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

Authors:

Cathy MONTEITH PhD, Dublin, Ireland; Obstetrics & Gynecology, Royal College of Surgeons, Ireland.

Karen FLOOD MD, Dublin, Ireland; Obstetrics & Gynecology, Royal College of Surgeons, Ireland.

Ragamallika PINNAMANENI MRCPI, Cambridge, United Kingdom; Neonatology, Rosie Maternity Hospital, Cambridge, United Kingdom.

Terri A. LEVINE PhD, Belfast, Northern Ireland; School of Nursing and Midwifery, Queen's University Belfast.

Julia UNTERSCHEIDER PhD, Melbourne, Australia; Obstetrics & Gynecology, University of Melbourne, Royal Women's Hospital, Melbourne, Australia.

Fionnuala M. MCAULIFFE MD, Dublin, Ireland; Obstetrics & Gynecology, UCD Perinatal Research Centre, University College Dublin, National Maternity Hospital, Dublin, Ireland.

Fiona A. ALDERDICE BSSc, PhD, Belfast, Northern Ireland; School of Nursing and Midwifery, Queen's University Belfast. National Perinatal Epidemiology Unit, University of Oxford, Oxford, United Kingdom.

Patrick DICKER PhD, Dublin, Ireland, Epidemiology & Public Health, Royal College of Surgeons in Ireland, Dublin, Ireland.
Elizabeth C. TULLY PhD, Dublin, Ireland; Obstetrics & Gynecology, Royal College of Surgeons, Ireland.
Fergal D. MALONE MD, Dublin, Ireland; Obstetrics & Gynecology, Royal College of Surgeons, Ireland.
Adrienne FORAN MD, Dublin, Ireland; Neonatology, Royal College of Surgeons, Ireland.

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Corresponding author- Dr. Cathy Monteith RCSI, The Master's House, Rotunda Hospital, Parnell Square, Dublin 1, Ireland. Tel: 00353857805088, Fax:0035314022543. Email: cathymonteith@rcsi.ie

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Table 3 should appear in the print issue.

Condensation: An abnormal CPR in the setting of FGR is associated with poorer neurodevelopmental outcomes at three years.

Short Version of Title: Abnormal CPR and delayed neurodevelopment.

AJOG at a Glance:

A. Why was the study conducted?

   This study was conducted to evaluate whether children from pregnancies complicated by FGR with an abnormal antenatal CPR are at increased risk of adverse neurodevelopmental outcomes at three years of age.

B. What are the key findings?

   Children who had altered hemodynamics in the fetal brain as indicated by an abnormal Cerebroplacental ratio (CPR) demonstrated poorer neurodevelopmental outcomes in comparison to children with pregnancies complicated by either SGA or FGR with normal CPR Doppler indices.

C. What does this study add to what is already known?

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

Abstract: BACKGROUND: Fetal growth restriction (FGR) accounts for a significant proportion of perinatal morbidity and mortality. The cerebroplacental ratio (CPR) is gaining much interest as a useful tool in differentiating the "at-risk" fetus in both FGR and appropriate for gestational age (AGA) pregnancies. The Prospective Observational Trial to Optimize Pediatric Health in FGR (PORTO) group, have previously demonstrated that the presence of this 'brain-sparing' effect is significantly associated with adverse perinatal outcomes in the FGR cohort. However, data about neurodevelopment in children from pregnancies complicated by FGR are sparse and conflicting. OBJECTIVE: The aim of the PORTO NeuroDevelopmental Assessment Study (PANDA) was to determine whether children born after FGR pregnancies are at additional risk of adverse early childhood developmental outcomes compared to children born small for gestational age (SGA). The objective of this secondary analysis was to describe the role of CPR in the prediction of adverse early childhood neurodevelopmental outcome. MATERIALS AND METHODS: Participants were prospectively recruited from the Perinatal Ireland multicenter observational PORTO study cohort. FGR was defined as birth weight <10th with abnormal antenatal umbilical artery (UA) Doppler indices. SGA was similarly defined in the absence of abnormal Doppler indices. CPR was calculated using the pulsatility indices of the middle cerebral and divided by UA with an abnormal value <1. Children (n=375) were assessed at three years using the Ages and Stages Questionnaire and the Bayley Scales of Infant and Toddler Development, 3rd edition. SGA pregnancies with normal Doppler indices were compared with: 1) FGR cases with abnormal UA Doppler and normal CPR; or 2) FGR cases with both abnormal UA & CPR. Statistical analysis was performed using SAS version 9.2 via two-sample t-test with Bonferroni adjustment and p-value of 0.00625 significant. RESULTS: Assessments were performed on 198 SGA children; 136 FGR children with abnormal UA Doppler and normal CPR and 41 FGR children with both abnormal UA Doppler and CPR. At three years of age, while there were no differences in head circumference, children who also had an abnormal CPR had persistently shorter stature (p=0.005) and lower weight (p=0.18). Children from FGR affected pregnancies demonstrated poorer neurodevelopmental outcome than their SGA counterparts. FGR pregnancies with an abnormal CPR had significantly poorer neurological outcome at three years of age across all measured variables (Tables 1 & 2). CONCLUSION: We have demonstrated that growth restricted pregnancies with a CPR <1, have significantly increased risk of delayed neurodevelopment at three years of age when compared to pregnancies with abnormal UA Doppler alone. This study further substantiates the benefit of routine assessment of CPR in FGR pregnancies and for counseling parents regarding the long-term outcome of affected infants.

