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IS CEREBROPLACENTAL RATIO A MARKER OF IMPAIRED FETAL GROWTH VELOCITY AND ADVERSE PREGNANCY OUTCOME?

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This study was selected as one of the top abstracts at the 25th World Congress on Ultrasound in Obstetrics and Gynecology, organized by the International Society of Ultrasound in Obstetrics and Gynecology (ISUOG) in Montreal, Canada (11th-14th October 2015). It was also presented at the 18th Annual Conference of the British Maternal and Fetal Medicine Society (BMFMS) in Birmingham, UK (21st-22nd April 2016) and the 4th Annual International Conference on Fetal Growth in Barcelona, Spain (14th-16th September 2015).

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Condensation

Cerebroplacental ratio is a marker of impaired fetal growth velocity and adverse pregnancy outcome, even in fetuses whose size is considered appropriate for gestational age.

Short Title: Cerebroplacental ratio and fetal growth

TWEETABLE ABSTRACT

Cerebroplacental ratio is a marker of impaired fetal growth and adverse outcome, even in appropriately-sized fetuses.

A brief statement about what is known

Adding the assessment of fetal growth velocity to fetal size improves the prediction of perinatal morbidity in small for gestational age babies. Low cerebroplacental ratio is associated with adverse perinatal outcomes.

A brief statement about what the study adds

Even when corrected for fetal size and growth velocity, low cerebroplacental ratio remains significantly associated with operative delivery for fetal compromise. This suggests that cerebroplacental ratio is a potentially useful tool for the identification of at risk fetuses.

Why do you think that your study should be published in a general obstetrics/gynecology Journal, such as AJOG, rather than in a subspecialty Journal?

Fetal growth restriction, and the decisions around how to assess and when to deliver small for gestational age and growth restricted fetuses, are dilemmas faced by all practising obstetricians. This paper demonstrates how the cerebroplacental ratio could help clinicians distinguish growth restricted fetuses from those that are simply constitutionally small, and to identify those at risk of adverse perinatal outcome.

A summary in lay terms

It has long been recognised that babies that are small for their gestation are at increased risk of complications around the time of birth, such as instrumental (forceps/vacuum) delivery or cesarean section for 'fetal distress', poor condition at birth, and admission to the neonatal unit. However, it is increasingly recognised that it is important to differentiate those babies that are not growing well (that is, failing to reach their growth potential) and therefore at increased risk, from those that are simply constitutionally small but growing normally, and who are therefore unlikely to be at increased risk.

Fetuses that are failing to grow normally send more blood (and oxygen) to the brain and less to their lower extremities. This 'redistribution' of resources to the most critical organs at the expense of the less important can be assessed by comparing the blood flow in two fetal arteries – the cerebroplacental ratio (CPR). The lower the CPR, the greater the redistribution of blood and therefore, by implication, the greater the degree of compromise of and risk to the fetus.

This large study of almost 8,000 pregnancies examined the relationship between the CPR, slowing of the growth of the baby's abdomen, and complications around the time of birth. It found that low CPR was associated with several poor outcomes, including operative delivery for fetal distress and admission to the neonatal unit. Interestingly, being small (adjusted for gestation) was not associated with the risk of operative delivery for fetal distress whereas low CPR measured before birth was. This shows that

even babies considered to be of ‘normal’ size may not have been growing normally and may be at risk around the time of birth, while some small babies may have been growing normally and are not at risk. The implication is that, compared to the baby’s size, CPR measured before birth may be a better indicator of babies at risk of complications around the time of birth.

ABSTRACT

Background: The cerebroplacental ratio has been proposed as a marker of failure to reach growth potential near term. Low cerebroplacental ratio, regardless of the fetal size, is independently associated with the need for operative delivery for presumed fetal compromise and with neonatal unit admission at term.

Objective: The main aim of this study was to evaluate whether the cerebroplacental ratio at term is a marker of reduced fetal growth rate. The secondary aim was to investigate the relationship between low cerebroplacental ratio at term, reduced fetal growth velocity and adverse pregnancy outcome.

