed using any of the alternative models. Finally, IOL had no influence of IFC.

Conclusion

Despite their apparent normality, a proportion of fetuses growing over the 10^{th} centile suffer IFC. Some of them are suitable for detection by means of CPR.

KEY WORDS

Cerebroplacental ratio, fetal Doppler, fetal growth.

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INTRODUCTION

Fetal growth restriction (FGR) is known to increase perinatal morbidity and mortality[1]. In the last decade, an important effort has been done to diagnose FGR by means of biometrical and hemodynamical fetal evaluation[2,3]. However, as the majority of fetuses at the end of pregnancy present a normal birth weight (BW), the burden of perinatal complications, including stillbirth, occur unexpectedly in non-small fetuses [4-6]. In fact, until recently, late-onset fetal growth restriction (FGR) was considered a matter of small for gestational age (SGA) fetuses[7]. However, many SGA fetuses are in fact constitutionally small[8]. Furthermore, a proportion of non-small fetuses have not reached their growth potential and suffer poor nutrition at the end of pregnancy[9,10]. Therefore, the focus of interest has currently shifted towards these fetuses which characteristically present cerebral vasodilation, as they represent a poorly studied group of fetuses at risk of adverse outcome.

The cerebroplacental ratio (CPR) reflects the fetal cerebral redistribution in response to hypoxaemia[11,12]. As this may occur at all weight centiles[10], the CPR has been shown to associate with adverse perinatal outcome independently of fetal BW. Therefore, it can be considered as a marker of failure to reach growth potential in both non-small and SGA fetuses[9,10]. Many studies have shown the utility of the CPR in detecting small fetuses at risk of adverse outcome[13,14]. Unfortunately, studies evaluating the CPR in non-small fetuses are scarce[15-17]. The main aim of this study was to investigate the accuracy of CPR for the detection of intrapartum fetal compromise (IFC) in a cohort of non-small fetuses evaluated at term.

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MATERIAL AND METHODS

This was a prospective study of 569 low risk fetuses attending for routine ultrasound at the public tertiary maternity of La Fe hospital. The ultrasound examination was performed between 36+0 and 40+5 and included an estimated fetal weight, assessment of the amniotic fluid volume and Doppler evaluation of the umbilical (UA) and middle cerebral arteries (MCA) pulsatility indices (PI). The UA and MCA were recorded using color and pulse Doppler according to earlier descriptions[18-19] and the cerebroplacental ratio (CPR) was calculated as the simple ratio between the MCA PI and the UA PI[18,20]. All pregnancies were delivered in less than 4 weeks after the scan (28 days or less). Only one (the last) examination per fetus was included in the analysis.

In order to adjust for the effect of the GA, estimated fetal weight (EFW), and BW values were converted into centiles using the method described earlier by Yudkin[21] and CPR values were converted into multiples of median (MoM) dividing each value by the 50th centile at each gestational age as earlier described[18]. CPR medians (50th centile) were those used in recent studies and were represented by the equation[18]:

CPR 50th centile = -3.814786276 + 0.36363249 * GA (in weeks) – 0.005646672 * GA (in weeks)^2

All Doppler examinations were performed by the first author, a certified teaching expert in obstetric ultrasound by the Spanish Society of Obstetrics and Gynecology, using General Electric Voluson® (E8/E6/730) ultrasound machines with 2-8 MHz convex probes, during fetal quiescence, in the absence of fetal tachycardia, and keeping the insonation angle with the examined vessels as small as possible.

GA was determined according to the crown-rump length in the first trimester. Multiple pregnancies and those complicated by major congenital fetal abnormalities or aneuploidy were excluded from the study. Outcome data including BW, mode of delivery, Apgar score, cord arterial pH and admission to the neonatal care unit were collected after birth and a composite adverse outcome was determined. IFC was considered when the composite adverse outcome was positive for any of these 5 components: abnormal intrapartum fetal heart rate (according to the intrapartum fetal monitoring guidelines of the FIGO)[22], or intrapartum fetal scalp pH <7.20 requiring cesarean section, neonatal umbilical cord pH <7.20, 5 minute Apgar score <7, and postpartum admission to the neonatal intensive care unit or special care baby unit. As per local protocol, all fetuses were initially treated as low-risk AGA fetuses, and were subsequently managed according to their progression in labor. Cases with abnormal intrapartum fetal heart rate requiring instrumental delivery were not included if they were preceded by a normal heart rate or if fetal scalp pH or neonatal pH was>7.20. Elective cesarean deliveries were discarded, as we were specifically interested in labor progression.

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Statistical analysis

Descriptive statistics were performed evaluating maternal age, parity, GA at examination in weeks, GA at delivery in weeks, interval between ultrasound and delivery, EFW, EFW centile, Doppler parameters (UA PI, MCA PI, CPR, UA PI MoM, MCA PI MoM, CPR MoM), fetal gender, ethnicity, onset of labor (induction and spontaneous), mode of delivery (cesarean section, forceps, vacuum (ventouse), Thierry's spatulas spontaneous vaginal delivery), Apgar scores at 5 minutes, neonatal cord arterial pH, and baby destiny (maternity ward, neonates ward, intensive care unit). Continuous variables were presented as median and interquartile range (IQR), while categorical variables were presented as absolute and relative frequencies.

The accuracy of the CPR alone for the detection of IFC was evaluated calculating the ROC curve with the area under the curve (AUC) and the detection rate (sensitivity) for a false positive rate (FPR) (1-specificity) of 10%. The sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), positive likelihood ratio (LR+) and negative likelihood ratio (LR-) were obtained for two specific CPR MoM thresholds: the optimal threshold according to the ROC analysis and a CPR MoM of 0.6765 (the threshold used to define failure to reach growth potential in a previous study)[9].

