

## OBSTETRICS

# Evaluation of normalization of cerebro-placental ratio as a potential predictor for adverse outcome in SGA fetuses



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**BACKGROUND:** Intrauterine growth restriction accounts for a significant proportion of perinatal morbidity and mortality currently encountered in obstetric practice. The primary goal of antenatal care is the early recognition of such conditions to allow treatment and optimization of both maternal and fetal outcomes. Management of pregnancies complicated by intrauterine growth restriction remains one of the greatest challenges in obstetrics. Frequently, however, clinical evidence of underlying uteroplacental dysfunction may only emerge at a late stage in the disease process. With advanced disease the only therapeutic intervention is delivery of the fetus and placenta. The cerebroplacental ratio is gaining much interest as a useful tool in differentiating the at-risk fetus in both intrauterine growth restriction and the appropriate-for-gestational-age setting. The cerebroplacental ratio quantifies the redistribution of the cardiac output resulting in a brain-sparing effect. The Prospective Observational Trial to Optimize Pediatric Health in Intrauterine Growth Restriction group previously demonstrated that the presence of a brain-sparing effect is significantly associated with an adverse perinatal outcome in the intrauterine growth restriction cohort.

**OBJECTIVE:** The aim of the Prospective Observational Trial to Optimize Pediatric Health in Intrauterine Growth Restriction study was to evaluate the optimal management of fetuses with an estimated fetal weight <10th centile. The objective of this secondary analysis was to evaluate if normalizing cerebroplacental ratio predicts adverse perinatal outcome.

**STUDY DESIGN:** In all, 1116 consecutive singleton pregnancies with intrauterine growth restriction completed the study protocol over 2 years at 7 centers, undergoing serial sonographic evaluation and multivessel Doppler measurement. Cerebroplacental ratio was calculated using the pulsatility and resistance indices of the middle cerebral and umbilical artery. Abnormal cerebroplacental ratio was defined as <1.0. Adverse perinatal outcome was defined as a composite of intraventricular hemorrhage,

periventricular leukomalacia, hypoxic ischemic encephalopathy, necrotizing enterocolitis, bronchopulmonary dysplasia, sepsis, and death.

**RESULTS:** Data for cerebroplacental ratio calculation were available in 881 cases, with a mean gestational age of 33 (interquartile range, 28.7-35.9) weeks. Of the 87 cases of abnormal serial cerebroplacental ratio with an initial value <1.0, 52% (n = 45) of cases remained abnormal and 22% of these (n = 10) had an adverse perinatal outcome. The remaining 48% (n = 42) demonstrated normalizing cerebroplacental ratio on serial sonography, and 5% of these (n = 2) had an adverse perinatal outcome. Mean gestation at delivery was 33.4 weeks (n = 45) in the continuing abnormal cerebroplacental ratio group and 36.5 weeks (n = 42) in the normalizing cerebroplacental ratio group (P value <.001).

**CONCLUSION:** The Prospective Observational Trial to Optimize Pediatric Health in Intrauterine Growth Restriction group previously demonstrated that the presence of a brain-sparing effect was significantly associated with an adverse perinatal outcome in our intrauterine growth restriction cohort. It was hypothesized that a normalizing cerebroplacental ratio would be a further predictor of an adverse outcome due to the loss of this compensatory mechanism. However, in this subanalysis we did not demonstrate an additional poor prognostic effect when the cerebroplacental ratio value returned to a value >1.0. Overall, this secondary analysis demonstrated the importance of a serial abnormal cerebroplacental ratio value of <1 within the <34 weeks' gestation population. Contrary to our proposed hypothesis, we recognize that reversion of an abnormal cerebroplacental ratio to a normal ratio is not associated with a heightened degree of adverse perinatal outcome.