Design: retrospective cohort study of singleton pregnancies in a tertiary referral center. The abdominal circumference was measured at 20-24 weeks' gestation, and both abdominal circumference and fetal Dopplers recorded at or beyond 35 weeks, within two weeks of delivery. Abdominal circumference and birthweight values were converted into Z scores and centiles, respectively, and fetal Doppler parameters into multiples of median, adjusting for gestational age. Abdominal circumference growth velocity was quantified using the difference in abdominal circumference Z score, comparing the scan at or beyond 35 weeks with the scan at 20-24 weeks. Both univariable and multivariable logistic regression analyses were performed to investigate the association between low cerebroplacental ratio, low abdominal circumference growth velocity (in the lowest decile), and to identify and adjust for potential confounders. As a sensitivity analysis, we refitted the model excluding the data on pregnancies with small for gestational age neonates.

Results: The study included 7944 pregnancies. Low cerebroplacental ratio multiples of median was significantly associated with both low abdominal circumference growth

velocity (adjusted OR 2.10; 95%CI 1.71-2.57, p<0.001) and small for gestational age (adjusted OR 3.60; 95%CI 3.04-4.25, p<0.001). After the exclusion of pregnancies resulting in small for gestational age neonates, low cerebroplacental ratio multiples of median remained significantly associated with both low abdominal circumference growth velocity (adjusted OR 1.76; 95%CI 1.34-2.30, p<0.001) and birthweight centile (adjusted OR 0.99; 95%CI 0.998-0.995, p<0.001). The need for operative delivery for fetal compromise was significantly associated with low cerebroplacental ratio (adjusted OR 1.40; 95%CI 1.10-1.78, p=0.006), even after adjusting for both the umbilical artery pulsatility index multiples of median and middle cerebral artery pulsatility index multiples of median. The results were similar even after the exclusion of pregnancies resulting in small for gestational age neonates (adjusted OR 1.39; 95%CI 1.06-1.84, p=0.018). Low cerebroplacental ratio multiples of median remained significantly associated with the risk of operative delivery for presumed fetal compromise (p<0.001), even after adjusting for the known antenatal and intrapartum risk factors. These associations persisted even after exclusion of small for gestational age births. In appropriate for gestational age sized fetuses, abdominal circumference growth velocity was significantly lower in those with low cerebroplacental ratio multiples of median than in those with normal cerebroplacental ratio multiples of median (p<0.001).

Conclusion: Cerebroplacental ratio is a marker of impaired fetal growth velocity and adverse pregnancy outcome, even in fetuses whose size is considered appropriate using conventional biometry.

Keywords

Abdominal circumference; lowest decile; adverse pregnancy outcome; birthweight; cerebroplacental ratio; fetal growth restriction; growth velocity; impaired; second trimester; small for gestational age; third trimester.

INTRODUCTION

Fetal growth restriction is a major determinant of perinatal mortality and morbidity, in particular stillbirth, neonatal death, hypoxic ischemic encephalopathy and cerebral palsy.[1-4] Despite the fact that small for gestational age (SGA), defined as fetal/birth weight below the 10th centile for that gestation, is considered a proxy for fetal growth restriction, in reality the majority of SGA fetuses are not growth restricted and do not experience an adverse pregnancy outcome.[5] In order to assess fetal growth velocity, or growth restriction, an interval growth between two time points must be used to identify those fetuses deviating from their expected growth trajectory. Combined analysis of the fetal biometry in the third trimester and fetal growth velocity could identify the subset of SGA fetuses that are growth restricted and therefore at increased risk of neonatal morbidity.[6] A recent screening study reported that the combination of an estimated fetal weight below the 10th centile and abdominal circumference (AC) growth velocity in the lowest decile is associated with a relative risk (RR) of delivering an SGA infant with neonatal morbidity of 17.6;[6] this compares with an equivalent RR of 7.3 for fetuses with an estimated fetal weight below the 10th centile but normal AC growth velocity. A similar observation was reported in older studies, where the fetal growth velocity was slower in those that required operative delivery for fetal distress and in those requiring admission to the neonatal unit.[7]

Impaired fetal growth velocity, defined as arrest of growth or a shift in its rate measured longitudinally at least twice 3 weeks apart, can be used as a surrogate marker of growth restriction.[8] However, the assessment of serial fetal biometry is controversial for a number of reasons: firstly, absence of robust evidence that serial assessment would

improve the pregnancy outcome compared to cross sectional measurement; secondly, lack of agreed reference or standard to use; thirdly, lack of agreed gestational age at which fetal biometry should be measured; fourthly, lack of standardization which fetal biometry measure (e.g. AC) to use, and finally, the threshold to diagnose abnormal fetal growth is yet to be established.[9-17]