In order to try to improve the predictive accuracy of the CPR, a multivariate logistic regression analysis was performed including those clinical parameters that were significant in the previous univariate analysis. These selected parameters were used to create a combined prediction model, in which the odds ratios (OR) with their 95% confidence intervals (95% CI), the AUC and the sensitivity for a FPR of 10% were calculated. A univariate model using CPR alone was also shown for comparison purposes including the same statistical descriptors.

In addition to the model above indicated, 3 alternative combined models were also calculated. In the first the onset of labor (induction, spontaneous) was included among the explanatory variables in order to evaluate if induction was an important parameter explaining IFC. Also, in order to prove the strength of the prediction model, IFC was evaluated according to a brief composite adverse outcome that included only 2 parameters (neonatal pH and admission to postnatal pediatric care).

Comparisons were made with Mann-Whitney and Chi-Square tests. The Akaike Information Criterion (AIC) was used to select the best prediction model by mean of a lower AIC, which indicated a higher accuracy. Statistical analysis[17] and graphs were performed using the R-software® (version 3.3.2). Significance was considered with a p value of less than 0.05. IRB permission was obtained for this study (Reference 2014/0063). The authors report no conflicts of interest.

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RESULTS

Table 1 shows the characteristics of the study population. The study included 569 singleton pregnancies, of which 54.7% were male and 45.3% female fetuses, The majority of the study cohort were Caucasian (96.3%), 1.4% were of black ethnic origin, 1.6% South Asian and 0.7% East Asian. Most of the pregnancies had a spontaneous onset of labor (53.4%) and had also a spontaneous vaginal delivery (57.6%), with neonates born uneventfully and sent together with the mother to the maternity ward (97.7%). Only two fetuses (0.4%) had an Apgar score <7 at 5 minute, while 73 (12.8%) had a neonatal cord pH <7.20 and 13 (2.3%) needed admission to the neonatal unit. Abnormal intrapartum fetal heart rate or intrapartum scalp pH (<7.20) requiring emergency cesarean section were recorded in 4.4% of the pregnancies. The composite outcome of IFC was seen in 17.9% of the pregnancies (Figure 1).

Table 2 compares the characteristics of the pregnancies according to the study outcome. There were more nulliparous women (p=0.03) and male fetuses (p=0.01) in the adverse outcome group. When compared to the fetuses with normal outcome, the UA PI MoM was significantly higher (p=0.008), while the MCA PI MoM (p=0.004) and the CPR MoM (p<0.001) were significantly lower in the group with adverse outcome (Figure 2). There were no significant differences in the maternal age (p=0.61), ethnicity (p=0.35), GA at ultrasound (p=0.71) or delivery (p=0.55), interval ultrasound-delivery (p=0.54), EFW (p=0.21), EFW centile (p=0.19), BW (p=0.13) and BW centile (p=0.09).

Figure 3 shows the CPR ROC analysis with an AUC of 0.62 (95 CI 0.55, 0.68, p<0.001). For a FPR of 10%, the detection rate was 30.4. The best threshold was seen at a CPR value of 0.827 MoM (95% CI 0.792, 0.431). As indicated in table 3, using this cut-off, 141 fetuses were selected as abnormal (44 were true positive and 97 true negative). The sensitivity, specificity, PPV, NPV, LR+ and LR- were 43%, 79%, 31%, 86%, 2.08 and 0.72, respectively. Alternatively, using a CPR cut-off of 0.6765 MoM (the threshold we used to define failure to reach growth potential in a previous study), 54 fetuses were selected as abnormal (25 were true positive and 29 true negative), and the sensitivity, specificity, PPV, NPV, LR+ and LR- were 25%, 94%, 46%, 85%, 3.95 and 0.80, respectively.

Table 4 shows the multivariate logistic regression model explaining IFC at term that presented the lowest AIC. As indicated above, only those clinical parameters that showed significance in the previous univariate comparisons were included. In the upper part of the table we can see the CPR univariate model for comparison purposes. In this model, only the CPR, fetal gender and parity were selected as significant parameters. The model showed that the CPR obtained the highest OR (0.23, p<0.001), which was at least twice

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the OR of the following parameters, fetal gender (1.96, $p<0.005$) and parity (OR= 0.51, $p=0.018$). There were no ponderal parameter selected in the explanation of IFC. The accuracy of this combined model (CPR plus fetal gender and parity) was slightly better than that of the CPR model alone: Sensitivity 30.7% for a FPR of 10% versus 30.4% for a FPR of 10%.

Figure 4 shows the ROC analysis of the multi parametric combined model. The AUC was 0.67 (95 CI 0.60, 0.73, $p<0.001$) and the optimal cut-off -1.216 (95% CI 0.794, 0.495). As indicated in Table 3, at this cut-off point, 145 fetuses were selected as abnormal (49 were true positive and 96 true negative), and the sensitivity, specificity, PPV, NPV, LR + and LR- were 49%, 79%, 34%, 88%, 2.36 and 0.65, respectively.

Finally, table 5 and 6 show the accuracies and the OR of the alternative models (A, B, C), which evaluated the influence of induction of labor on IFC and the accuracy of the models using a composite adverse outcome of only two parameters.

In model A the above model was again evaluated including the onset of labor in the explanatory variables. Detection rate was 19.8% for a false positive rate of 5% and 33.6% for a false positive rate of 10%. The AUC was 0.674 (95% CI 0.614, 0.735, $p<0.001$). No differences were observed in comparison with the model excluding the parameter onset of labor. In addition, the onset of labor was not selected as a variable explaining IFC ($p=0.07$).

