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TITLE PAGE

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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CONDENSATION

Brainsparing in the IUGR fetus demonstrated by abnormal CPR is significantly associated with adverse perinatal outcomes.

SHORT VERSION OF THE TITLE

Brainsparing in IUGR

ABSTRACT

Objective

The aim of the Prospective Observational Trial to Optimize Pediatric Health in IUGR (PORTO) Study was to evaluate the optimal management of fetuses with estimated fetal weight (EFW) <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.

Methods

Over 1,100 consecutive singleton pregnancies with IUGR were recruited over two years at seven centers, undergoing serial sonographic evaluation including multi-vessel Doppler measurement. CPR was calculated using the pulsatility (PI) and resistance (RI) indices of the middle cerebral (MCA) and umbilical artery (UA) Adverse perinatal outcome was defined as a composite of intraventricular haemorrhage, periventricular leukomalacia, hypoxic ischaemic 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 (IQR 28.7-35.9) Of the 146 cases with CPR <1, 18% (n=27) had an adverse perinatal outcome. This conferred an 11-fold increased risk (OR 11.7, p<0.0001) when compared to cases with normal CPR (2%; 14/735). 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 employed, brainsparing is significantly associated with 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.

Words: 244

Key words: brainsparing, cerebroplacental ratio, intrauterine growth restriction.

MAIN TEXT

Introduction

It is well recognized that intrauterine growth restriction (IUGR) confers a significant risk of adverse perinatal outcome on affected pregnancies. Advances in Doppler ultrasonography have improved our surveillance with particular focus on cerebral blood flow which is believed to reflect a compensatory ‘brain-sparing’ effect. [1- 3] The cerebroplacental ratio (CPR), which was initially reported by Arbeille *et al* in 1987, quantifies redistribution of cardiac output by dividing the Doppler indices of the middle cerebral artery (MCA) with that of the umbilical artery (UA). [4] As the CPR reflects both the placental status and fetal response, it has been reported as being a more sensitive Doppler index for predicting perinatal outcome.[5-7] However, CPR calculation is not implemented in routine practice. This may in part be explained by the fact that previous studies have used different parameters to calculate CPR. It has been calculated using various Doppler indices: resistance index (RI) [8,9] and pulsatility index (PI) [7,10] to quantify the UA and MCA Doppler waveforms. When the RI is used, the Doppler waveform is only represented on a scale from 0 to 1 and has been reported as having a linear relationship with gestational age [2,3,5] unless large numbers are used. [8] In comparison, it is felt that use of the PI allows continuous waveform analysis over a more extensive range of waveform patterns in addition to having a quadratic relationship with gestational age. [10] There is a lack of data however comparing the effect of using RI versus PI indices on CPR prediction of perinatal outcomes.

Various categorical cut-offs (<1, <1.08) to predict adverse outcomes have been described [5, 10, 11] however there are concerns that the validity of the CPR may vary with gestational age.[9, 12] Indeed it has been reported that the CPR calculation is more predictive at less than 34 weeks gestation.[10] This has led to the development of gestational-age based normograms based on both cross-sectional [7, 8,12] and longitudinal studies.[13]

The goal of the prospective multicenter PORTO Study was to evaluate the optimal surveillance of fetuses with EFW<10th centile[14]. The objective of this particular 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.

Material and Methods

The PORTO Trial (Prospective Observational Trial to Optimize Pediatric Health in IUGR) is a multicenter prospective study conducted at seven academic maternity centers in Ireland. In this study, intrauterine growth restriction (IUGR) was defined as estimated fetal weight (EFW) below the 10th centile based on sonographic measurements of fetal biparietal diameter, head circumference, abdominal circumference and femur length (Hadlock-4).[15] The PORTO Study recruited 1,200 consecutive ultrasound-dated singleton pregnancies between January 2010 and June 2012. Inclusion criteria included gestational age between 24 0/7 and 36 6/7 weeks' and an EFW greater than or equal to 500grams. Fetuses found to have major structural and/ or chromosomal abnormalities were not included the final analysis. Institutional Review Board approval was obtained at each participating center, and written informed consent was obtained from all study participants.