Interestingly, in fetuses with suspected growth restriction and abnormal umbilical artery Doppler, reduced fetal growth rate is strongly associated with an abnormal cerebroplacental ratio (CPR).[18] In contrast, if the CPR is normal, even in the setting of abnormal umbilical artery Doppler findings, fetuses grow at a rate similar to that of fetuses with normal umbilical artery findings.[18] CPR is emerging as a marker of failure to reach growth potential near term. We have reported that lower fetal CPR, regardless of the fetal size, was independently associated with the need for operative delivery for presumed fetal compromise and with neonatal unit admission at term.[19,20] If CPR is truly a marker of failure to reach growth potential, it would be expected to reflect impaired fetal growth velocity. The main aim of this study was to evaluate whether the CPR at term is a marker of reduced fetal growth rate. The secondary aim was to investigate the relationship between low CPR at term, reduced fetal growth velocity and adverse pregnancy outcome.

MATERIALS AND METHODS

This was a retrospective cohort study in a tertiary referral center over a 14-year period from 2000 to 2013. Cases were identified by searching the electronic database (ViewPoint 5.6.8.428, ViewPoint Bildverarbeitung GmbH, Weßling, Germany) in the

Fetal Medicine Unit, St George's Hospital. The inclusion criteria were singleton pregnancies in which the fetal biometry, including the AC, was recorded at 20-24 weeks' gestation and at or beyond 35 weeks' gestation, within two weeks of delivery. The primary outcome was the relationship between low CPR at term and reduced fetal growth velocity. The secondary outcome was the relationship between low CPR at term, reduced fetal growth velocity and adverse pregnancy outcome.

Growth velocity was quantified using the difference in AC, based on gestational age-specific Z score, comparing the scan at or beyond 35 weeks with the scan at 20-24 weeks. We generated deciles by use of the distribution in the study cohort. We defined as abnormal the lowest decile of AC growth velocity. The lowest decile of the difference of Z score between the AC in the third trimester and the AC in the second trimester was -1.4408. This is very similar to the value (-1.4808) reported by Sovio et al.[6] The umbilical artery and middle cerebral artery Dopplers were also recorded at the same visit at or beyond 35 weeks' gestation. In our unit, umbilical artery and middle cerebral artery Dopplers are routinely recorded at all ultrasound scans in the third trimester. The indications for the ultrasound assessment performed in the third trimester included suspected poor/excessive fetal growth, reduced fetal movements, history of SGA or large for gestational age baby, high mid-trimester uterine artery Doppler indices or gestational diabetes. These pregnancies were therefore at risk of fetal growth disorders. Pregnancies complicated by fetal abnormality, aneuploidy or genetic syndrome, and those with missing pregnancy outcome data, were excluded from the analysis.

Gestational age was calculated from the crown-rump length measurement at 11-13 weeks' gestation and only the last examination was included in the analysis.[21,22] Routine fetal biometry was performed according to a standard protocol and the estimated fetal weight calculated.[23] The umbilical artery and middle cerebral artery Doppler waveforms were recorded using color Doppler, and the pulsatility index (PI) calculated according to a standard protocol.[24,25] In brief, middle cerebral artery PI values were obtained in the space where the artery passes by the sphenoid wing close to the Circle of Willis, and umbilical artery PI values were obtained from one of the umbilical arteries in a free loop of umbilical cord. When three similar consecutive waveforms were obtained, the PI was measured. The measurements were obtained in the absence of fetal movement, and keeping the insonation angle with the examined vessels at less than 30^{o}. The CPR was calculated as the simple ratio between the middle cerebral artery PI and the umbilical artery PI.[26] The CPR values were not available to the clinicians as the values were calculated as part of the data analysis for this study. All Doppler indices were converted into multiples of median (MoM), correcting for gestational age using reference ranges ([27], umbilical and middle cerebral [28]), and birthweight values were converted into centiles.[29] When individuals had more than one ultrasound with Doppler values during the pregnancy, the last one before delivery was used in the analysis.