In model B, IFC was defined according to a composite adverse outcome of 2 parameters (pH and baby destiny). This composite adverse outcome was seen in 14.6% of the pregnancies. Detection rate was 21.7% for a false positive rate of 5% and 31.3% for a false positive rate of 10%. The AUC was 0.677 (95% CI 0.611, 0.743, $p<0.001$). No differences were observed in comparison with the other combined models.

In model C, IFC was also defined according to a composite adverse outcome of only 2 parameters (pH and baby destiny). In addition, the explanatory variables included the onset of labor (induction, spontaneous). Detection rate was 20.5% for a false positive rate of 5% and 32.5% for a false positive rate of 10%. The AUC was 0.679 (95% CI 0.613, 0.744, $p<0.001$). No differences were observed in comparison with the other combined models. In addition, like in model A, the onset of labor was not selected as a parameter explaining IFC ($p=0.534$).

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DISCUSSION

Summary of the study findings

Our results suggest that fetuses that grow over the 10th but experience IFC tend to show lower CPR values weeks before delivery and therefore could be partially identified antenatally. The CPR on its own could identify only one third of these fetuses. The fact that the onset of labor was not included in any model proved that induction of labor had no influence on fetal outcome.

Clinical and research implications

Most of small fetuses do not experience adverse outcome[8]. This condition has been recognized as constitutional smallness, in contraposition to growth restriction[23]. However, the contrary, i.e. the existence of growth restriction in fetuses that are not small seems to be a foreign concept, which questions the norm[10]. In fact, the current RCOG/NICE guidelines consider that only SGA fetuses could potentially suffer growth restriction[24]. According to this rationale, diverse protocols have been developed[25]. In general, screening for adverse outcome starts with the evaluation of the EFW and if the fetus is over the 10th centile, the fetus is considered to be normal. Alternatively, when the fetus is below the 10th centile and Doppler examinations are between normal limits, the fetus is considered constitutionally small. Unfortunately, despite small fetuses are more likely to experience adverse outcome, most of adverse outcome in absolute numbers, including stillbirth, occur in fetuses growing over the 10th centile[4-6], and therefore, the majority of fetuses with potential IFC are not selected for a closer follow up.

Our work confirms that a proportion of non-small fetuses, regardless of the type of labor onset are at risk of IFC. According to our results, one third of these fetuses can be detected by evaluating the CPR, an easy and cheap procedure. This approach could potentially be applied to help selection of the low risk pregnancies that are suitable for home planned births[26]. Another application could be when faced with the dilemma of prolonging pregnancy beyond 40 or 41 weeks[27], as fetuses with lower CPR might be more likely to show unexpected adverse outcomes due to fetal compromise and may therefore be advised not to prolong of pregnancy.

Interpretation of our findings and comparison with the published literature

Despite the fact that the predictive accuracy of the CPR is not optional, the CPR on its own could identify one third of these fetuses. Although this seems a low figure, it is important however to point out the current absence of good predictors of fetal compromise at the end of pregnancy especially in AGA fetuses. In this scenario, the detection rate of 30% for a false positive rate of 10%, is similar to the screening of aneuploidies based on maternal age, and therefore could be used until more advanced approaches are designed.

Very few studies have evaluated the CPR in non-small fetuses[28]. In a series of articles we have reported the association of the CPR with a variety of adverse perinatal outcomes[15-17, 29,30]. However, its predictive accuracy for intrapartum adverse outcome was not investigated. Other studies have attempted to examine the performance of the CPR for intrapartum fetal compromise. In one of these articles, Prior et al studied 400 fetuses with apparent normal growth immediately before established labor, and have reported that at the optimal threshold, the CPR yielded a positive predictive value for fetal compromise of 36.4% with a sensitivity of 32.5% for a false positive ratio of 6.8%[31]. In a similar work the same authors evaluated, before the active phase of labor, 775 fetuses with apparent normal health and an EFW over the 10th centile. Using our published threshold to define failure to reach growth potential (CPR 0.6765 MoM), they found that fetuses with abnormal CPR presented 2 times higher risk of abnormal fetal heart monitoring and 3 times higher risk of cesarean section due to fetal compromise. Concerning the risk of cesarean delivery due to fetal compromise, they obtained a PPV

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of 36.7%, a NPV of 88.7% and a sensitivity of 18% for a false positive rate of 4.6%[32]. Although in these two studies the CPR performance was similar to that shown in this work, most of labors were induced and examinations were done just before the active phase of labor. Contrarily, the majority of our fetuses had a spontaneous onset of labor and ultrasound examinations were performed days or weeks before the onset of labor. This is an important difference, as the predictive ability of the CPR is known to decrease in proportion to the ultrasound-delivery interval. Furthermore, induction of labor has been shown to be a risk factor for cesarean section as it imposes a certain stress on the functional placental reserve[33].

A third study by the same group evaluated the CPR at 35-37 weeks for IFC. Although the sensitivity and predictive values were not provided, the AUC was 0.61, which was very similar to our result. Unfortunately, in this work small fetuses were not excluded[34].

Finally, in a recent work these authors studied 437 AGA fetuses from 36 weeks' gestation. The proportion of fetuses with a composite adverse neonatal outcome (ANO) was 17.9%. For this outcome, the CPR less than the 10th centile yielded the best test performance, with an AUC of 0.58 and a sensitivity of 28.2% for a false positive rate of 12%. The +LR and -LR were respectively 2.36 and 0.82. Although they obtained exactly the same proportion of fetuses with adverse outcome, their results were slightly poorer that ours. A shortcoming of this study was that contrarily to ours, a notable proportion of their fetuses were finally small. In fact 7.1% presented a BW below the 10th centile[35].