**Key words:** adverse neonatal outcome, brain sparing, brain-sparing effect, cerebroplacental ratio, intrauterine growth restriction, middle cerebral artery Doppler, small for gestational age, umbilical artery Doppler

## Introduction

Intrauterine growth restriction (IUGR) accounts for a significant proportion of perinatal morbidity and mortality currently encountered in obstetric practice.<sup>1</sup> The primary goal of antenatal

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## EDITORS' CHOICE

care is the early recognition of such conditions to allow treatment and optimization of both maternal and fetal outcomes. Management of pregnancies complicated by IUGR remains one of the greatest challenges in obstetrics. The morbidity, both maternal and fetal, associated with IUGR is considerable.<sup>1-6</sup> However, the antenatal detection of IUGR via clinical examination is sub-optimal with a reported detection rate of 1 in 3.<sup>7-9</sup> As a result many pregnancies

complicated by IUGR remain undetected and this translates to an >8-fold increased risk of stillbirth when compared to normal controls: 19.8 vs 2.4/1000.<sup>10</sup> Frequently, however, clinical evidence of underlying uteroplacental dysfunction may only emerge at a late stage in the disease process. With advanced disease the only therapeutic intervention is delivery of the fetus and placenta. Prolonging the pregnancy is associated with the risk of increasing maternal morbidity, maternal mortality, and in utero fetal demise. Gardosi et al<sup>10</sup>

demonstrated that in the setting of diagnosed IUGR where patients delivered on average 10 days earlier, this resulted in a reduction in the overall stillbirth rate.

The cerebroplacental ratio (CPR) is gaining much interest as a useful tool in differentiating the at-risk fetus in both IUGR and the appropriate-for-gestational-age setting.<sup>2,11-15</sup> The CPR, first reported by Arbeille et al,<sup>16,17</sup> quantifies the redistribution of the cardiac output resulting in a brain-sparing effect. The CPR has been calculated by either the pulsatility index (PI) or resistance index of the middle cerebral artery (MCA) and umbilical artery (UA) Doppler waveforms. The Prospective Observational Trial to Optimize Pediatric Health in IUGR (PORTO) group previously demonstrated that the presence of a brain-sparing effect is significantly associated with an adverse perinatal outcome

in the IUGR cohort. In addition, a difference did not emerge when comparing the use of PI or resistance index to quantify the waveform.<sup>18</sup> Various categorical cutoffs (<1.00, <1.08) have been described.<sup>19-21</sup> However, neither has demonstrated a clear superior ability in the prediction of adverse perinatal outcome.<sup>18,22</sup> Some studies demonstrated that the CPR may vary with gestational age<sup>23-25</sup> and it has been reported that the CPR is more predictive at <34 completed weeks of gestation.<sup>21</sup> As a result, there is no clear consensus of the “normal” parameters of CPR.

The goal of the PORTO study was to evaluate the optimal surveillance of fetuses with an estimated fetal weight (EFW) <10th centile. The objective of this secondary analysis was to evaluate if a normalizing CPR provides an additional prediction of adverse perinatal outcome. Our hypothesis is that when an

IUGR fetus with a CPR <1 returns to >1 that this is an additional predictor of adverse outcome due to the loss of the compensatory mechanism of brain sparing.

## Materials and Methods

The PORTO study is a multicenter prospective study conducted at the 7 largest academic centers in Ireland. For the purpose of this study IUGR was defined as <10th centile based on sonographic measurements of fetal biparietal diameter, head circumference, abdominal circumference, and femur length (Hadlock-4).<sup>26</sup> From January 2010 through June 2012, the PORTO study recruited 1200 consecutive ultrasound-dated singleton pregnancies. Inclusion criteria were a gestational age between 24+0 and 36+6 weeks and an EFW  $\geq$ 500 g. The exclusion criteria included all major structural and/or chromosomal abnormalities, which were excluded retrospectively from the final analysis. Institutional ethical approval was obtained from each participating clinical site and written informed consent was obtained from all participants.

Referral to the study occurred if a fetus was suspected to be small for gestational age due to clinical evaluation in the antenatal setting. All eligible pregnancies underwent an anatomical survey at enrollment. Serial sonographic evaluation of fetal weight was performed at 2 weekly intervals until birth and normally formed fetuses underwent evaluation of amniotic fluid volume, biophysical profile scoring, and multivessel Doppler at each subsequent contact with the research sonographer until birth. The ultrasound data were recorded in the ultrasound software system (Viewpoint; MDI Viewpoint, Jacksonville, FL) and uploaded onto a live World Wide Web–based central consolidated database.