The study cohort was divided into four groups according to a combination of a birth weight cut-off of the 10^{th} centile (SGA) and a CPR cut-off of 0.6765 MoM (the 5^{th} centile of the group with birthweight above the 90^{th} centile [Large for Gestational Age] which is least likely to present with failure to reach growth potential). This was to assess the difference between the SGA model, which relies on fetal biometry, and the failure to

reach growth potential/placental insufficiency model, which relies on fetal hemodynamic assessment.[127] Therefore the groups are: 1) SGA, low CPR, 2) SGA, normal CPR, 3) Appropriate for Gestational Age (AGA), low CPR and 4) AGA, normal CPR.

Intrapartum data included whether the labor was induced or spontaneous, presence or absence of meconium stained liquor (grade 2 or 3), cardiotocograph abnormalities (classified according to National Institute for Health and Care Excellence guidelines),[30] ST analysis abnormalities,[31] use of oxytocin for slow progress of labor, intrapartum pyrexia, intrapartum hemorrhage, use of epidural analgesia for labor, and mode of delivery. Data on maternal baseline characteristics and pregnancy outcomes were collected from hospital obstetric and neonatal records. The two adverse pregnancy outcomes examined in this study were operative delivery for presumed fetal compromise and admission to the neonatal unit. The neonatal morbidity is the subject of another study. Operative delivery included both cesarean section and instrumental delivery. The diagnosis of fetal compromise was based on cardiotocograph abnormalities, ST analysis abnormalities, abnormal fetal scalp blood sample pH or a combination of these. Pregnancies which had an elective cesarean section were excluded from the analysis for this outcome. The study was exempted from review by Wandsworth Research Ethics Committee. Some of the pregnancies reported in this study were included in a previous study.[19]

Statistical Analysis

Data are presented as median and interquartile ranges (IQR) for continuous data and as n (%) for categorical variables. Categorical variables were compared by X^2-test or Fisher's exact test, while continuous data were compared using Mann-Whitney U-test. Comparison among the 4 study groups was performed using the Mann-Whitney test with post-hoc Bonferroni correction for multiple comparisons ($p<0.025$). Univariable and multivariable logistic regression analyses were performed to assess the relationship between low CPR MoM and AC growth velocity in the lowest decile. Logistic regression models were constructed for the two clinical outcomes included in this study: operative delivery for fetal compromise and admission to the neonatal unit. The variables included were maternal age, body mass index, parity, ethnicity, smoking, history of drug abuse, the AC growth velocity in the lowest decile, low CPR MoM, umbilical artery PI, middle cerebral artery PI, gestational age at delivery, SGA, induction of labor, use of epidural analgesia in labor, intrapartum pyrexia, intrapartum hemorrhage, presence of meconium grade 2 or 3, and the use of oxytocin for slow progress. As a sensitivity analysis, we refitted the model excluding the data on pregnancies with SGA neonates. We also investigated the antenatal risk factors separately from the intrapartum risk factors; although the latter potentially influence the two clinical outcomes investigated in this study, they are not available during the pregnancy and therefore are not considered during antenatal management. Both unadjusted and adjusted odds ratios (OR) were calculated. All p values were two-tailed; p values <0.05 were considered statistically significant.

The analysis was performed using the statistical software packages SPSS 18.0 (SPSS Inc., Chicago, IL, USA), Stata 11 (release 11.2. College Station, Texas, USA) and GraphPad Prism® 5.0 for Windows (InStat, GraphPad Software Inc., San Diego, California, USA).

RESULTS

We included 7944 pregnancies in the analysis. The maternal demographics, including age, body mass index, parity, ethnicity, smoking and drug use are shown in Table 1. The prevalence of SGA in this cohort was 14.5%. The overall operative delivery rate for presumed fetal compromise was 15.6%, while the neonatal unit admission rate was 3.7%. The ultrasound parameters and pregnancy outcome data are also shown in Table 1. The median (IQR) interval between the second and third trimester ultrasound scans was 18.4 (16.6-19.6) weeks. The median (IQR) gestational age at delivery was 41.1 (39.4-41.9) weeks and the interval between the third trimester ultrasound scan and delivery was 0.6 (0.3-1.0) weeks.

