

The role of brain sparing in the prediction of adverse outcomes in intrauterine growth restriction: results of the multicenter PORTO Study

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OBJECTIVE: The aim of the Prospective Observational Trial to Optimize Pediatric Health in IUGR Study was to evaluate the optimal management of fetuses with an estimated fetal weight less than the 10th centile. The objective of this secondary analysis was to describe the role of the cerebroplacental ratio (CPR) in the prediction of adverse perinatal outcome.

STUDY DESIGN: More than 1100 consecutive singleton pregnancies with intrauterine growth restriction (IUGR) were recruited over 2 years at 7 centers, undergoing serial sonographic evaluation including multivessel Doppler measurement. CPR was calculated using the pulsatility and resistance indices of the middle cerebral and umbilical artery. 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 CPR calculation was available in 881 cases, which was performed at a mean gestational age of 33 weeks (interquartile range, 28.7–35.9). Of the 146 cases with CPR less than 1, 18% ($n = 27$) had an adverse perinatal outcome. This conferred an 11-fold increased risk (odds ratio, 11.7; $P < .0001$) when compared with cases with normal CPR (2%; 14 of 735). An abnormal CPR was present in all 3 cases of mortality. Prediction of adverse outcomes was comparable when using all definitions of abnormal CPR.

CONCLUSION: Irrespective of the CPR calculation used, brain sparing is significantly associated with an adverse perinatal outcome in IUGR. This adds further weight to integrating CPR evaluation into the clinical assessment of IUGR pregnancies. The impact of this finding on long-term neurodevelopmental outcomes in this patient cohort is underway.

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BACKGROUND AND OBJECTIVE

Intrauterine growth restriction (IUGR) confers a significant risk of adverse perinatal outcome on affected pregnancies. Advances in Doppler ultrasonography have improved surveillance with particular focus on cerebral blood flow, which is believed to reflect a compensatory brain-sparing effect.

EDITORS' ★ CHOICE

The cerebroplacental ratio (CPR) quantifies redistribution of cardiac output by dividing the Doppler indices of the middle cerebral artery (MCA) with that of the umbilical artery (UA). It has been calculated with the use of the resistance index (RI) and the pulsatility

index (PI) to quantify UA and MCA Doppler waveforms.

Various categorical cutoffs (<1 , <1.08) to predict adverse outcomes have been described, although the validity of the CPR may vary with gestational age. This has led to the development of gestational-age based normograms based on cross-sectional and longitudinal studies.

The goal of the prospective multicenter Prospective Observational Trial to Optimize Pediatric Health in Intrauterine Growth Restriction (PORTO) Study was to evaluate the optimal surveillance of fetuses with estimated fetal weight (EFW) less than the 10th centile. The objective of this analysis was to determine the role of CPR in the prediction of adverse perinatal outcome in our large patient cohort. The influence of the various CPR parameters described was also evaluated.

MATERIALS AND METHODS

In this study, IUGR was defined as EFW less than the 10th centile. The PORTO

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Study recruited 1200 consecutive ultrasound-dated singleton pregnancies from January 2010 through June 2012. Inclusion criteria included a gestational age of 24 0/7 to 36 6/7 weeks and EFW of 500 g or greater.

All eligible pregnancies underwent serial sonographic evaluation of fetal weight at 2 week intervals until delivery. Surveillance included evaluation of amniotic fluid volume, biophysical profile scoring, and multivessel Doppler of UA and MCA at every subsequent contact. Because the CPR was calculated retrospectively, this result was not made available to the clinician; therefore, CPR results did not influence management decisions.

Adverse perinatal outcome was defined as a composite outcome of intraventricular hemorrhage, periventricular leukomalacia, hypoxic ischemic encephalopathy, necrotizing enterocolitis, bronchopulmonary dysplasia, sepsis, and death. CPR was calculated using both the PI and RI to quantify the waveforms (MCA PI/UA PI and MCA RI/UA RI), with a result less than 1 considered abnormal. The first abnormal CPR result was used for analysis. Adverse outcome prediction was calculated based on other CPR calculation parameters, including the categorical cutoff of less than 1.08 and gestational age-specific reference values (less than the fifth centile).

