An abnormal cerebroplacental ratio (CPR) is predictive of early childhood delayed neurodevelopment in the setting of fetal growth restriction

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BACKGROUND: Fetal growth restriction accounts for a significant proportion of perinatal morbidity and death. The cerebroplacental ratio is gaining much interest as a useful tool in differentiating the "at-risk" fetus in both fetal growth restriction and appropriate-for-gestational-age pregnancies. The Prospective Observational Trial to Optimize Pediatric Health in Fetal Growth Restriction group has demonstrated previously that the presence of this "brain-sparing" effect is associated significantly with adverse perinatal outcomes in the fetal growth restriction cohort. However, data about neurodevelopment in children from pregnancies that are complicated by fetal growth restriction are sparse and conflicting.

OBJECTIVE: The aim of the Prospective Observational Trial to Optimize Pediatric Health in Fetal Growth Restriction NeuroDevelopmental Assessment Study was to determine whether children born after fetal growth-restricted pregnancies are at additional risk of adverse early childhood developmental outcomes compared with children born small for gestational age. The objective of this secondary analysis was to describe the role of cerebroplacental ratio in the prediction of adverse early childhood neurodevelopmental outcome.

STUDY DESIGN: Participants were recruited prospectively from the Perinatal Ireland multicenter observational Prospective Observational Trial to Optimize Pediatric Health in Fetal Growth Restriction study cohort. *Fetal growth restriction* was defined as birthweight <10th percentile with abnormal antenatal umbilical artery Doppler indices. *Small for gestational age* was defined similarly in the absence of abnormal Doppler indices. Cerebroplacental ratio was calculated with the pulsatility indices of the middle cerebral artery and divided by umbilical artery with an abnormal value <1. Children (n=375) were assessed at 3 years with the use of the Ages and Stages Questionnaire and the Bayley Scales of Infant and Toddler Development, 3rd edition. Small-for-gestational-age pregnancies with normal Doppler indices were compared with (1) fetal growth-restricted cases with abnormal umbilical artery Doppler and normal cerebroplacental ratio or (2) fetal growth restriction cases with both abnormal umbilical artery and cerebroplacental ratio. Statistical analysis was performed with statistical software via 2-sample *t*-test with Bonferroni adjustment, and a probability value of .00625 was considered significant.

RESULTS: Assessments were performed on 198 small-for-gestational-age children, 136 fetal growth-restricted children with abnormal umbilical artery Doppler images and normal cerebroplacental ratio, and 41 fetal growth-restricted children with both abnormal umbilical artery Doppler and cerebroplacental ratio. At 3 years of age, although there were no differences in head circumference, children who also had an abnormal cerebroplacental ratio had persistently shorter stature (P=.005) and lower weight (P=.18). Children from fetal growth restriction–affected pregnancies demonstrated poorer neurodevelopmental outcome than their small-for-gestational-age counterparts. Fetal growth-restricted pregnancies with an abnormal cerebroplacental ratio had significantly poorer neurologic outcome at 3 years of age across all measured variables.

CONCLUSION: We have demonstrated that growth-restricted pregnancies with a cerebroplacental ratio <1 have a significantly increased risk of delayed neurodevelopment at 3 years of age when compared with pregnancies with abnormal umbilical artery Doppler evidence alone. This study further substantiates the benefit of routine assessment of cerebroplacental ratio in fetal growth-restricted pregnancies and for counseling parents regarding the long-term outcome of affected infants.