There was a significant positive association between the AC growth velocity and both the birthweight centile (R^2=0.09, p<0.001) and the CPR MoM (R^2=0.02, p<0.001). Reduced AC growth velocity (in the lowest decile) was significantly associated with umbilical artery PI MoM (OR 3.54; 95%CI 2.49-5.03, p<0.001), middle cerebral artery PI MoM (OR 0.43, 95%CI 0.33-0.57, p<0.001), CPR MoM (OR 0.28, 95%CI 0.21-0.38, p<0.001), birthweight centile (OR 0.98, 95%CI 0.978-0.983, p<0.001) and SGA (OR 2.65, 95%CI 2.24-3.14, p<0.001). The results of the multivariable logistic regression

analysis demonstrated that low CPR MoM was significantly associated with both reduced AC growth velocity (adjusted OR 2.10; 95%CI 1.71-2.57, p<0.001) and SGA (adjusted OR 3.60; 95%CI 3.04-4.25, p<0.001). After the exclusion of pregnancies resulting in SGA neonates, reduced AC growth velocity was significantly associated with the umbilical artery PI MoM (OR 2.35; 95%CI 1.49-3.69, p<0.001), middle cerebral artery PI MoM (OR 0.69, 95%CI 0.51-0.93, p=0.017), CPR MoM (OR 0.47, 95%CI 0.33-0.65, p<0.001) and birthweight centile (OR 0.98, 95%CI 0.979-0.986, p<0.001). Low CPR MoM remained significantly associated with both reduced AC growth velocity (adjusted OR 1.76; 95%CI 1.34-2.30, p<0.001) and birthweight centile (adjusted OR 0.99; 95%CI 0.998-0.995, p<0.001).

The prevalence of reduced AC growth velocity (in the lowest decile) in the 4 study groups according to the fetal size (SGA or not) and the CPR MoM is shown in Figure 1. Reduced AC growth velocity was most common (31%) in group 1 (SGA, low CPR), when compared to the remaining 3 groups (p<0.001 for all). Reduced AC growth velocity was more common in group 3 (AGA, low CPR) than in group 4 (AGA, normal CPR) (14.3% vs 7.9%, p<0.001). A comparison of the AC growth velocity among the 4 study groups according to the fetal size (SGA or not) and the CPR MoM is shown in Figure 2. The AC growth velocity was significantly lower in group 1 (SGA, low CPR) when compared to the remaining 3 groups (p<0.001 for all). The AC growth velocity was significantly lower in group 3 (AGA, low CPR) than in group 4 (AGA, normal CPR) (median -0.15 and IQR -0.94, 0.66 vs median 0.12 and IQR -0.63, 0.84, p<0.001).

The need for operative delivery for presumed fetal compromise was significantly associated with low CPR (adjusted OR 1.40; 95%CI 1.10-1.78, p=0.006), even after adjusting for both the umbilical artery PI MoM and middle cerebral artery PI MoM. The results were similar even after the exclusion of pregnancies resulting in SGA neonates; in this subset, after adjusting for both the umbilical artery PI MoM and middle cerebral artery PI MoM, the need for operative delivery for presumed fetal compromise remained significantly associated with low CPR (adjusted OR 1.39; 95%CI 1.06-1.84, p=0.018). The results of the univariable logistic regression analysis for operative delivery for presumed fetal compromise are shown in Table 2. Low CPR MoM (p<0.001), umbilical artery PI (p=0.016), but not the middle cerebral artery PI (p=0.195), reduced AC growth velocity (p=0.087) or SGA (p=0.395), were significantly associated with the risk of operative delivery for presumed fetal compromise. The results of the multivariable logistic regression analysis for operative delivery for presumed fetal compromise are shown in Table 3. Low CPR MoM remained significantly associated with the risk of operative delivery for presumed fetal compromise (p=0.023), even after adjusting for the known risk factors, fetal size and reduced AC growth velocity. These associations persisted even after exclusion of SGA cases from the cohort (Tables 2 and 3). Low CPR MoM (p<0.001), umbilical artery PI (p=0.015), reduced AC growth velocity (p=0.022), but not the middle cerebral artery PI (p=0.107), were significantly associated with the risk of operative delivery for presumed fetal compromise. Low CPR MoM remained significantly associated with the risk of operative delivery for presumed fetal compromise (p=0.026), even after adjusting for the known risk factors and reduced AC growth velocity.