Keywords: brain sparing, cerebroplacental ratio, intrauterine

growth restriction, neurodevelopment, small for gestational age,

fetal growth, fetal size, Doppler velocimetry, middle cerebral artery, umbilical artery, pulsatility index, Doppler waveform analysis, neurodevelopmental outcome.

Background

Fetal growth restriction (FGR) accounts for a significant proportion of perinatal morbidity and mortality 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 (IUGR). McGowan et al performed a review of six international guidelines on growth restriction. The inconsistencies in the definition of SGA were reported as either an estimated fetal weight (EFW) or birthweight <10th centile and often described as the “constitutionally small”. Similar inconsistencies arose with FGR described on ultrasound as an EFW <10th centile, abdominal circumference (AC) <10th centile or AC <5th centile. High risk FGR was variable in definition as an EFW <3rd centile, oligohydramnios, abnormal umbilical artery (UA) or middle cerebral artery (MCA) 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 (AGA) pregnancies.(3, 8) The CPR was first reported by Arbeille et al., and quantifies the redistribution of cardiac output to the fetal brain, resulting in a 'brain-sparing' effect.(9, 10) The Prospective Observational Trial to Optimize Pediatric Health in FGR (PORTO) group, have previously demonstrated that the presence of this brain sparing effect is significantly associated with an adverse perinatal outcome in FGR pregnancies.(11) A recent publication by Akolekar et al reported CPR at time of routine sonography between 35+6 to 37+6 week's gestation in over 47,000. This study defined an abnormal CPR as <10th centile and included both AGA and FGR pregnancies. They found the predictive accuracy to be low in both groups. However, a low CPR was associated with increased risk of adverse perinatal outcome, cesarean delivery for presumed fetal compromise in labor, and birth of neonates with birthweight <3rd centile.(12) This may in part be explained by a negative bias as the study did not blind managing clinicians to CPR results and previous studies have highlighted that CPR is best interpreted <34 weeks gestational age (GA).(13, 14)

Data surrounding neurodevelopment in children from pregnancies complicated by FGR are sparse and conflicting. Fattal- Valevski et al. found that at three years of age children with FGR (without reference to Doppler studies) are more likely to be developmentally delayed when compared to unaffected controls.(15) Baschat et al. similarly assessed children from FGR pregnancies and interrogated the impact of reversed end-diastolic volume (REDV) in the umbilical artery (UA) Doppler, abnormal ductus venosus or an abnormal biophysical profile on developmental outcomes. This study demonstrated that UA- REDV, but not abnormal ductus venosus or biophysical profile, was an independent contributor to delayed neurodevelopment.(16) Another study by Llurba et al. differentiated FGR and SGA pregnancies using abnormal UA or internal carotid artery Doppler findings, and did not find any difference in developmental outcomes at three years using the Stanford-Binet Intelligence scale.(17) Recent systematic reviews have identified a deficit in current knowledge of the effects of FGR on neurodevelopmental outcomes.(18, 19) There has been an increase in the reporting of long-term neurodevelopmental sequelae in the FGR fetus.(20-22) Meher et al have proposed a hypothesis of neurological injury occurring prior to an abnormal CPR as a response to the altered fetal hemodynamic adaption to hypoxia.(5) Their review also suggested that the presence of an abnormal MCA Doppler might in

fact 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 complicated by FGR were at increased risk of neurodevelopmental delay, academic difficulties, health complications and reduced physical growth at age three 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 exposed to altered neurological hemodynamics in utero as demonstrated by an abnormal CPR will have poorer neurodevelopmental outcomes.