Key words: cerebroplacental ratio, Doppler, growth restriction, neurodevelopment, pulsatility index, small for gestational age, umbilical artery

Fetal growth restriction (FGR) accounts for a significant proportion of perinatal morbidity and death currently encountered in obstetric practice.[1] There is much debate when describing FGR. It is often reported interchangeably with the terms *small for gestational age* (SGA) or *intrauterine growth restriction*. McGowan et al[2] performed a review of 6 international guidelines on growth restriction. The inconsistencies in the definition of SGA were reported as either an estimated fetal weight (EFW) or birthweight <10th percentile and often described as the "constitutionally small." Similar inconsistencies arose with FGR described on ultrasound imaging as an EFW <10th percentile, abdominal circumference <10th percentile or <5th percentile. High-risk FGR was variable in definition as an EFW <3rd percentile, oligohydramnios, abnormal umbilical artery (UA), or middle cerebral artery Doppler indices or suboptimal growth velocity.[2]

The cerebroplacental ratio (CPR) is attracting interest as a useful tool in differentiating the "at-risk" fetus in both FGR and appropriate-for-gestational-age pregnancies.[3,4] The CPR was first reported by Arbeille et al[5,6] and quantifies the redistribution of cardiac output to the fetal brain, resulting in a "brain-sparing" effect. The Prospective Observational Trial to Optimize Pediatric

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AJOG at a Glance

Why was this study conducted?

This study was conducted to evaluate whether children from pregnancies that are complicated by fetal growth restriction with an abnormal antenatal cerebroplacental ratio are at increased risk of adverse neurodevelopmental outcomes at 3 years of age.

Key findings

Children who had altered hemodynamics in the fetal brain as indicated by an abnormal cerebroplacental ratio demonstrated poorer neurodevelopmental outcomes in comparison with children of pregnancies that were complicated by either small for gestational age or fetal growth restriction with normal cerebroplacental ratio Doppler indices.

What does this add to what is known?

In this secondary analysis of the PORTO NeuroDevelopmental Assessment Study (PANDA) study, we demonstrate that the clinical relevance of a cerebroplacental ratio <1 extends beyond the perinatal period as previously described.

Health in FGR (PORTO) group has previously demonstrated that the presence of this brain-sparing effect is associated significantly with an adverse perinatal outcome in FGR pregnancies.[7] A recent publication by Akolekar et al[8] reported CPR at the time of routine sonography between 35+6 to 37+6 weeks gestation in >47,000 pregnancies. This study defined an abnormal CPR value as <10th percentile and included both appropriate-for-gestational-age and FGR pregnancies. They found the predictive accuracy to be low in both groups. However, a low CPR value was associated with an increased risk of adverse perinatal outcome, cesarean delivery for presumed fetal compromise in labor, and birth of neonates with birthweight <3rd percentile. This may be explained, in part, by a negative bias because the study did not blind managing clinicians to CPR results and previous studies have highlighted that CPR value is best interpreted at <34 weeks gestational age (GA).[9,10]

Data surrounding neurodevelopment in children from pregnancies that are complicated by FGR are sparse and conflicting. Fattal-Valevski et al[11] found that, at 3 years of age, children with FGR (without reference to Doppler studies) are more likely to be developmentally delayed when compared with unaffected control subjects. Baschat et al[12] similarly assessed children from FGR pregnancies and investigated the impact of reversed end-diastolic volume in the UA Doppler study, abnormal ductus venosus, or an abnormal biophysical profile on developmental outcomes. This study demonstrated that UA-reversed end-diastolic volume, but not abnormal ductus venosus or biophysical profile, was an independent contributor to delayed neurodevelopment. Another study by Llurba et al[13] differentiated FGR and SGA pregnancies using abnormal UA or internal carotid artery Doppler findings and did not find any difference in developmental outcomes at 3 years with the use of the Stanford-Binet Intelligence scale. Recent systematic reviews have identified a deficit in current knowledge of the effects of FGR on neurodevelopmental outcomes.[14,15] There has been an increase in the reporting of long-term neurodevelopmental sequelae in the FGR fetus.[16–18] Meher et al[19] have proposed an hypothesis of neurologic injury that occurs before an abnormal CPR value as a response to the altered fetal hemodynamic adaption to hypoxia. Their review also suggested that the presence of an abnormal middle cerebral artery Doppler finding might be a late event in the overall fetal brain redistribution of blood flow.