Contribution of other parameters to the prediction of IFC

Among the studied parameters, only parity and fetal gender contributed to the prediction of IFC. In fact, both nulliparity[36-38] and male sex[39-43] are well known risk factors for perinatal adverse outcome including IFC. Contrarily, maternal age might not represent by itself a risk factor in well-grown fetuses without gestational complications[44]. In addition, fetal weight has proven to associate with adverse outcome worse than fetal CPR and probably does not contribute significantly to IFC prediction in fetuses presenting normal growth[16,17,30]. Finally it is important to underline the residual influence of induction of labor on IFC. According to our data, induction of labor does not influence the outcome of the fetus, which would be only affected by CPR, gender and parity. This finding agrees with recent publications and systematic reviews indicating the benefit of induction in comparison with expectant management at the end of pregnancy, which might reduce the prevalence of adverse outcome without increasing the risk of operative delivery[45-48].

Strengths and limitations

The main strengths of this study include the presence of a homogeneous population of non-small fetuses (selected not only according to their EFW but also to their final BW), and the paucity of earlier studies evaluating the CPR in non-small fetuses. Therefore, the findings of this study are useful addition to the existing literature. In addition, the

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presence of similar predictive values in the alternative models proved that the analysis and our approach was somewhat robust.

The main shortcoming was the relatively small number of pregnancies, although it compared favorably with that of the referred publications. Also, the number of adverse outcomes could be considered high. Despite this figure was similar to that published by Bligh et al[35], this proportion might be reflecting the tertiary nature of our hospital.

Conclusions

Despite their apparent normal size and regardless of the type of labor onset, some of the fetuses growing over the 10^{th} centile present intrapartum compromise. Although the performance of CPR alone or in combination with selected clinical parameters is still poor. It could be useful to select a proportion of the affected fetuses at an affordable false positive rate.

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Table 1. Characteristics of the study population N=569.

Parameter	Median (1st, 3rd Quartile)
Maternal age in years	33 (29, 36)
Parity	0 (0,1)
Gestational age at ultrasound in weeks	39.6 (38.9, 40)
Gestational age at delivery in weeks	40.57 (40, 41)
Interval ultrasound-delivery in days	6 (3, 9)
Estimated fetal weight in grams	3300 (3053, 3557)
Estimated fetal weight centile	42.27 (25.26, 63.33)
Umbilical artery (UA) pulsatility index (PI)	0.79 (0.68, 0.9)
UA PI multiple of median (MoM)	1.04 (0.9, 1.19)
Middle cerebral artery (MCA) PI	1.37 (1.16, 1.58)
MCA PI MoM	0.96 (0.82, 1.12)
Cerebroplacental ratio (CPR)	1.77 (1.46, 2.1)
CPR MoM	1.01 (0.83, 1.2)
Birth weight in grams	3350 (3150, 3650)
Birth weight centile	38.2 (24.18, 62.84)
Arterial cord pH	7.28 (7.23, 7.32)
Parameter	**N (%)**
Nulliparity	310 (54.5)
Multiparity	259 (45.5)
Fetal gender	
Female	258 (45.3)
Male	311 (54.7)
Ethnicity	
East Asian	4 (0.7)

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Black	8 (1.4)
Caucasian	548 (96.3)
South Asian	9 (1.6)
Onset of labor	
Induction	265 (46.6)
Spontaneous	304 (53.4)
Mode of delivery	
Cesarean	87 (15.3)
Forceps	14 (2.5)
Thierry's spatulas	7 (1.2)
Vacuum (Ventouse)	133 (23.4)
Spontaneous	328 (57.6)
Apgar score <7 at 5 minute	2 (0.4)
Neonatal cord arterial pH <7.20	73 (12.8)
Baby transfer after delivery	
Maternity ward	556 (97.7)
Neonatal special care unit	12 (2.1)
Neonatal intensive care unit	1 (0.2)
Abnormal intrapartum fetal heart rate or fetal scalp pH requiring cesarean section	25 (4.4)

Table 2. Comparison of the maternal and pregnancy parameters according to the study outcome.

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Parameter N=569	Normal outcome (n=467)	Adverse outcome (n=102)	
	Median (1st, 3rd Quartile)	Median (1st, 3rd Quartile)	**P-value**
Maternal age in years	33 (29, 36)	34 (29, 37)	P = 0.61
Parity	0.66 (0.92), 0 (0, 1)	0.44 (0.71), 0 (0, 1)	P = 0.02
Gestational age at ultrasound in weeks	39.6 (38.9, 40)	39.6 (38.4, 40)	P = 0.71
Gestational age at delivery in weeks	40.57 (40, 41)	40.57 (40.03, 41)	P = 0.55
Interval ultrasound-delivery in days	6 (3, 9)	7 (3, 12)	P = 0.54
Estimated fetal weight in grams	3306 (3058, 3559.5)	3285.5 (2941.5, 3551.75)	P = 0.21
Estimated fetal weight centile	43.12 (25.3, 64.18)	38.84 (22.52, 61.78)	P = 0.19
Umbilical artery (UA) pulsatility index (PI)	0.78 (0.68, 0.89)	0.82 (0.73, 0.92)	P = 0.006
UA PI multiple of median (MoM)	1.03 (0.89, 1.18)	1.08 (0.96, 1.23)	P = 0.008
Middle cerebral artery (MCA) PI	1.38 (1.19, 1.58)	1.29 (1.07, 1.55)	P = 0.01
MCA PI MoM	0.97 (0.84, 1.12)	0.92 (0.78, 1.05)	P = 0.004
Cerebroplacental ratio (CPR)	1.78 (1.51, 2.13)	1.6 (1.19, 1.96)	P < 0.001
CPR MoM	1.02 (0.87, 1.22)	0.92 (0.68, 1.13)	P < 0.001
Birth weight in grams	3360 (3170, 3650)	3340 (3100, 3613.75)	P = 0.13
Birth weight centile	39.49 (25.05, 63.4)	36.09 (19.85, 60.58)	P = 0.09
Arterial cord pH	7.29 (7.25, 7.32)	7.18 (7.15, 7.21)	P<0.001
	N (%)	N (%)	
Nulliparity	244 (52.2)	66 (64.7)	P=0.03
Multiparity	223 (47.8)	36 (35.3)	
Gender			
Female fetal gender	224 (48)	34 (33.3)	P=0.01
Male fetal gender	243 (52)	68 (66.7)	
Ethnicity			
East Asian	2 (0.4)	2 (2)	P = 0.35
Black	7 (1.5)	1 (1)	
Caucasian	450 (96.4)	98 (96.1)	
South Asian	8 (1.7)	1 (1)	
Onset of labor			
Induction of labor	207 (44.3)	58 (56.9)	P= 0.028
Spontaneous	260 (55.7)	44 (43.1)	
Mode of delivery			
Cesarean	56 (12)	31 (30.4)	P < 0.001
Forceps	10 (2.1)	4 (3.9)	
Thierry’s spatulas	7 (1.5)	0 (0)	
Vacuum (ventouse)	102 (21.8)	31 (30.4)	
Spontaneous	292 (62.5)	36 (35.3)	
Apgar score <7 at 5 minute	0 (0)	2 (2)	
Umbilical cord arterial pH <7.20	0 (0)	73 (71.6)	
Baby transfer after delivery			