The results of all study examinations were filed in the patient’s medical record and made available to the managing clinician who decided on the frequency of surveillance, management, timing, and mode of delivery. Given that the PORTO study was observational and

**TABLE 1**  
**Maternal demographics and fetal characteristics of Prospective Observational Trial to Optimize Pediatric Health in Intrauterine Growth Restriction population, n = 1116**

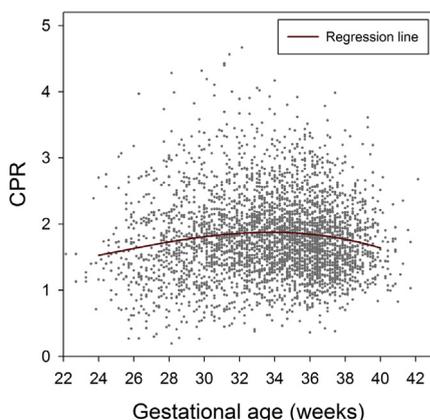
Characteristic	n (%) / mean $\pm$ SD
Age, y	30 $\pm$ 6
Ethnicity, white European	907 (83%)
Spontaneous conception	1100 (99%)
Maternal height, cm	162 $\pm$ 12
Maternal weight at booking, kg	64 $\pm$ 13
BMI, kg/m <sup>2</sup>	24.1 $\pm$ 4.7
Smokers	261 (23%)
Hypertensive disease/preeclampsia	134 (12%)
GA at enrollment, wk	30.1 $\pm$ 3.9
GA at delivery, wk	37.8 $\pm$ 3.0
Weight at delivery, g	2495 $\pm$ 671
NICU admission	312 (28%)
Adverse perinatal outcome	57 (5%)
Apgar score <75	13 (1%)
Stillbirths	3 (1:370)
Neonatal deaths	3 (1:370)

Continuous variables are summarized with mean  $\pm$  SD and categorical variables with n (%).

BMI, body mass index; GA, gestational age; NICU, neonatal intensive care unit.

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**FIGURE**  
Cerebroplacental ratio (CPR)  
values in correlation to  
gestational age



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descriptive in nature, there were no prespecified management or delivery criteria. This was to reflect contemporary real-world practice. Decisions regarding management and delivery were made by the lead clinician treating each patient, but were not prespecified by the study design. However, all women were delivered  $\leq 34$  weeks' gestation

when there was absent end-diastolic flow in the UA Doppler. Tertiary-level neonatal care facilities were available in all 7 trial centers. Adverse perinatal outcome was defined as a composite of intraventricular hemorrhage, periventricular leukomalacia, hypoxic ischemic encephalopathy, necrotizing enterocolitis, bronchopulmonary dysplasia, sepsis, and death. These outcomes were defined using the Vermont Oxford Network manual and neonates were assessed for same at the time of first hospital discharge.

In this retrospective secondary analysis the CPR was calculated by dividing the PI of the MCA with that of the UA. For the purpose of this analysis an abnormal CPR value was defined as  $<1.0$ . The CPR was calculated retrospectively, therefore this result was not available to the clinician, and therefore, CPR results did not influence management decisions.

Prior to statistical analysis, all ultrasound and outcome data were screened for anomalous records or potential outliers and followed up with sonographers for resolution. The CPR groups were compared using the 2-sample *t* test and the  $\chi^2$  tests, for continuous and

categorical data, respectively. Software (SAS, Version 9.3; SAS Institute Inc, Cary, NC) was used for data management and statistical analysis.

## Results

A total of 1200 cases with an EFV  $<10$ th centile were recruited to the PORTO study. Of those recruited pregnancies, 32 (2.7%) were excluded due to major structural and/or chromosomal abnormalities, 13 (1%) withdrew their consent, 13 (1%) delivered outside Ireland, and a further 26 (2.2%) were lost to follow-up. This resulted in 1116 patients completing the study protocol. [Table 1](#) outlines the demographics of all participants completing the study protocol.

This secondary analysis was performed to assess the role of CPR and its normalization. Of the 1116 patients completing the study protocol it was possible to retrospectively calculate a CPR value in 881 pregnancies. The remaining 235 pregnancies did not have both UA and MCA Doppler indices performed and as such we were unable to retrospectively calculate a CPR value.