The goal of the prospective multicenter observational PORTO-Associated Neuro Developmental Assessment (PANDA) study was to evaluate whether children from pregnancies that were complicated by FGR were at increased risk of neurodevelopmental delay, academic difficulties, health complications, and reduced physical growth at age 3 years. The objective of this secondary analysis was to evaluate if an abnormal antenatal CPR value correlates to an increased risk of adverse early childhood neurodevelopment. Our hypothesis was that FGR children who are exposed to altered neurologic hemodynamics in utero, as demonstrated by an abnormal CPR value, will have poorer neurodevelopmental outcomes.

Materials and Methods

PORTO was a multicenter prospective study conducted at the 7 largest academic obstetric centers in Ireland. Between January 2010 and June 2012, the PORTO recruited 1200 women with consecutive ultrasound-dated singleton pregnancies. Inclusion criteria were a GA between 24+0 and 36+6 weeks and an EFW ≥500 g. Fetuses with major structural and/or chromosomal abnormalities 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 SGA because of clinical evaluation in the antenatal setting and had an EFW <10th percentile on sonography. All eligible pregnancies underwent an anatomic survey at enrolment. 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 imaging 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

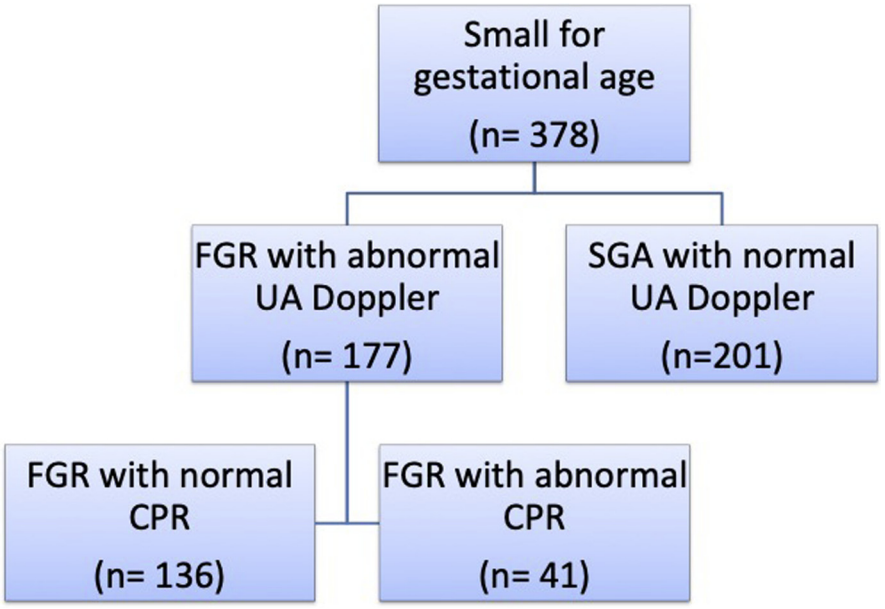
uploaded onto a live, web-based central consolidated database.

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, and timing and mode of delivery. Given that the PORTO Study was observational and descriptive in nature and to reflect contemporary obstetric practice, there were no prespecified management or delivery criteria. This was to reflect contemporary real-world practice. Tertiary level neonatal care facilities were available in all 7 trial centers.

The CPR value was calculated by dividing the pulsatility indices of the middle cerebral artery with that of the UA. For the purpose of this these analyses, an abnormal CPR value was defined as <1.0. The CPR value was calculated retrospectively; therefore, this result was not available to the clinician, and CPR results did not influence management decisions.