Materials and Methods

PORTO was a multicenter prospective study conducted at the seven largest academic obstetric centers in Ireland. Between January 2010 and June 2012, the PORTO recruited 1,200 women with consecutive ultrasound-dated singleton pregnancies. Inclusion criteria were a GA between 24^{+0} and 36^{+6} weeks, and an estimated fetal weight (EFW) greater than or equal to 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 due to clinical evaluation in the antenatal setting and had an EFW <10th centile on sonography. All eligible pregnancies underwent an anatomical survey at enrolment. Serial sonographic evaluation of fetal weight was performed at two weekly intervals until birth, and normally formed fetuses underwent evaluation of amniotic fluid volume, biophysical profile scoring, and multi-vessel 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, 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 in order to reflect

contemporary obstetric practice, there were no pre-specified 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 was calculated by dividing the pulsatility indices of the middle cerebral artery (MCA) with that of the umbilical artery (UA). For the purpose of this these analyses, 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.

The PORTO NeuroDevelopmental Assessment Study (PANDA) prospectively recruited infants from the PORTO cohort. For the purpose of this analysis, Fetal growth restriction (FGR) was defined as birth weight <10th centile with abnormal antenatal Doppler indices (when plotted on the WHO gender specific Neonatal and infant close monitoring charts).(23) Small for gestational age (SGA) was similarly defined 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 (ASQ) 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 and normal CPR group; 76% statistical power to detect a difference between those with/ without an abnormal CPR with abnormal UA Doppler. However, based on the assumption of higher variation in developmental outcomes (SD= 15points), the power reduces to 84% and 46% respectively. Adjustments for multiple testing were not made in determining power.

Children were assessed at age three years using the ASQ (24, 25) and the Bayley Scales of Infant and Toddler Development, 3rd edition.(26) SGA pregnancies with normal Doppler indices were compared with 1) FGR cases with abnormal UA Doppler and normal CPR, and; or 2) FGR cases with both abnormal UA and CPR Doppler indices. Data management and statistical analysis were performed using SAS version 9.3. Group comparisons were made using the two-sample t-test or the chi square test, as appropriate for the type of data. A nominal 5% level of significance was assumed and the Bonferroni correction for multiple testing was used. For sub-scales of the Ages and Stages Questionnaire and the Bayley Scales of Infant and Toddler Development, 3rd edition assessment, a p-value of <0.00625 was deemed significant following Bonferroni correction for the eight variables assessed.

Results

Study population

A total of 1,200 cases with an EFW below the 10th 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 while 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 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 three study groups, with a median [interquartile range (IQR)] of 4 [2-6] assessments per patient for each study group. The

median [IQR] GA at assessment was 35.6 [32.3 -37.7] weeks. The median [IQR] GA of first abnormal CPR determination was 33.7 [28.6 – 36.0] weeks. The median [IQR] time interval between abnormal CPR value and delivery was 5.0 [1 -14] days. The presence of a single abnormal CPR PI <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, FGR children with an abnormal UA Doppler and normal CPR was 36.82 ±4.64 weeks ($p<0.001$ in comparison to SGA), FGR children with an abnormal UA Doppler and an abnormal CPR was and 33.62 ±4.29 weeks ($p<0.001$ in comparison to SGA). When compared to SGA counterparts, FGR children with an abnormal UA Doppler and an abnormal CPR had a higher rate of cesarean section in 33% vs. 83%, ($p<0.001$), a higher rate of 5-minute Apgar score of <7 at 0.5% vs. 7.3%, ($p=0.002$), and a higher rate of Neonatal intensive care unit (NICU) admission of 20% vs. 83%, ($p<0.001$).