When the logistic regression analysis was limited to the antenatal risk factors only, low CPR MoM (adjusted OR 1.26; 95%CI 1.02-1.57, p=0.033), SGA (adjusted OR 1.44; 95%CI 1.17-1.77, p=0.001), maternal age (adjusted OR 1.05; 95%CI 1.03-1.06, p<0.001), gestational age at delivery (adjusted OR 1.32; 95%CI 1.25-1.40, p<0.001), multiparity (adjusted OR 0.23; 95%CI 0.19-0.27, p<0.001), maternal body mass index (adjusted OR 1.02; 95%CI 1.00-1.03, p=0.028) and ethnicity (adjusted OR 1.10; 95%CI 1.03-1.17, p=0.005), but not reduced AC growth velocity (p=0.289), smoking (p=0.739) and drug abuse (p=0.551), were significantly associated with the risk of operative delivery for presumed fetal compromise.

The results of the univariable and multivariable logistic regression analyses for neonatal unit admission are shown in Table 4. The univariable regression analysis demonstrated that both low CPR MoM (p=0.001), umbilical artery PI (p=0.001), middle cerebral artery PI (p=0.025) and SGA (p=0.024), but not reduced AC growth velocity (p=0.752), were significantly associated with the risk of neonatal unit admission. Using multivariable logistic regression, both low CPR MoM and SGA were no longer significantly associated with the risk of neonatal unit admission (p>0.05). The only antenatal variable which remained significantly associated with the risk of neonatal unit admission was the umbilical artery PI (adjusted OR 2.33, 95% CI 1.05-5.20, p=0.039).

When the logistic regression analysis was limited to the antenatal risk factors only, low CPR MoM (adjusted OR 1.61; 95%CI 1.12-2.32, p=0.010), multiparity (adjusted OR 0.63; 95%CI 0.47-0.83, p=0.001) and maternal body mass index (adjusted OR 1.03;

95%CI 1.01-1.05, p=0.010) were significantly associated with the risk of neonatal unit admission. However, reduced AC growth velocity (p=0.632), SGA (p=0.374), gestational age at delivery (p=0.713), maternal age (p=0.528), ethnicity (p=0.411), smoking (p=0.517) and drug abuse (p=0.622) were not significantly associated with the risk of neonatal unit admission.

DISCUSSION

Main Findings

The results of this study demonstrate that low CPR – a functional marker of fetal hypoxemia and cerebral redistribution - is significantly associated with impaired fetal AC growth velocity, a biometric marker of failure to reach growth potential, even in fetuses which are considered to be of appropriate size (≥ the 10th percentile). The AC growth velocity in the lowest decile is significantly associated with being SGA, low CPR MoM and operative delivery for presumed fetal compromise, but not the risk of neonatal unit admission. Low CPR MoM was significantly and independently associated with the risk of operative delivery for presumed fetal compromise, while SGA was not. Both low CPR and SGA were significantly associated with the risk of admission to the neonatal unit, when tested in univariable logistic regression and multivariable logistic regression models adjusting for antenatal risk factors, but not when adjusting for both antenatal and intrapartum risk factors.

Interpretation of the findings and comparison with existing literature

The findings of this study are consistent with existing literature and our previous findings.[6,18,19,31] Recent studies have demonstrated that low CPR is significantly associated with adverse pregnancy outcomes, including operative delivery for presumed fetal compromise, neonatal unit admission, stillbirth and neonatal morbidity.[18,19,32-34]

The role of CPR as a marker of failure to reach growth potential has recently gained interest among researchers and clinicians.[19,20,35,36] This study therefore represents a useful addition to the literature investigating the role of CPR as a measure of cerebral redistribution or brain sparing. Most studies have focused on small fetuses, reporting a promising role for CPR in identifying SGA fetuses at risk of adverse outcomes. In a recent meta-analysis, low CPR was associated with an increased risk of cesarean section for fetal distress (OR 4.49; 95% CI 1.63-12.42), low APGAR score (OR 4.01; 95% CI 2.65-6.08), neonatal unit admission (OR 9.65; 95% CI 3.02-30.85) and neonatal complications (OR 11.00; 95% CI 3.64-15.37).[35] The findings of the PORTO study have reiterated the significant role of the CPR in identifying fetuses at risk.[34] Small fetuses with abnormal CPR had an 11-fold increased risk of adverse pregnancy outcome, in particular neonatal morbidity, when compared to those with normal CPR.[34]