The PANDA study prospectively recruited infants from the PORTO cohort. For the purpose of this analysis, FGR was defined as birthweight <10th percentile with abnormal antenatal Doppler indices (when plotted on the World Health Organization gender-specific neonatal and infant close monitoring charts).[20] SGA was defined similarly in the absence of abnormal Doppler indices. The PORTO study had a 54% growth restriction with normal UA Doppler (SGA) and 46% growth restriction with an abnormal UA Doppler (FGR), of whom 37% had a normal CPR result and 9% had an abnormal CPR result. Assuming similar proportions of Doppler abnormalities in the follow-up study, a standard deviation (SD) of 10 points on an Ages and Stages Questionnaire or Bayley's Scale item, a 5-point difference between groups, and a nominal 5% level of significance, the study had 99% statistical power to detect a difference between the FGR group with abnormal UA Doppler finding and the normal CPR group and a 76% statistical power to detect a difference between those with/ without an abnormal CPR value with abnormal UA Doppler.

FIGURE 1
Flowchart



Flowchart details participants in the PORTO NeuroDevelopmental Assessment Study by Doppler indices

CPR, cerebroplacental ratio; *FGR*, fetal growth restriction; *SGA*, small for gestational age; *UA*, umbilical artery.

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However, based on the assumption of higher variation in developmental outcomes (SD=15 points), the power reduces to 84% and 46%, respectively. Adjustments for multiple testing were not made in determining power.

Children were assessed at age 3 years with the Ages and Stages Questionnaire[21,22] and the Bayley Scales of Infant and Toddler Development, 3rd edition.[23] SGA pregnancies with normal Doppler indices were compared with FGR cases with abnormal UA Doppler and normal CPR value, and/or FGR cases with both abnormal UA and CPR Doppler indices. Data management and statistical analysis were performed with the use of SAS statistical software (version 9.3; SAS Institute Inc, Cary, NC). Group comparisons were made with the use of the 2-sample *t*-test or the chi square test, as appropriate for the type of data. A nominal 5% level of significance was assumed; the Bonferroni correction for multiple testing was used. For subscales of the Ages and Stages Questionnaire and the Bayley Scales of Infant and Toddler Development, 3rd edition assessment, a probability value of <.00625 was deemed significant after Bonferroni correction for the 8 variables that were assessed.

Results

Study population

A total of 1200 cases with an EFW <10th percentile were recruited to the PORTO study. Of those recruited pregnancies, 32 (2.7%) were excluded because of 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.

Figure 1 describes the enrollment into the PANDA study, with breakdown according to Doppler indices. Assessments were performed with 201 SGA children, 136 FGR children with an abnormal UA Doppler and normal CPR Doppler indices, and 41 children with both an abnormal UA Doppler and abnormal CPR Doppler indices.

This secondary analysis was performed to assess the role of CPR and its correlation with suboptimal neurodevelopmental outcome in

TABLE 1
Maternal demographics, perinatal factors, and childhood measurements of children recruited to the PANDA study