Referral for consideration for enrollment to the study occurred if there was clinical suspicion of a small-for-dates fetus. A PORTO research sonographer then confirmed that EFW was below the 10th centile, and performed a detailed evaluation of the fetal anatomy. All eligible pregnancies underwent serial sonographic evaluation of fetal weight at 2-weekly intervals until delivery. All prenatal and ultrasound data was recorded on the ultrasound software system (Viewpoint; MDI Viewpoint, Jacksonville, FL) and uploaded onto a live web-based central consolidated database. Surveillance included evaluation of amniotic fluid volume, biophysical profile scoring (BPP) and multivessel Doppler of umbilical artery (UA), middle cerebral artery (MCA), ductus venosus (DV), aortic isthmus (AoI) and myocardial performance index (MPI) at every subsequent contact with the research sonographers until birth. A report of all sonographic findings was recorded in the patient’s case file and was readily available to the managing clinician. As the CPR was calculated retrospectively, this result was not made available to the clinician and therefore CPR results did not influence management decisions.

A small group of 10 research sonographers performed all Doppler evaluations. Prior to study commencement, structured training was provided by maternal-fetal medicine subspecialists, and quality assurance assessments were carried out at regular intervals. All data was interpreted using published, standardized references for various Doppler parameters as outlined previously.[16]

Timing and mode of delivery was decided autonomously by the lead clinician managing each case. Tertiary-level neonatal care facilities were available in all seven maternity centers.

Infants requiring neonatal intensive care admission had their outcomes recorded by neonatal medical or nursing staff. Adverse perinatal outcome was defined as a composite outcome of intraventricular hemorrhage (IVH), periventricular leucomalacia (PVL), hypoxic ischemic encephalopathy (HIE), necrotizing enterocolitis (NEC), bronchopulmonary dysplasia (BPD), sepsis and death. Given that all study sites were members of the Vermont Oxford Network[17], definitions for IVH, PVL, HIE, NEC, BPD and sepsis were standardized accordingly. Pediatric outcomes for infants not requiring neonatal intensive care were recorded by the research sonographers and uploaded onto the database.

A secondary analysis of the PORTO study was to evaluate the role of CPR calculation with respect to the prediction of adverse perinatal outcome. CPR was calculated using both the pulsatilty index (PI) and resistance index (RI) to quantify the waveforms (MCA PI /UA PI and MCA RI/ UA RI) with a result <1 considered abnormal. The first abnormal CPR result was used for analysis. The sensitivity and specificity of adverse outcome prediction was also calculated based on other CPR calculation parameters that are considered abnormal including a cut-off of the categorical cut-off of <1.08 and gestational age-specific reference values (<5th centile). Gestational-age dependent reference ranges for CPR used the cross-sectional data of Baschat and Gembruch [12] : estimated mean CPR = - 0.0059 × GA2 + 0.383 × GA − 4.0636 plus a weighted estimate of the standard deviation= - 0.00013 × GA2 + 0.7156 × GA − 0.67418 (derived from Table 1, Baschat-Gembruch [12]). Gestational-age dependent reference ranges based on longitudinal data as given in Ebbing *et al* [13], were also compared for sensitivity and specificity.

Use of Statistics

Prior to statistical analysis, all ultrasound and outcome data were screened for anomalous records or potential outliers and followed-up with sonographers for resolution. Diagnostic test criteria were used to evaluate CPR detection rates of the composite perinatal outcome and mortality. Logistic regression was used to model composite outcomes with abnormal CPR determinations as predictors. Multiple Logistic regression analysis was used to assess effect of multiple predictors (e.g. abnormal UA plus abnormal CPR). The kappa coefficient was used to describe correlations between CPR abnormalities. SAS® Version 9.2 was used for data management and statistical analysis.

Results

Of 1,200 recruited pregnancies with EFW below the 10th centile, 32 (2.7%) were excluded due to chromosomal and/ or structural abnormalities, 13 (1%) withdrew their consent, 13 (1%) delivered outside Ireland while a further 26 (2.2%) were lost to follow-up. This resulted in 1,116 patients completing the study protocol. Comprehensive data to allow accurate CPR calculation was available in 881 cases. The mean maternal age was 30 years, the mean BMI was 24.2 and the vast majority of women were of white European descent. This is consistent with the demographic profile of the overall PORTO cohort [ref] and indeed the obstetric population attending for antenatal care in Ireland[17], reflecting an unselected group of recruited pregnancies. Overall, the mean gestational age was 37.7 weeks. The demographic details and perinatal outcomes of the CPR cohort are outlines in Table 1.