RESULTS

Comprehensive data to allow accurate CPR calculation were available in 881 cases. There were 146 cases (16.6%) with an abnormal CPR (PI) less than 1, detected at a mean gestational age of 33 weeks. Of these, 93 (64%) were admitted to the neonatal intensive care unit for a mean length of stay of 31 days, which was significantly greater than that of cases with a CPR PI of 1 or greater (163 of 735; 22%), whose mean length of stay was 14 days ($P < .0001$). Of the cases with a CPR PI less than 1, 27 (18%) ultimately had an adverse perinatal outcome, significantly more than those with CPR of 1 or greater (14 of 735; 2%; $P < .0001$). This finding conferred an 11-fold increased risk of adverse perinatal outcome (odds ratio [OR], 11.7;

TABLE
Various CPR calculations and the prediction of adverse perinatal outcomes

Predictor	Adverse perinatal outcome		
	Sensitivity	Specificity	OR (95% CI)
CPR (PI) <1.0	66% (27/41)	85% (721/840)	11.7 6.0–22.9
CPR (RI) < 1.0	66% (27/41)	84% (698/831)	11.8 5.8–24.1
CPR (PI) <1.08	73% (30/41)	80% (675/840)	11.2 5.5–22.7
CPR (PI) less than fifth centile (Baschat and Gembruch)	80% (33/41)	60% (505/840)	6.2 2.8–13.6
CPR (PI) less than fifth centile (Ebbing et al)	85% (35/41)	41% (345/840)	4.1 1.7–9.8
CPR (PI) <1 before 34 wks	67% (26/39)	84% (451/540)	11.8 5.6–23.4
CPR (PI) <1 after 34 wks	14% (1/7)	89% (634/713)	10.7 2.4–48.7

Perinatal outcome was defined as a composite outcome of intraventricular hemorrhage, periventricular leukomalacia, hypoxic ischemic encephalopathy, necrotizing enterocolitis, bronchopulmonary, sepsis, and death.

CI, confidence interval; CPR, cerebroplacental ratio; OR, odds ratio; PI, pulsatility index; RI, resistance index.

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$P < .0001$) vs cases with a normal CPR. An abnormal CPR less than 1 was present in all 3 cases of perinatal mortality. The Table describes the prediction results ascertained using CPR cutoff threshold definitions.

The sensitivity and specificity of CPR PI less than 1 was compared with an abnormal UA, defined as a PI greater than the 95th centile or a PI greater than the 95th centile plus absent or reversed end-diastolic flow. When using multiple logistic regression to determine the additive benefit of 1 parameter to the other, we found that the UA (PI greater than the 95th centile) was associated with an OR of 3.4 (95% confidence interval, 1.9–9.1; $P < .0001$); however, the addition of a CPR PI less than 1 increased the OR to 7.6 (95% confidence interval, 3.0–19.1; $P < .0001$).

COMMENT

The presence of a brain-sparing effect was significantly associated with adverse perinatal outcome in our IUGR cohort. There was no discernible difference

when we compared the use of the PI or RI to quantify the waveforms.

The major strengths of the PORTO Study included the prospective study design and the large number of recruited pregnancies, which were subjected to a high degree of fetal surveillance. The sensitivity of the various CPR parameters used in our study is similar to those previously reported. In such a high-risk group, improved sensitivity is optimal; however, specificity needs to be appropriate to avoid influencing intervention such as iatrogenic premature delivery. Overall the categorical thresholds of 1 and 1.08 were appropriate and probably more simply achievable in the clinical setting.