Variable	Small for gestational age (n=201)	Fetal growth restriction			
		With normal cerebroplacental ratio (n=136)	*P*value[a]	With abnormal cerebroplacental ration (n=41)	*P*value[b]
Maternal age, y[c]	30±5	32±6	.003	32±6	.026
Nulliparous, n (%)	116 (59)	76 (56)	.678	17 (43)	.062
Body mass index, kg/m^2[c]	23.8±4.3	24.4±5.2	.253	26.1±5.1	.003
Smoker, n (%)	28 (14)	29 (21)	.076	7 (17)	.602
Highest level of maternal education, n (%)					
Primary	1 (0.5)	1 (0.8)	.201	0 (0.0)	.889
Incomplete secondary	12 (6.0)	17 (14)		4 (11)	
Complete secondary	31 (15)	21 (18)		4 (11)	
Incomplete undergrad	38 (19)	26 (22)		6 (17)	
Undergraduate complete	41 (20)	29 (24)		9 (25)	
Postgraduate	57 (28)	24 (20)		13 (36)	
White, n (%)	177 (88)	123 (90)	.464	35 (85)	.633
European ethnicity, n (%)	7 (3.5)	10 (7.4)	.119	5 (12)	.019
Maternal risk factors[d]					
Sonographic-evidence, n (%)					
Absent end-diastolic flow in umbilical artery Doppler		19 (14)		20 (49)	
Reversed end diastolic flow in umbilical artery Doppler		4 (2.9)		3 (7.3)	
Perinatal risk factors					
Gestational age at delivery, wk[c]	38.5 ± 2.6	36.8 ± 4.6	<.001	33.6 ± 4.3	<.001
Birthweight, g[c]	2693±610	2336±696	<.001	1603±684	<.001
Cesarean delivery, n (%)	67 (33)	65 (48)	.008	34 (83)	<.001
Indication for cesarean delivery was fetal distress/NRCTG, n (%)	21 (10)	26 (19)	.024	11 (27)	.005
5-Minute Apgar score <7, n (%)	1 (0.5)	1 (0.7)	.780	3 (7.3)	.002
Arterial cord pH, n (%)	4 (13)	4 (11)	.822	2 (8.7)	.627
Neonatal intensive care unit admission, n (%)	40 (20)	44 (32)	.010	34 (83)	<.001
Male gender, n (%)	78 (39)	55 (40)	.763	21 (51)	.141

NRCTG, nonreassuring cardiotocograph.

[a] Comparison between the normal Doppler indices (n=201) and abnormal umbilical artery Doppler group and the normal cerebroplacental group (n=136); [b] Comparison between the normal Doppler indices (n=201) group and the abnormal umbilical artery Doppler and abnormal cerebroplacental group (n=41); [c] Data are given as mean±standard deviation; [d] Included a previous history of hypertension, growth-restricted pregnancy, or diabetes mellitus.

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growth-restricted infants. A total 1253 CPR assessments were available in our study population, with a total 122 (10%) recorded as abnormal. The number of CPR assessments was similar across the 3 study groups, with a median of 4 (interquartile range [IQR], 2-6) assessments per patient for each study group. The median GA at assessment was 35.6 weeks (IQR, 32.3−37.7 weeks). The median GA of first abnormal CPR determination was 33.7 weeks (IQR, 28.6−36.0 weeks). The median time interval between abnormal CPR value and delivery was 5.0 days (IQR, 1−14 days). The presence of a single abnormal CPR pulsatility index <1 resulted in inclusion to the abnormal CPR group.

Descriptive results

Table 1 details maternal demographics and perinatal outcomes. The mean GA at time of delivery of SGA children was 38.52±2.48 weeks, of FGR children with

an abnormal UA Doppler index and normal CPR value was 36.82±4.64 weeks ($P<.001$ in comparison to SGA), and of FGR children with an abnormal UA Doppler index and an abnormal CPR value was 33.62±4.29 weeks ($P<.001$ in comparison to SGA). The distribution of gestational age and birthweight if further described across the three groups in Figure 2. When compared with SGA counterparts, FGR children with an abnormal UA Doppler index and an abnormal CPR value had a higher rate of cesarean deliveries in 33% vs 83% ($P<.001$), a higher rate of 5-minute Apgar score of <7 at 0.5% vs 7.3% ($P=.002$), and a higher rate of neonatal intensive care unit admission of 20% vs 83% ($P<.001$).