There were 146 cases (16.6%) with an abnormal CPR (PI) <1 which was detected at a mean gestational age of 33 weeks (IQR 28.7-35.9 weeks). The mean interval from diagnosis of an abnormal CPR to delivery was 7 days (IQR 2-15 days). Of the 146 cases with CPR PI <1 a total of 93 (64%) were admitted to the neonatal intensive care unit (NICU) with a mean length of stay of 31 days which was significantly increased when compared to those with CPR PI >=1 (163/735 (22%) , mean length of stay 14 days,(P<0.0001). 27 (18%) of the cases with CPR PI <1 ultimately had an adverse perinatal outcome which was significantly increased when compared to those with CPR >=1 (14/735 ,(2%), P<0.0001). This conferred an
11 -fold increased risk of adverse perinatal outcome (OR 11.7, p<0.0001) when compared to cases with normal CPR. There was a strong agreement between CPR calculations based on PI and RI (Kappa coefficient=0.84) highlighted further by the comparable sensitivity and specificity in predicting adverse outcomes (Table 2). An abnormal CPR <1 was present in all 3 cases of perinatal mortality. The prediction results ascertained using other CPR cut-off threshold definitions are outlined in Table 2. When using a gestational age cut-off for analysis there were 116 abnormal CPR PI calculations prior to 34 weeks and 83 after 34 weeks. There were 26 cases of adverse perinatal outcomes in those with an abnormal CPR PI before 34 weeks compared to only one case with normal CPR PI after 34 weeks (Table 2).
The sensitivity and specificity of CPR PI <1 was also compared to an abnormal UA defined as PI >95th centile or PI >95th centile plus absent or reversed end-diastolic flow (Table 3). This analysis compares the Doppler parameters separately. When using multiple logistic regression to determine the additive benefit of one parameter to the other we found that the UA (PI>95th centile) was associated with an OR of 3.4 (95% CI=1.9-9.1, P<0.0001 however the addition of CPR PI <1 increased the OR to

7.6 (95% CI=3.0-19.1, P<0000.1). With an abnormal UA (PI>95th centile, AEDF, REDF) the OR was 7.9 (95% CI=3.7-16.8, P<0000.1) and again there was a significant increase with the addition of CPR PI <1 with an OR 13.0 (95% CI=4.0-41.8, P<0000.1).

Comment

We have demonstrated that the presence of a brainsparing effect was significantly associated with adverse perinatal outcome in our IUGR cohort. Indeed all three cases of perinatal mortality were associated with an abnormal CPR PI < 1. There was no discernible difference when comparing the use of PI or RI to quantify the waveforms. The limitation of solely using the categorical cut-off of 1 was acknowledged and led to further evaluation using the various parameters described in the literature. Odibo *et al* previously compared the impact of using gestational age-specific reference values of the CPR with a categorical threshold of 1.08 in the prediction of adverse perinatal outcomes in IUGR pregnancies and found both approaches to be similar in efficacy. [18] However their study was limited by its retrospective design and small sample size. 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 using the most advanced Doppler techniques performed by trained research sonographers. This allowed us to extensively evaluate the role of the CPR in the setting of IUGR pregnancies. Complete MCA Doppler results to allow accurate CPR calculation were not available in our entire cohort and analysis was limited to 79% of those recruited. Nevertheless, the remaining sample of 881 cases was the largest cohort to date in the assessment of CPR in IUGR fetuses.

The sensitivity of the various CPR parameters used in our study is similar to those previously reported.[5, 10, 18] We found that achieving an increased sensitivity was confounded by decreasing specificity. In such a high risk group improved sensitivity is optimal, however, the specificity needs 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. It was difficult to interpret whether CPR calculation is more predictive before 34 weeks gestation given the small number of adverse outcomes beyond this gestation.