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Maternity ward	466 (99.8)	90 (88.2)	P=0.002
Neonatal special care unit	1 (0.2)	11 (10.8)	
Neonatal intensive care unit	0 (0)	1 (1)	
Abnormal intrapartum fetal heart rate or fetal scalp pH requiring cesarean section	0 (0)	25 (24.5)	P<0.001

Table 3

Accuracy statistics of the CPR models for the prediction of IFC. IFC was defined according to a composite adverse outcome of 4 perinatal parameters (neonatal pH, Apgar score, intrapartum CTG or fetal scalp pH requiring cesarean section and admission to postnatal pediatric care). Measurements were obtained in appropriate for gestational age fetuses examined at the end of pregnancy within 1 month of delivery.

CPR alone model. Cut off of the univariate model= -1.2587, corresponding to a CPR MoM = 0.827 (best cut off according to the ROC analysis)			
	Abnormal outcome	Normal outcome	Total
Low CPR	44	97	141
Normal CPR	58	370	428
Total	102	467	569
	%	95% CI	
Apparent prevalence	25	21-29	
True prevalence	18	15-21	
Sensitivity (detection rate)	43	33-53	
Specificity	79	75-83	
Positive predictive value	31	24-40	
Negative predictive value	86	83-90	
Positive likelihood ratio	2.08	1.56-2.76	
Negative likelihood ratio	0.72	0.60-0.86	
CPR alone model. Cut off of the univariate model= -1.01887, corresponding to a CPR MoM = 0.6765 (used to describe failure to reach growth potential)			
	Abnormal outcome	Normal outcome	Total
Low CPR	25	29	54
Normal CPR	77	438	515
Total	102	467	569
	%	95% CI	
Apparent prevalence	9	7-12	
True prevalence	18	15-21	
Sensitivity (detection rate)	25	17-34	
Specificity	94	91-96	
Positive predictive value	46	33-60	
Negative predictive value	85	82-88	
Positive likelihood ratio	3.95	2.42-6.44	
Negative likelihood ratio	0.80	0.72-0.90	

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Combined model (CPR plus fetal gender and parity) Cut off = -1.216 (best cut off according to the ROC analysis)			
	Abnormal outcome	Normal outcome	Total
Poor outcome (predicted)	49	96	145
Good outcome (predicted)	52	371	423
Total	101	467	568
	%	95% CI	
Apparent prevalence	26	22-29	
True prevalence	18	15-21	
Sensitivity (detection rate)	49	38-59	
Specificity	79	75-83	
Positive predictive value	34	26-42	
Negative predictive value	88	84-91	
Positive likelihood ratio	2.36	1.80-3.09	
Negative likelihood ratio	0.65	0.53-0.79	

Notes: IFC: Intrapartum fetal compromise, CPR: cerebroplacental ratio, MoM: multiples of the median, 95% CI: 95% confidence interval.

Table 4

CPR alone model			
	OR	**95% CI**	**P-value**
Intercept	1.061	0.467, 2.428	0.888
CPR MoM	0.203	0.087, 0.458	<0.001
Detection rate of 14.7% for a false positive rate of 5%			
Detection rate of 30.4% for a false positive rate of 10%			
AUC 0.619, 95% CI [0.554, 0.684], p<0.001			
CPR combined model			
	OR	**95% CI**	**P-value**
CPR MoM	0.229	0.092-0.545	0.001
Fetal gender (male)	1.958	1.238-3.147	0.005
Parity	0.511	0.287-0.877	0.018
Intercept	0.522	0.089-2.956	0.466
EFW centile	0.998	0.988-1.008	0.658
Maternal age	1.012	0.070-1.056	0.588
Interval examination-labor	1.064	0.773-1.471	0.706
Detection rate of 19.8% for a false positive rate of 5%			
Detection rate of 30.7% for a false positive rate of 10%			
AUC 0.667, 95% CI [0.604, 0.729], p<0.001			
AIC = 523.83			
Nagelkerke R Squared = 8.28%			

Note: IFC: intrapartum fetal compromise, CPR: cerebroplacental ratio, MoM: multiples of the median, EFW: estimated fetal weight (Hadlock), OR: odds ratio, 95% CI: 95% confidence intervals.

Models for the prediction of IFC using CPR. IFC was defined according to a composite adverse outcome of 4 perinatal parameters (neonatal pH, Apgar score, intrapartum CTG or fetal scalp pH requiring cesarean section and admission to postnatal pediatric care). Measurements were obtained in appropriate for gestational age fetuses examined at the end of pregnancy within 1 month of delivery.