Developmental results

FGR children with abnormal CPR had lower mean scores across all variables compared to SGA children. While FGR children with

normal CPR also had lower mean scores compared to SGA children, only 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 identifying 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 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 to SGA children. When comparison was made between both FGR groups a significant difference was only demonstrated in composite Motor scores in the Bayley Scales of Infant and Toddler Development, 3rd edition ($p=0.002$).

Comment

Principal Findings

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

Results

The PORTO group have previously demonstrated that the presence of an abnormal CPR was significantly associated 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.(11, 13) In this secondary analysis of the PANDA study, we have demonstrated that the clinical relevance of a CPR <1 extends beyond the perinatal period previously described. Growth restricted pregnancies with a CPR <1, have significantly increased risk of delayed neurodevelopment at three years of age when compared to pregnancies complicated by SGA and pregnancies complicated with FGR but with normal CPR values.

Clinical implications

At present the routine inclusion of antenatal evaluation of CPR 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.(27-29) The addition of our research further advocates for the routine assessment of CPR when evaluating the FGR fetus given the previously described adverse perinatal outcomes and the additional suboptimal neurodevelopmental outcomes at three years of age. The data at present does not support the use of a CPR PI <1 as a measure to assist clinicians regarding timing of delivery in this high-risk cohort. In addition at time of neonatal discharge Doppler status is not routinely considered when

determining risk for poor neurodevelopmental outcome. However, this knowledge of poorer developmental outcomes in the setting of FGR with an abnormal CPR PI <1 present neonatologists and pediatricians with a simple measurement to identify those infants who might benefit from early intervention to optimize neurodevelopmental outcomes.

Strengths and limitations

The authors acknowledge that children in the FGR group with abnormal CPR were born at an earlier gestation and had lower birth weights than their SGA peers. The American Academy of Pediatrics advises that corrected GA should be used only for children up to three years who were born preterm.(30) The need to adjust for delivery at earlier GA remains controversial. Applying corrected age for too long can mask early recognition of developmental delay whereas not correcting may lead to underestimating an ex-preterm's abilities.

In the paper by Morsan et al., from 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 in motor and inconclusive

evidence to correct in language domain. (31) Similarly Greene et al., reported that the classification of developmental delay is not stable in the first 2 years with one in six children reported not to have a language delay at eight months being reclassified as having language delay at 20 months. They also found the converse with one in ten children being reported with gross motor delay being reclassified as having no delay present at 20 months.(32) Traditionally many studies, which form the evidence base advocating for the use of corrected age are from a different era with different management of the preterm neonate. As such advances in the preterm neonatal management and improving survival and changing morbidity needs to be considered and highlights the need for further research to describe the current population of ex-preterm children.(33) A large Dutch study assessing 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, as the chronological age scores at 2 years were in fact equal or better than the term born peers. This study concluded that corrected age should only be applied to 12 months but that at 2 years corrected age was no longer necessary.(34)

In this analysis we did not adjust for prematurity as the children were older than three years and to reflect the current practice of

applying scores to the corrected age until 24 months using both the Ages and Stages Questionnaire(24, 25) and the Bayley Scales of Infant and Toddler Development, 3rd edition.(26) By not correcting for GA this allowed authors to yield unbiased exposure/ outcome results. Gestational age poses a conundrum in perinatal epidemiology as 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 epidemiology this can be problematic and leads to severe biases such as over adjustment and collider stratification biases.(35, 36)

The strengths of the PANDA study are that it is the largest multicenter prospective observational study to date with intensive antenatal surveillance examining the FGR fetus and prospective neurodevelopmental follow-up study of growth restricted children at three 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 gestational age to allow

comparison to unaffected controls. 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 abstaining from the childhood follow-up. Nethertheless, this is the largest cohort to date to evaluate the role of an abnormal CPR value in the setting of FGR pregnancy on early childhood neurodevelopmental outcomes. This study further substantiates the need for further large prospective studies interrogating fetal Doppler studies and longer-term adolescent developmental outcomes.