Developmental results

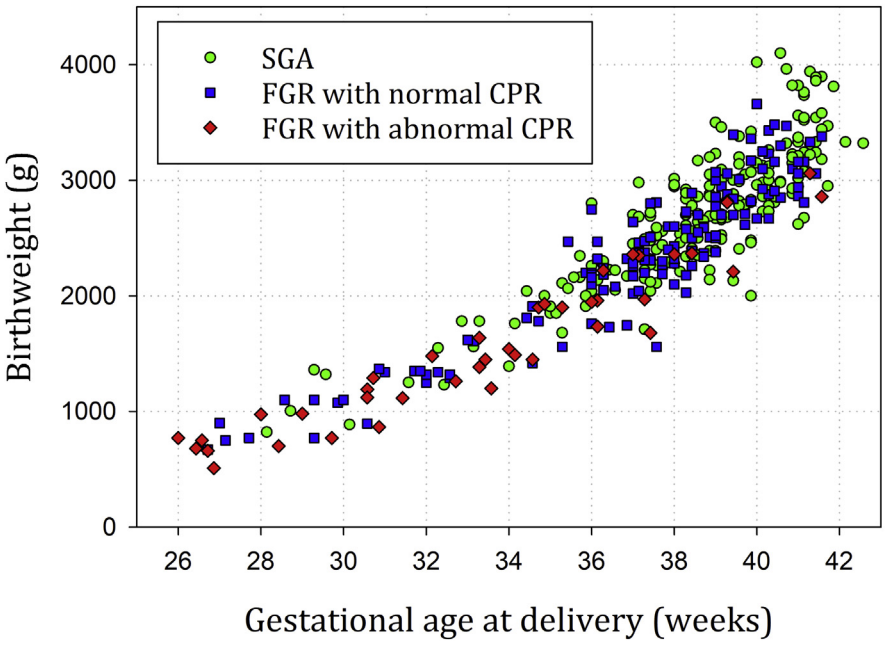
FGR children with abnormal CPR value had lower mean scores across all variables compared with SGA children. Although FGR children with normal CPR value also had lower mean scores compared with SGA children, only the differences in gross and fine motor development reached statistical significance. These results are further described in Table 2. The clinical significance of this was further assessed in Table 3 by identification of the proportion of children in each group who achieved a below average score. As seen with the mean reported scores, children born from pregnancies with FGR and an abnormal CPR value consistently had higher rates of poor performance in the Ages Stages questionnaire and each aspect of the Bayley Scales of Infant and Toddler Development, 3rd edition, composite scores when compared with SGA children. When comparison was made between both FGR groups, a significant difference was demonstrated only in composite motor scores in the Bayley Scales of Infant and Toddler Development, 3rd edition ($P=.002$).

Comment

Principal findings

The presence of altered in utero neurologic hemodynamics as detailed by an abnormal CPR value is associated with poorer neurodevelopmental outcome in comparison to children from pregnancies complicated by SGA.

FIGURE 2
A description of the distribution of gestational age and birthweight by study group



CPR, cerebroplacental ratio; *FGR*, fetal growth restriction; *SGA*, small for gestational age.

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Results

The PORTO group have previously demonstrated that the presence of an abnormal CPR value was associated significantly with an adverse perinatal outcome in the FGR cohort and that the subsequent return to a normal value was not an additional indicator of a poor prognosis.[7,9] In this secondary analysis of the PANDA study, we have demonstrated that the clinical relevance of a CPR value <1 extends beyond the perinatal period previously described. Growth-restricted pregnancies with a CPR value <1 have increased risk of delayed neurodevelopment significantly at 3 years of age when compared with pregnancies that are complicated by SGA and pregnancies that are complicated with FGR but with normal CPR values.

Clinical implications

At present, the routine inclusion of antenatal evaluation of CPR value has yet to be adopted by American College of Obstetricians and Gynecologists, the Royal College of Obstetricians and Gynaecologists, or the Institute of Obstetrics and Gynaecology in Ireland.[24–26] The addition of our research further advocates for the routine assessment of CPR value with the evaluation of the FGR fetus, given the previously described adverse perinatal outcomes and the additional suboptimal neurodevelopmental outcomes at 3 years of age. The data at present do not support the use of a CPR pulsatility index <1 as a measure to assist clinicians regarding timing of delivery in this high-risk cohort. In addition, at the time of neonatal discharge, Doppler status routinely is not considered when the determination of risk for poor neurodevelopmental outcome is made. However, this knowledge of poorer developmental outcomes in the setting of FGR with an abnormal CPR pulsatility index <1 present neonatologists and pediatricians with a simple measurement to identify those infants who might benefit from early intervention to optimize neurodevelopmental outcomes.