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Table 5. Accuracy statistics of the alternative combined models for the prediction of IFC using CPR. Measurements were obtained in appropriate for gestational age fetuses examined at the end of pregnancy within 1 month of delivery.

Model A: explanatory variables included also the onset of labor (induction of labor, spontaneous onset of labor).

Model B: composite adverse outcome included only pH and baby destiny.

Model C: composite adverse outcome included only pH and baby destiny. In addition, explanatory variables included also the onset of labor (induction of labor, spontaneous onset of labor).

Model A Cut off = -1.462 (best cut off according Youden Index)			
	Abnormal outcome	Normal outcome	Total
Poor outcome (predicted)	64	163	227
Good outcome (predicted)	37	304	341
Total	101	467	568
	%	95% CI	
Apparent prevalence	40	36-44	
True prevalence	18	15-21	
Sensitivity (detection rate)	63	53-73	
Specificity	65	61-69	
Positive predictive value	28	22-35	
Negative predictive value	89	85-92	
Positive likelihood ratio	1.82	1.50-2.20	
Negative likelihood ratio	0.56	0.43-0.73	

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Model B Cut off = -1.798 (best cut off according to the ROC analysis)			
	Abnormal outcome	Normal outcome	Total
Poor outcome (predicted)	57	196	253
Good outcome (predicted)	26	289	315
Total	83	485	568
	%	95% CI	
Apparent prevalence	45	40-49	
True prevalence	15	12-18	
Sensitivity (detection rate)	69	58-78	
Specificity	60	55-64	
Positive predictive value	23	18-28	
Negative predictive value	92	88-95	
Positive likelihood ratio	1.70	1.42-2.04	
Negative likelihood ratio	0.53	0.38-0.73	
Model C Cut off = -1.674 (best cut off according Youden Index)			
	Abnormal outcome	Normal outcome	Total
Poor outcome (predicted)	51	160	211
Good outcome (predicted)	32	325	357
Total	83	485	568
	%	95% CI	
Apparent prevalence	37	33-41	
True prevalence	15	12-18	
Sensitivity (detection rate)	61	50-72	
Specificity	67	63-71	
Positive predictive value	24	19-31	
Negative predictive value	91	88-94	
Positive likelihood ratio	1.86	1.51-2.30	
Negative likelihood ratio	0.58	0.44-0.76	

Notes: IFC: intrapartum fetal compromise, CPR: cerebroplacental ratio, 95% CI: 95% confidence interval.

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Table 6. Alternative combined models for the prediction of IFC using CPR. Measurements were obtained in appropriate for gestational age fetuses examined at the end of pregnancy within 1 month of delivery.

Model A: IFC was defined according to a composite adverse outcome of 4 perinatal parameters (neonatal pH, Apgar score, intrapartum CTG or fetal scalp pH requiring cesarean section and admission to postnatal pediatric care). In order to evaluate the importance of induction, explanatory variables included the onset of labor (induction, spontaneous)

Model B: IFC was defined according to a composite adverse outcome of only 2 perinatal parameters (pH and baby destiny).
Model C: IFC was defined according to a composite adverse outcome of only 2 perinatal parameters (pH and baby destiny). Explanatory variables included also the onset of labor (induction, spontaneous).

Model A			
	OR	**95% CI**	**P-value**
CPR MoM	0.236	0.095-0.563	0.001
Fetal gender (male)	1.980	1.250-3.188	0.004
Parity	0.544	0.305-0.940	0.033
Intercept	0.477	0.081-2.704	0.407
EFW centile	0.998	0.988-1.008	0.709
Maternal age	1.008	0.966-1.052	0.729
Interval examination-labor	1.032	0.747-1.433	0.848
Onset of labor (induction)	1.518	0.967-2.395	0.071
Detection rate of 19.8% for a false positive rate of 5%			
Detection rate of 33.6% for a false positive rate of 10%			
AUC 0.674, 95% CI [0.614, 0.735], p<0.001			
Model B			
	OR	**95% CI**	**P-value**
CPR MoM	0.257	0.096-0.654	0.005
Fetal gender (male)	2.066	1.255-3.482	0.005
Parity	0.421	0.220-0.772	0.007
Intercept	0.514	0.077-3.302	0.487
EFW centile	0.998	0.987-1.008	0.655
Maternal age	1.004	0.96-1.051	0.871
Interval examination-labor	1.033	0.731-1.467	0.856
Detection rate of 21.7% for a false positive rate of 5%			
Detection rate of 31.3% for a false positive rate of 10%			
AUC 0.677, 95% CI [0.611, 0.743], p<0.001			
Model C			
	OR	**95% CI**	**P-value**
CPR MoM	0.229	0.092-0.545	0.001
Fetal gender (male)	1.958	1.238-3.147	0.005
Parity	0.511	0.287-0.877	0.018
Intercept	0.522	0.089-2.956	0.466
EFW centile	0.998	0.988-1.008	0.658
Maternal age	1.012	0.070-1.056	0.588
Interval examination-labor	1.064	0.773-1.471	0.706
Onset of labor (induction)	1.167	0.716-1.904	0.534
Detection rate of 20.5% for a false positive rate of 5%			
Detection rate of 32.5% for a false positive rate of 10%			
AUC 0.679, 95% CI [0.613, 0.744], p<0.001			