Research implications

Future antenatal research might seek to address if there are structural changes identifiable in the FGR fetus via in-utero magnetic resonance imaging (MRI) and whether these structural changes are present prior to the development of an abnormal CPR as hypothesized by Meher et al.(5) Neurological structure changes have been observed in the neonatal and pediatric populations in the setting of FGR.(37) In addition, further longitudinal data is required into adolescence and adulthood to examine the neurodevelopmental outcome of our current population of ex-preterm infants.

Conclusions

Despite advances in neonatal care and improved survival rates in the very low birth weight and preterm infants the rates of severe developmental delay remain relatively stable internationally.(38) A better understanding of the etiology 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 develop early intervention plans to minimize the potential deficit.

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FC – Royal College of Surgeons in Ireland- Rotunda Hospital, Dublin, Ireland

HOK – Royal College of Surgeons in Ireland- Rotunda Hospital, Dublin, Ireland

ED - Coombe Women and Infants University Hospital, Dublin, Ireland

CM - National Maternity Hospital, Dublin, Ireland

AK- Cork University Maternity Hospital, Cork, Ireland

PG - Royal Jubilee Maternity Hospital, Belfast, Ireland

AB - University Hospital Galway, Galway, Ireland,

EV - University Hospital Galway, Galway, Ireland,

WO - University Hospital Limerick, Limerick, Ireland

AA – University Hospital Limerick, Limerick, Ireland

FM – Royal College of Surgeons in Ireland- Rotunda Hospital, Dublin, Ireland

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Tables:

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

Abbreviations: n, number; UA, umbilical artery; CPR, cerebroplacental ratio; BMI, body mass index; GA, gestational age; CS, caesarean section; min, minute; NICU, neonatal intensive care unit. Maternal risk factors included a previous history of hypertension, growth restricted pregnancy, or diabetes. Numeric variables are summarized as mean ± SD with categorical variables with n (percentage). *p-value comparison between normal Doppler indices (n=201) and abnormal UA Doppler and normal CPR group (n=136). **p-value comparison between normal Doppler indices (n=201) and abnormal UA Doppler and abnormal CPR group (n=41).

Variable	**SGA (n=201)**	**FGR with normal CPR (n=136)**	***p-value**	**FGR with abnormal CPR (n=41)**	****p-value**
Maternal Age, years	30 ± 5	32 ± 6	0.003	32 ± 6	0.026
Nulliparous	116 (59%)	76 (56%)	0.678	17 (43%)	0.062
BMI	23.8 ± 4.3	24.4 ± 5.2	0.253	26.1 ± 5.1	0.003
Smokers	28 (14%)	29 (21%)	0.076	7 (17%)	0.602
Highest level of maternal education					
Primary	1 (0.5%)	1 (0.8%)	0.201	0 (0.0%)	0.889
Incomplete Secondary	12 (6.0%)	17 (14%)		4 (11%)	
Complete Secondary	31 (15%)	21 (18%)		4 (11%)	

Incomplete Undergraduate	38 (19%)	26 (22%)		6 (17%)	
Complete Undergraduate	41 (20%)	29 (24%)		9 (25%)	
Postgraduate	57 (28%)	24 (20%)		13 (36%)	
White European ethnicity	177 (88%)	123 (90%)	0.464	35 (85%)	0.633
Maternal risk factors	7 (3.5%)	10 (7.4%)	0.119	5 (12%)	0.019
Sonographic Evidence of AEDF in UAD	-	19 (14%)	-	20 (49%)	-
Sonographic Evidence of REDF in UAD	-	4 (2.9%)	-	3 (7.3%)	-
Perinatal risk factors					
GA at delivery, weeks	38.5 ± 2.6	36.8 ± 4.6	<0.001	33.6 ± 4.3	<0.001
Birthweight, grams	2693 ± 610	2336 ± 696	<0.001	1603 ± 684	<0.001
CS	67 (33%)	65 (48%)	0.008	34 (83%)	<0.001
Indication for CS was fetal Distress/ NRCTG	21 (10%)	26 (19%)	0.024	11 (27%)	0.005
5-min Apgar <7	1 (0.5%)	1 (0.7%)	0.780	3 (7.3%)	0.002
Arterial cord pH	4 (13%)	4 (11%)	0.822	2 (8.7%)	0.627

NICU admission	40 (20%)	44 (32%)	0.010	34 (83%)	<0.001
Male Gender	78 (39%)	55 (40%)	0.763	21 (51%)	0.141

Table 2. Early childhood neurodevelopmental outcomes in fetal growth restricted pregnancies with pregnancies with abnormal Doppler indices.