As one of the main outcomes of the PORTO trial to date was the consistent association between an abnormal UA Doppler and adverse perinatal outcome [16] we also sought to evaluate whether there is an additive role in performing CPR. This was clearly demonstrated with the significantly increased OR when assessing the predictive value using multiple logistic regression. The detection of AEDF or REDF when interrogating the UA provides clarity when managing the IUGR fetus. We would argue that the additive benefit of CPR calculation is most evident when an abnormal UA Doppler defined as PI >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 >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 longterm morbidity for the IUGR fetus is being increasingly reported [19] however the role of cerebral compensation in the affected fetus and CPR in prediction of adverse longterm morbidities is needed in large studies. We feel the correlation of CPR in predicting poor perinatal outcome adds further weight to integrating CPR evaluation into clinical assessment in IUGR. The impact of an abnormal CPR on long-term developmental outcomes in the PORTO cohort is underway.

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References

1. Peeters LLH, Sheldon RE, Jones MD, Makowski EL, Meschis A. Blood flow to fetal organs as a function of arterial oxygen content. Am J Obstet Gynecol 1979; 135:637-42.
2. Wladimiroff JW, Tonge HM, Stewart PA. Doppler ultrasound assessment of cerebral blood flow in the human fetus. Br J Obstet Gynaecol 1986; 93: 471–475.
3. Arbeille P, Maulik D, Fignon A, Stale H, Berson M, Bodard S,Locatelli A. Assessment of the fetal pO2 changes by cerebraland umbilical Doppler on lamb fetuses during acute hypoxia.Ultrasound Med Biol 1995; 21: 861–870.
4. Arbeille P, Roncin A, Berson M, Patat F, Pourcelot L. Exploration of the fetal cerebral flow by duplex Doppler linear array system in normal and pathological pregnancies.Ultrasound Med Biol 1987;13:329-37.
5. Gramellini D, Folli MC, Raboni S, Vadora E, MerialdiA.Cerebral-umbilical Doppler ratio as a predictor of adverseperinatal outcome. ObstetGynecol 1992; 79: 416–420.
6. Wladimiroff JW, van den Wijngaard JAGN, Degani S, Noordam MJ, van Eyck J, Tonge HM. Cerebral and umbilical arterial blood flow velocity waveforms in normal and growth retarded pregnancies: a comparative study. Obstet Gynecol 1987;69:705-9.

7. Arduini D, Rizzo G. Normal values of pulsatility index from fetal vessels: a cross-sectional study on 1556 healthy fetuses. J PerinatMed 1990; 18: 165–172.
8. Kurmanavicius J, Florio I, Wisser J, Hebisch G, Zimmermann R, Muller R, Huch R, Huch A. Reference resistance indices of the umbilical, fetal middle cerebral and uterine arteries at 24–42 weeks of gestation. Ultrasound Obstet Gynecol 1997; 10: 112–120.
9. Gaziano EP, Gaziano C, Terrell CA, Hoekstra RE.The cerebroplacental Doppler ratio and neonatal outcome in diamnionic monochorionic and dichorionic twins J Matern Fetal Med. 2001 Dec;10(6):371-5.
10. Bahado-Singh RO, Kovanci E, Jeffres A, Oz U, Deren O,Copel J, Mari G. The Doppler cerebroplacental ratio and perinatal outcome in intrauterine growth restriction. Am J ObstetGynecol 1999; 180: 750–756.
11. Arias F. Accuracy of the middle-cerebral-to-umbilical-artery resistance index ratios in the prediction of neonatal outcome in patients at high risk for fetal and neonatal complications. Am J Obstet Gynecol 1994; 171:1541–1545.
12. Baschat AA and Gembruch U.The cerebroplacental Doppler ratio revisited. Ultrasound ObstetGynecol2003; 21: 124–127.
13. Ebbing C, Rasmussen S, Kiserud T. Middle cerebral artery blood flow velocities and pulsatility index and the cerebroplacental pulsatility ratio: longitudinal reference ranges and terms for serial measurement. Ultrasound Obstet Gynecol 2007;30:287-296.
14. Unterscheider J, Daly S, Geary MP, Kennelly MM, McAuliffe FM, O'Donoghue K, Hunter A, Morrison JJ, Burke G, Dicker P, Tully EC, Malone FD. Optimizing the definition of intrauterine growth restriction: the multicenter prospective PORTO Study. Am J Obstet Gynecol. 2013 Apr; 208(4):290.
15. Hadlock FP, Harrist RB, Sharman RS, Deter RL, Park SK. Estimation of fetal weight with the use of head, body, and femur measurements – a prospective study. Am J Obstet Gynecol 1985; 151(3):333-337.
16. Unterscheider J, Daly S, Geary MP, Kennelly MM, McAuliffe FM, O'Donoghue K, Hunter A, Morrison JJ, Burke G, Dicker P, Tully EC, Malone FD. Predictable progressive Doppler deterioration in IUGR: does it really exist? Am J Obstet Gynecol. 2013 Dec;209 (6):539.