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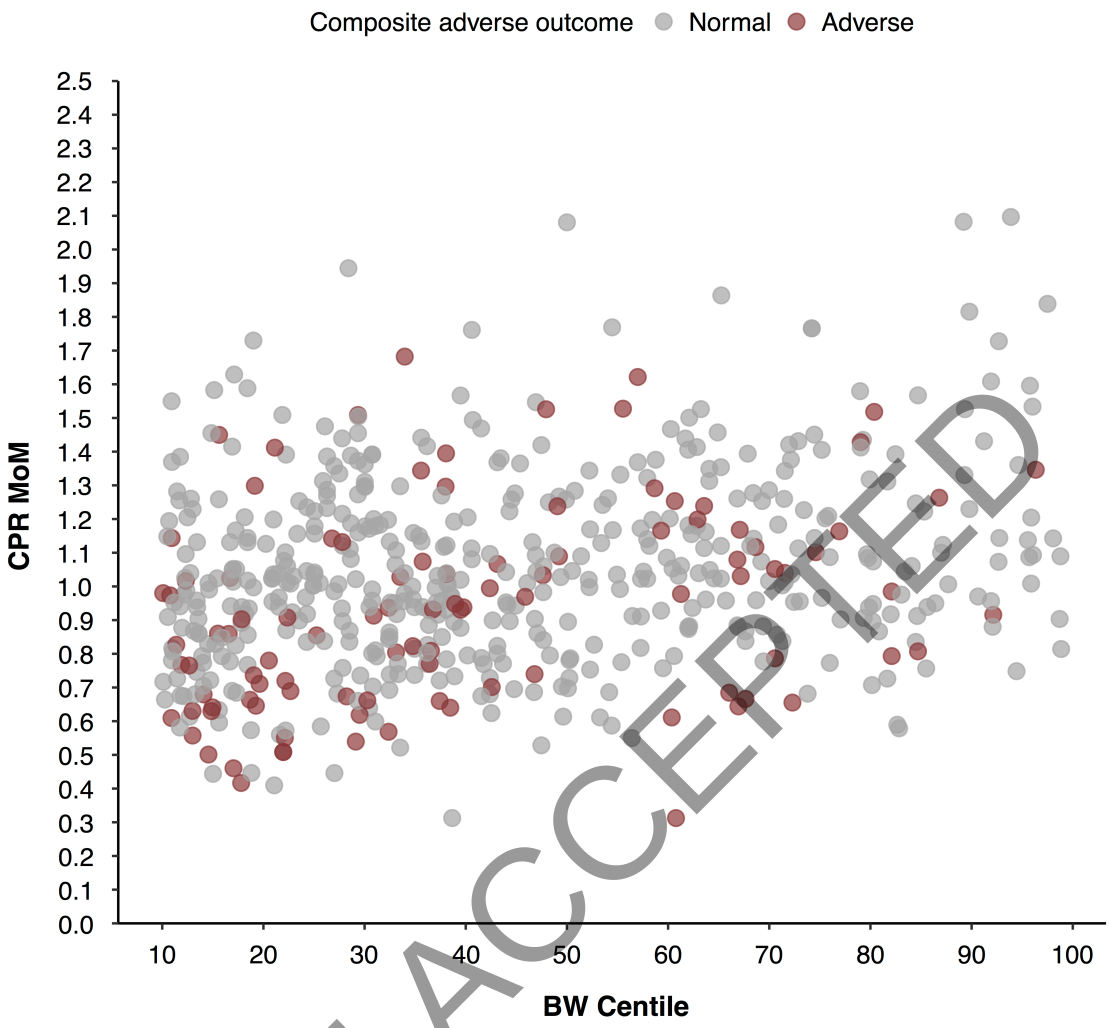

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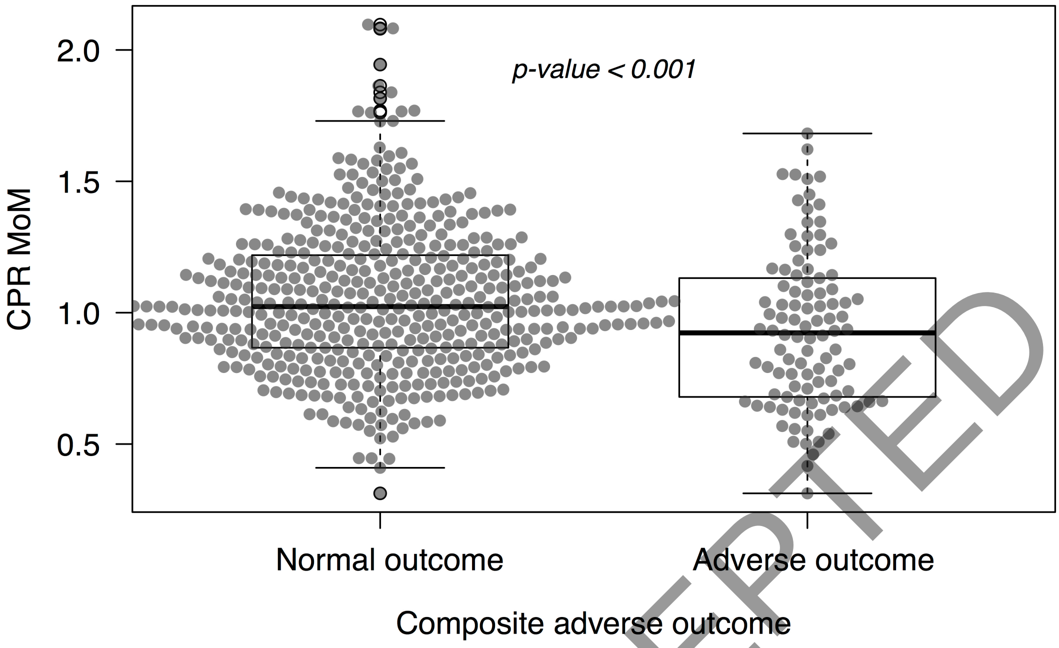