TABLE 2
Early childhood neurodevelopmental outcomes in fetal growth-restricted pregnancies with pregnancies with abnormal Doppler indices

Variable	Small for gestational age (n=201)[a]	Fetal growth restriction			
		With normal cerebroplacental ratio (n=136)[a]	*P* value	With abnormal cerebroplacental ration (n=41)[a]	*P* value
Gestational age at delivery, wk	38.5±2.6	36.82±4.64	<.001	33.62±4.29	<.001
At 3 years					
Age at assessment, mo	39.9±1.9	40.0±1.9	.717	38.6±2.1	.004
Height, cm	95.1±4.2	94.7±4.6	.532	92.3±4.4	.006
Weight, kg	15.0±2.0	15.9±2.3	.952	13.9± 1.7	.020[b]
Head circumference, cm	49.5±1.4	49.3±1.7	.526	49.0±1.8	.254
Ages and Stages Questionnaire					
Communication	54±11	51±15	.014[b]	46±17	<.001
Gross motor	54±11	50±16	.002	49±12	.007
Fine motor	49±13	44±17	.002	38±20	<.001
Problem solving	56±8	53±12	.013[b]	47±14	<.001
Personal social	53±9	51±11	.046[b]	46±15	<.001
Bayley Scales of Infant and Toddler Development, 3rd ed, composite scores					
Cognitive	103±12	101±13	.290	94±13	.002
Language	109±13	106±14	.179	100±20	.006
Motor	110±15	104±17	.032[b]	92±16	<.001

[a] Data are given as mean±standard deviation; [b] Highlights nonsignificant results.

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Strengths and limitations

The authors acknowledge that children in the FGR group with abnormal CPR values were born at an earlier gestation and had lower birthweights than their SGA peers. The American Academy of Pediatrics advises that corrected GA should be used only for children up to 3 years who were born preterm.[27] The need to adjust for delivery at earlier GA remains controversial. Application of corrected age for too long can mask early recognition of developmental delay, whereas not correcting may lead to underestimation of an ex-preterm infant's abilities.

In the article by Morsan et al[28] who studied 73 infants at 12 months age, they reported that correction for prematurity should be applied differently across the cognitive, language, and motor domains of the Bayley Scales of Infant and Toddler Development, 3rd edition. At 12 months age, they reported that only cognitive scores should be corrected, with less need to correct motor and inconclusive evidence to correct in the language domain. Similarly Greene et al[29] reported that the classification of developmental delay is not stable in the first 2 years, with 1 in 6 children reported not to have a language delay at 8 months being reclassified as having language delay at 20 months. They also found the converse with 1 in 10 children being reported with gross motor delay being reclassified as having no delay present at 20 months.

Traditionally many studies that form the evidence base that advocates for the use of corrected age are from a different era with different treatment of the preterm neonate. As such, advances in the preterm neonatal treatment and improving survival and changing morbidity need to be considered and highlight the need for further research to describe the current population of ex-preterm children.[30] A large Dutch study that assessed 555 preterm children demonstrated that, at 12 months, corrected scores were equivocal to their term born peers. However, at 24 months, this adjustment was no longer necessary, because the chronologic age scores at 2 years were in fact equal or better than the term-born peers. This study concluded that corrected age should be applied only to 12 months but that, at 2 years of age, corrected age was no longer necessary.[31]

In this analysis, we did not adjust for prematurity because the children were >3 years; we reflected the current practice of the application of scores to the corrected age until 24 months using both the Ages and Stages Questionnaire[21,22] and the Bayley Scales of Infant and