There were a total of 3583 CPR determinations calculated over the 881 pregnancies. A total of 159 (18%) women had just 1 CPR determination and 722 (82%) had  $>1$  measurement. This resulted in a median of 3 CPR values per pregnancy. The median time interval between individual CPR determinations was 7 (interquartile range 5-14) days. Of the 3583 CPR values recorded, 146 (17%) had an abnormal CPR PI  $<1$  and 735 (83%) had a normal CPR. The median time interval between an abnormal CPR value and delivery was 7 (interquartile range 2-15) days. The [Figure](#) details the retrospective CPR calculations in relation to gestational age at time of performance.

Within this cohort, 146 cases had an abnormal CPR PI  $<1$ , and 87 had at least 1 subsequent serial CPR examination. The remaining 59 cases were either delivered prior to repeat sonography or did not have both the UA and MCA parameters recorded in repeat sonography to allow for the

**TABLE 2**  
All cases with cerebroplacental ratio value  $<1$

Characteristic/outcome	All cases (N = 146)	CPR $<1$ $<34$ wk N = 83	CPR $<1$ $>34$ wk N = 63	Pvalue
Nulliparous	74 (52%)	44 (54%)	30 (49%)	.544
Composite	27 (18%)	26 (31%)	1 (2%)	$<.001$
<b>Outcomes</b>				
GA at delivery, wk	$34 \pm 4$	$32 \pm 4$	$37 \pm 2$	$<.001$
Delivery by LSCS	110 (75%)	69 (83%)	41 (65%)	
Indication for LSCS	126 (86%)	74 (89%)	52 (83%)	.249
<b>fetal distress/NRCTG</b>				
Apgar score $<75$	5 (3%)	3 (4%)	2 (3%)	.885
NICU admission	93 (64%)	61 (74%)	32 (51%)	.005
NICU length of stay, d	$31 \pm 27$	$43 \pm 27$	$11 \pm 7$	$<.001$

Continuous variables are summarized with mean  $\pm$  SD and categorical variables with n (%).

CPR, cerebroplacental ratio; GA, gestational age; LSCS, lower segment cesarean delivery; NICU, neonatal intensive care unit; NRCTG, nonreassuring cardiotocograph.

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**TABLE 3**  
**Table addressing outcomes based on cerebroplacental ratio <1 <34 wk**

Characteristic/outcome	Normalizing n = 25	CPR remaining <1 n = 34	Pvalue
Nulliparous	16 (67%)	15 (45%)	.112
Composite	2 (8%)	10 (29%)	.044
<b>Outcomes</b>			
GA at delivery, wk	35 ± 4	32 ± 3	<.001
Delivery by LSCS	17 (68%)	30 (88%)	.056
Indication for LSCS	19 (76%)	33 (97%)	.013
<b>fetal distress/NRCTG</b>			
Apgar score <7 at 5 min	0	1 (3%)	.387
NICU admission	12 (48%)	29 (85%)	.002
NICU length of stay, d	33 ± 23	40 ± 20	.354

Continuous variables are summarized with mean ± SD and categorical variables with n (%).

CPR, cerebroplacental ratio; GA, gestational age; LSCS, lower segment cesarean delivery; NICU, neonatal intensive care unit; NRCTG, nonreassuring cardiotocograph.

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retrospective repeated CPR calculation. Table 2 details a comparison of all 146 cases where an abnormal CPR <1 was recorded and compares those recorded at a gestational age <34 weeks and >34 completed weeks. Within our cohort when the CPR was performed and

abnormal <34 weeks' gestation those infants had earlier delivery ( $P < .001$ ).