17. Horbar JD. The Vermont Oxford Network: evidence based quality improvement for neonatology. *Pediatrics* 1999;103:350-359.
18. Odibo AO, Riddick C, Pare E, Stamilio DM, Macones GACerebroplacental Doppler ratio and adverse perinatal outcomes in intrauterine growth restriction: evaluating the impact of using gestational age-specific reference values. J Ultrasound Med. 2005 Sep; 24(9):1223-8.
19. von Beckerath AK, Kollmann M, Rotky-Fast C, Karpf E, Lang U, Klaritsch P Perinatal complications and long-term neurodevelopmental outcome of infants with intrauterine growth restriction. Am J Obstet Gynecol. 2013 Feb;208 (2):130.e1-6.

Table 1. Maternal Demographic Details and Perinatal Outcomes

Characteristic	n (%) / Mean ± SD
Age (years)	30 ± 6
Ethnicity (White European)	708 (82%)
Spontaneous Conception	868 (99%)
BMI (kg/m^2)	24.2 ± 4.8
GA at enrolment (weeks)	30.1 ± 3.9
GA at delivery (weeks) overall	37.7 ± 3.0
GA at delivery (weeks) CPR PI >1	38.3 +/- 2.3
GA at delivery (weeks) CPR PI <1	34.6 +/- 3.9
Weight at delivery (grams)	2471 ± 663
Weight at delivery (grams) CPR PI >1	2611 +/- 559
Weight at delivery (grams) CPR PI <1	1763 +/- 695
Admission to NICU overall	256 (29%)
Adverse Perinatal Outcome	41 (4.65%)
Perinatal Death	3 (0.34%)

Table 2. 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) < 5th centile (Baschat and Gembruch)	80% (33/41)	60% (505/840)	6.2 2.8 – 13.6
CPR (PI) < 5th centile (Ebbing)	85% (35/41)	41% (345/840)	4.1 1.7 – 9.8
CPR (PI) <1 before 34 weeks	67% (26/39)	84% (451/540)	11.8 5.6 – 23.4
CPR (PI) <1 after 34 weeks	14% (1/7)	89% (634/713)	10.7 2.4 – 48.7

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

Perinatal outcome defined as composite outcome of intraventricular hemorrhage ,periventricular leucomalacia , hypoxic ischemic encephalopathy ,necrotizing enterocolitis , bronchopulmonary ,sepsis and death

Table 3. CPR in Comparison to UA Doppler in the Prediction of Adverse Perinatal Outcomes

Predictor	Adverse Perinatal Outcome		
	Sensitivity	Specificity	OR (95% CI)
Umbilical Artery (PI >95th centile)	85% (35/41)	54% (454/840)	6.9 2.9-16.5
Umbilical Artery (PI >95th centile, AEDF, REDF)	90% (37/41)	54% (452/831)	10.8 3.8-30.5
CPR (PI) <1.0	66% (27/41)	85% (721/840)	11.7 6.0 – 22.9

CPR, cerebroplacental ratio; PI, pulsatility index; OR, odds ratio; CI,confidence interval; AEDF, absent end diastolic flow;REDF, reversed end diastolic flow

Perinatal outcome defined as composite outcome of intraventricular hemorrhage ,periventricular leucomalacia , hypoxic ischemic encephalopathy ,necrotizing enterocolitis , bronchopulmonary ,sepsis and death