TABLE 3
Proportion of abnormal early childhood neurodevelopmental outcomes in fetal growth-restricted pregnancies with abnormal Doppler indices

Variable	Small for gestational age (n=201)[a]	Fetal growth restriction			
		With normal cerebroplacental ratio (n=136)[a]	*P* value	With abnormal cerebroplacental ration (n=41)[a]	*P* value
Gestational age at delivery, wk[a]	38.5±2.6	36.82±4.64	<.001	33.62±4.29	<.001
Ages and Stages Questionnaire: below average scores, n (%)					
Communication	11 (5.6)	15 (11)	.058	7 (18)	.007
Gross motor	11 (5.6)	25 (19)	<.001	4 (11)	.262
Fine motor	7 (3.6)	14 (11)	.011[b]	8 (21)	<.001
Problem solving	4 (2.1)	9 (6.9)	.030[b]	6 (16)	<.001
Personal social	8 (4.1)	16 (12)	.006	8 (21)	<.001
Bayley Scales of Infant and Toddler Development, 3rd ed, composite scores, n (%)					
Cognitive					
Above average	27 (27)	18 (23)	.488	3 (12)	.099
Average	69 (69)	55 (69)	.971	17 (65)	.724
Below average	4 (4.0)	7 (8.8)	.186	6 (23)	.001
Language					
Above average	48 (48)	32 (40)	.256	7 (27)	.049[b]
Average	45 (45)	39 (49)	.660	14 (54)	.446
Below average	6 (6.1)	9 (11)	.213	5 (19)	.035[b]
Motor					
Above average	55 (57)	33 (41)	.041[b]	3 (12)	<.001
Average	33 (34)	35 (44)	.185	14 (54)	.065
Below average	9 (9.3)	12 (15)	.241	9 (35)	.001

[a] Data are given as mean±standard deviation; [b] Highlights nonsignificant results.

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Toddler Development, 3rd edition.[23] By not correcting for GA, this allowed us to yield unbiased exposure/outcome results. GA poses a conundrum in perinatal epidemiologic findings because opinions differ on whether it is a confounder or an intermediate variable. Obstetricians often wish to adjust for intermediate variables, GA in particular, to assess if the intermediate variable is the driver of observed associations. In perinatal epidemiologic findings, this can be problematic and leads to severe biases, such as over adjustment and collider stratification biases.[32,33]

The strengths of the PANDA study are that it was the largest multicenter prospective observational study to date with intensive antenatal surveillance that examined the FGR fetus and prospective neurodevelopmental follow-up study of growth-restricted children at 3 years of age. 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 the lack of inclusion of a group of appropriately grown infants for GA to allow comparison with unaffected control subjects. Findings of this study are further limited by the observational nature of its design and the resultant selection bias secondary to a large number of parents who abstained from the childhood follow up. Nevertheless, this is the largest cohort to date to evaluate the role of an abnormal CPR value in the setting of FGR pregnancy in early childhood neurodevelopmental outcomes. This study further substantiates the need for further large prospective studies that will investigate fetal Doppler studies and longer-term adolescent developmental outcomes.

Research implications

Future antenatal research might seek to address whether there are structural

changes that are identifiable in the FGR fetus via in utero magnetic resonance imaging and whether these structural changes are present before the development of an abnormal CPR value, as hypothesized by Meher et al.[19] Neurologic structure changes have been observed in the neonatal and pediatric populations in the setting of FGR.[34] In addition, further longitudinal data are required for adolescence and adulthood to examine the neurodevelopmental outcome of our current population of ex-preterm infants.

Conclusion

Despite advances in neonatal care and improved survival rates in the very low birthweight and preterm infants, the rates of severe developmental delay remain relatively stable internationally.[35] A better understanding of the causes and risk factors for adverse neurodevelopmental outcomes among preterm FGR children can allow for better counseling of the parents of these children and help healthcare providers to develop early intervention plans to minimize the potential deficit. ■

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