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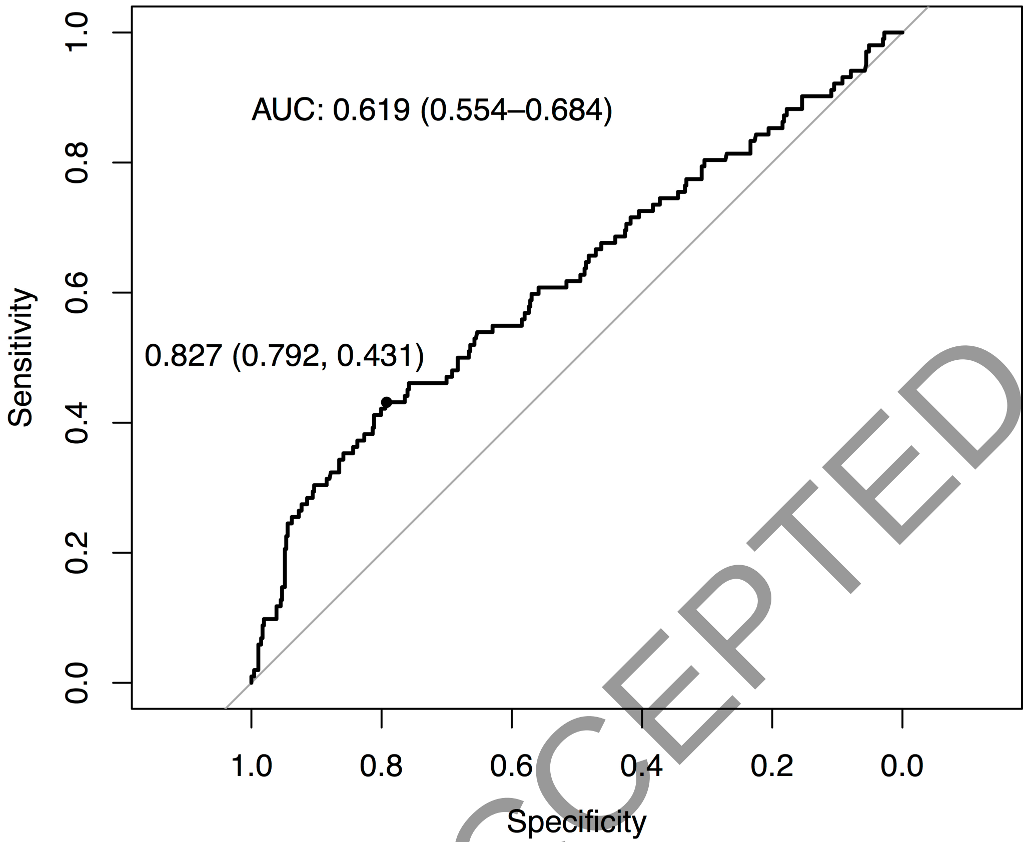

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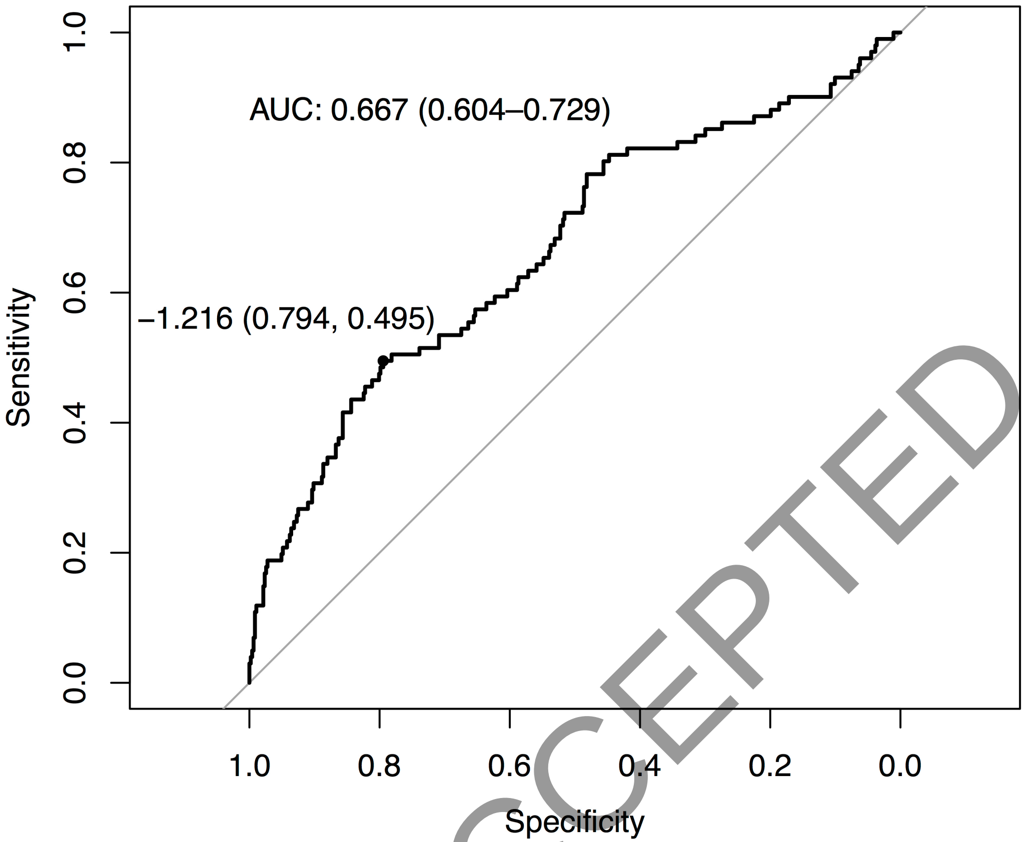

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