Of the 87 cases with an abnormal CPR value <1, 52% ( $n = 45$ ) of cases remained abnormal and 22% of these ( $n = 10$ ) had an adverse perinatal outcome. The mean gestational age at

delivery for those whose CPR value did not normalize ( $n = 45$ ) was 33.4 weeks. The remaining 48% of cases with initial abnormal CPR ( $n = 42$ ) demonstrated normalizing CPR on serial sonography, and 5% of these ( $n = 2$ ) had an adverse perinatal outcome. The gestational age at delivery for those who normalized ( $n = 42$ ) was 36.5 weeks, which was statistically significant when compared to the persistently abnormal CPR group ( $P$  value <.001). As a result we have compared both groups where the CPR remains abnormal and where the CPR normalizes at a gestational age <34 weeks as detailed in Table 3. Overall a normalizing CPR at both gestational age <34 weeks and gestational age >34 weeks (Table 4) demonstrated a better neonatal outcome.

## Comment

### Principal findings

In this subanalysis we have not demonstrated an additional poor prognostic effect when an abnormal CPR value returns to a value >1.0.

### Meaning of the findings

The PORTO group previously demonstrated that the presence of a brain-sparing effect was significantly associated with an adverse perinatal outcome in our IUGR cohort.<sup>18</sup> Our hypothesis was that when an IUGR fetus with previously detected abnormal CPR <1 value returns to >1 that this is an additional predictor of adverse outcome due to the loss of the compensatory mechanism of brain sparing.

As detailed in the Figure, we have demonstrated that there is a spread of normal values of CPR that exist with advancing gestational age, which is similar to that previously reported.<sup>23-25</sup> Our findings were also in agreement with previous studies, which suggested that an abnormal CPR value was best interpreted at <34 weeks' gestation.<sup>21</sup>

Overall, this secondary analysis has again demonstrated the importance of a serial abnormal CPR value of <1 within the <34 weeks' gestation population. CPR measurement is not currently

**TABLE 4**  
**Cerebroplacental ratio <1 >34 wk**

Characteristic/outcome	Normalizing n = 17	CPR remaining <1 n = 11	Pvalue
Nulliparous	9 (53%)	7 (64%)	.577
Composite	0	0	—
<b>Outcomes</b>			
GA at delivery, wk	38 ± 1	37 ± 2	.151
Delivery by LSCS	8 (47%)	9 (82%)	.066
Indication for LSCS	13 (76%)	8 (74%)	.823
<b>fetal distress/NRCTG</b>			
Apgar score <75	0	1 (9%)	.206
NICU admission	5 (29%)	7 (64%)	.074
NICU length of stay, d	8 ± 5	8 ± 7	.829

Continuous variables are summarized with mean ± SD and categorical variables with n (%).

CPR, cerebroplacental ratio; GA, gestational age; LSCS, lower segment cesarean delivery; NICU, neonatal intensive care unit; NRCTG, nonreassuring cardiotocograph.

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recommended in international guidelines to form a routine part of fetal surveillance in pregnancies complicated by IUGR. However, the evidence supporting its use as an additional predictor of poor perinatal outcome is building.<sup>11,12,14,18,21,23</sup>

There has been an increase in the reporting of long-term neurological sequelae in the IUGR fetus.<sup>27</sup> Meher et al<sup>4</sup> also proposed a hypothesis of neurological injury occurring prior to an abnormal CPR as a response to the altered fetal hemodynamic adaptation to hypoxia. Their review also suggested that an abnormal MCA Doppler may in fact be a late event in the overall fetal brain redistribution of blood flow.

### Clinical implications

Contrary to our proposed hypothesis, in cases where the CPR normalizes, the pregnancy may in fact be prolonged, which in turn may avoid the possible morbidities associated with iatrogenic premature delivery.

### Strengths and weaknesses

The strengths of the PORTO study are that it is a large prospective observational trial with intensive surveillance examining the IUGR fetus and allowing us to evaluate a normalizing CPR value in a normal clinical setting. Recruited pregnancies underwent a high degree of fetal surveillance by trained research sonographers. Additionally practitioners were blinded to the CPR results and as such were not influenced by the CPR value when planning the timing of delivery of affected pregnancies. A limitation of the study is that incomplete MCA data did not permit serial CPR values for the entire cohort. Nevertheless, this is the first cohort to date to evaluate the role of a normalizing CPR value in the IUGR setting.

### Future research implications

This further substantiates the need for further large prospective studies interrogating fetal Doppler studies and the associated short- and long-term pediatric outcomes. ■

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