The detection of absent end diastolic flow (AEDF) or reversed end diastolic flow (REDF) during interrogation of the UA provides clarity in managing the IUGR fetus. The additive benefit of CPR calculation is most evident when an abnormal UA Doppler defined as a PI greater than the 95th centile is found. The additional finding of an abnormal CPR improves the OR to a level similar

to that of AEDF/REDF in UA Doppler. Therefore, in the setting of UA Doppler PI greater than the 95th centile but without AEDF/REDF, interrogation of the MCA Doppler and CPR calculation should be considered to further guide risk assessment of the IUGR fetus. The impact of an abnormal CPR on long-term developmental outcomes in the PORTO cohort is underway.

CLINICAL IMPLICATIONS

- The detection of an abnormal cerebroplacental ratio (CPR) was significantly associated with an adverse perinatal outcome in our intrauterine growth restriction cohort.
- The benefit of the CPR calculation is most evident when an abnormal umbilical artery Doppler, defined as a

PI greater than the 95th centile, is found because it increases the prediction of an adverse outcome to a level similar to that of absent/reversed end diastolic flow in umbilical artery Doppler.

- Future research is needed to determine the impact of an abnormal CPR on long-term developmental outcomes in intrauterine growth restriction fetuses. ■

Elevated neonatal insulin-like growth factor I is associated with fetal hypertrophic cardiomyopathy in diabetic women

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OBJECTIVE: We sought to determine if fetal hypertrophic cardiomyopathy (HCM) or cardiac dysfunction is associated with elevated maternal or neonatal insulin-like growth factor (IGF)-I levels in women with diabetes.

STUDY DESIGN: In a prospective cohort study, fetal echocardiogram findings at 36 weeks' gestation in women with pregestational diabetes mellitus were compared to those in women without diabetes mellitus. HCM was defined as septal or free wall thickness ≥ 5 mm and cardiac dysfunction as a modified myocardial performance index ≥ 0.43 . Cord serum IGF-I levels at delivery were measured with enzyme-linked immunosorbent assay. Neonates with abnormal fetal echocardiogram were followed up until resolution or 6 months of life.

RESULTS: In all, 75 participants completed fetal echocardiography (55 diabetics and 20 controls). In the diabetic group, 33 of 55 (60%) had abnormal fetal echocardiograms with cardiac dysfunction in 21 of 55 (38.2%) and HCM in 8 of 55 (14.5%) and both in 4 of 55 (7.3%). At 6 months of age, 1 of 12 (8%) had persistent HCM. None in the comparison group had abnormal findings. There were no significant clinical differences in those diabetic women with normal vs abnormal fetal echocardiograms. However, among diabetic women, mean neonatal IGF-I was significantly higher in fetuses with HCM (80 ± 16 ng/mL) as compared to those without HCM (61 ± 18 ng/mL), ($P < .001$).

CONCLUSION: Elevated neonatal IGF-I appears to be associated with fetal HCM in fetuses of diabetic women.

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BACKGROUND AND OBJECTIVE

Hypertrophic cardiomyopathy (HCM) can be induced by fetal or neonatal hyperinsulinemia. Cardiac dysfunction and HCM are evident even with excellent maternal glycemic control. In

animal models, insulin-like growth factor (IGF)-I signaling pathways are implicated in the development of HCM.

Elevated maternal IGF-I may be predictive of fetal cardiovascular overgrowth. The objective of this study was to evaluate

the incidence of fetal cardiovascular overgrowth and cardiac dysfunction in patients with pregestational diabetes and to determine whether abnormal cardiac development or function is associated with elevated maternal or neonatal serum IGF-I levels.

MATERIALS AND METHODS

Eligible women had type 1 or type 2 diabetes mellitus with a singleton pregnancy and a nonanomalous fetus at ≤ 36 weeks' gestation. Nondiabetic women with a singleton pregnancy and a nonanomalous fetus at ≤ 36 weeks with a normal 1-hour glucose tolerance test served as our comparison group.

A comprehensive fetal echocardiogram was performed at 36-36 6/7 weeks'

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