Abbreviations: GA, gestational age; N, number; HC, head circumference; UA, umbilical artery; CPR, cerebroplacental ratio. Numeric variables are summarized as mean ± SD with categorical variables with n (percentage), # highlights non-significant results.

Variable	**SGA (n=201)**	**FGR with normal CPR (n=136)**	**p-value**	**FGR with abnormal CPR (n=41)**	**p-value**
GA at delivery, Weeks	38.5 ± 2.6	36.82 ± 4.64	<0.001	33.62 ± 4.29	<0.001
At 3 years					
Age at assessment, months	39.9 ± 1.9	40.0 ± 1.9	0.717	38.6 ± 2.1	0.004
Height, cm	95.1 ± 4.2	94.7 ± 4.6	0.532	92.3 ± 4.4	0.006
Weight, kg	15.0 ± 2.0	15.9 ± 2.3	0.952	13.9± 1.7	0.020#
HC, cm	49.5 ± 1.4	49.3 ± 1.7	0.526	49.0 ± 1.8	0.254
Ages and Stages Questionnaire					
Communication	54 ± 11	51 ± 15	0.014 #	46 ± 17	<0.001
Gross Motor	54 ± 11	50 ± 16	0.002	49 ± 12	0.007
Fine Motor	49 ± 13	44 ± 17	0.002	38 ± 20	<0.001
Problem Solving	56 ± 8	53 ± 12	0.013#	47 ± 14	<0.001
Personal social	53 ± 9	51 ± 11	0.046#	46 ± 15	<0.001
Bayley – III Composite scores					
Cognitive	103 ± 12	101 ± 13	0.290	94 ± 13	0.002

Language	109 ± 13	106 ± 14	0.179	100 ± 20	0.006
Motor	110 ± 15	104 ± 17	0.032#	92 ± 16	<0.001

Table 3. Proportion of abnormal early childhood neurodevelopmental outcomes in fetal growth restricted pregnancies with abnormal Doppler indices. Abbreviations: GA, gestational age; N, number; UA, umbilical artery; CPR, cerebroplacental ratio. Numeric Continuous variables are summarized presented as mean ± SD, and with categorical variables with are presented as n (percentage), # highlights non-significant results.

Variable	**SGA (n=201)**	**FGR with normal CPR (n=136)**	**p-value**	**FGR with abnormal CPR (n=41)**	**p-value**
GA at delivery, weeks	38.5 ± 2.6	36.82 ± 4.64	<0.001	33.62 ± 4.29	<0.001
Ages and Stages Questionnaire: Below average scores					
Communication	11 (5.6%)	15 (11%)	0.058	7 (18%)	0.007
Gross Motor	11 (5.6%)	25 (19%)	<0.001	4 (11%)	0.262
Fine Motor	7 (3.6%)	14 (11%)	0.011#	8 (21%)	<0.001
Problem Solving	4 (2.1%)	9 (6.9%)	0.030#	6 (16%)	<0.001
Personal social	8 (4.1%)	16 (12%)	0.006	8 (21%)	<0.001
Bayley – III Composite scores					
Cognitive					
Above average	27 (27%)	18 (23%)	0.488	3 (12%)	0.099
Average	69 (69%)	55 (69%)	0.971	17 (65%)	0.724
Below average	4 (4.0%)	7 (8.8%)	0.186	6 (23%)	0.001
Language					
Above average	48 (48%)	32 (40%)	0.256	7 (27%)	0.049#
Average	45 (45%)	39 (49%)	0.660	14 (54%)	0.446
Below average	6 (6.1%)	9 (11%)	0.213	5 (19%)	0.035#

Motor					
Above average	55 (57%)	33 (41%)	0.041#	3 (12%)	<0.001
Average	33 (34%)	35 (44%)	0.185	14 (54%)	0.065
Below average	9 (9.3%)	12 (15%)	0.241	9 (35%)	0.001

Figure 1. Flow chart detailing participants in the PANDA study by Doppler indices.

Figure 2. A description of the distribution of gestational age, birthweight by study group.