We recently reported that the CPR is a marker of failure to reach growth potential and adverse pregnancy outcomes, even in fetuses that are not considered at risk using current standards.[19,20] The role of the CPR in the assessment of fetal wellbeing in both SGA and AGA fetuses was appraised in a recent review.[36] The fact that CPR is a marker of impaired fetal growth velocity, even in AGA fetuses, and that it is associated

with adverse pregnancy outcome questions the current guidelines that have ignored the potential value of assessment of the fetal Doppler in AGA fetuses, simply because the estimated fetal weight is above the 10th centile.[37,38] Identification of the at-risk fetus at term is challenging, while its management is usually easy (delivery). Our finding of a potential additive value of the CPR, above and beyond its components (umbilical artery and middle cerebral artery Doppler), is consistent with the data from prospective studies.[32,39] Despite the fact that this study focused on the role of abnormal CPR near term, previous studies have demonstrated its potential value in early-onset FGR, in particular its association with a higher risk of perinatal death, higher rate of Cesarean delivery for fetal distress in labour, higher rate of Apgar scores less than 7 at 5 minutes, an increased rate of neonatal acidosis, and an increased rate of neonatal unit admission.[40-45]The role of impaired fetal growth in identifying fetuses at risk of neonatal morbidity has been demonstrated in a screening study involving 4512 nulliparous women recruited over 4 years in Cambridge, UK.[5] An estimated fetal weight below the 10th centile was associated with the risk of neonatal morbidity only if the fetal AC growth velocity was in the lowest decile.[6] These findings reinforce the importance of including assessment tools, other than simply estimated fetal weight less than the 10th centile, to identify those fetuses at risk of adverse outcome. Of note, this study did not report data on the fetal CPR or middle cerebral artery Doppler.[6] In fact, the association between fetal growth and adverse pregnancy outcome was previously reported in the older literature, where the fetal growth rate was significantly lower in pregnancies with operative delivery for presumed fetal distress (20.9 g/day) or neonatal unit admission (20.3 g/d) compared to those with uncomplicated outcome (21.9 g/day).[7] In contrast, our

study found no significant association between reduced AC growth velocity and neonatal unit admission. This difference could be explained by the different tool used to assess fetal growth velocity. In the study by de Jong et al,[7] the fetal weight gain in the third trimester was modeled using a minimum of five time points to derive a fetal weight curve for each pregnancy: a fixed second trimester point, representing Hadlock's mean value for fetal weight at 18 weeks, three or more third-trimester fetal weight estimates and the birthweight.[7] In our study we quantified the growth velocity using the difference in AC, based on gestational age-specific Z score, comparing the scan at or beyond 35 weeks with the scan at 20-24 weeks. We defined as abnormal the lowest decile of AC growth velocity. In the study by Regan et al, the growth rate was estimated by subtracting the index estimated fetal weight from the subsequent estimated fetal weight and dividing the value by the number of days between the sonographic examinations, in order to obtain an estimate of the growth rate in grams per day.[18] However, this assumes a uniform growth rate throughout that interval, which might not be true.

Clinical and research implications

There is no consensus regarding what constitutes normal or abnormal fetal growth, but the AC interval growth is one of the commonest parameters used in the clinical setting. It is important, though, to take into account the fact that interval growth assessment might be susceptible to inaccuracies in biometric measurements as a result of intra- and inter-observer variability.[46] This is most likely when the time interval between examinations is short. In our study, the median interval between the second and third trimester scans was 18 weeks. Recently, a consensus definition for placental fetal growth restriction was reached using a Delphi procedure: late fetal growth restriction

(beyond 32 weeks) was defined using four parameters: estimated fetal weight <10th percentile, AC <10th percentile, crossing centiles on growth charts of more than two quartiles, and CPR <5th percentile.[47] Even when corrected for fetal growth velocity, low CPR remains significantly associated with the risk of operative delivery for presumed fetal compromise. This suggests that CPR is a potentially useful tool for the identification of at risk fetuses.

Despite the promising potential role of fetal growth and Dopplers in improving the identification of fetuses at risk of adverse outcome, the extent to which these parameters could be used to predict perinatal morbidity and guide the mode of delivery merits further investigation. These studies should ascertain the gestational age at assessment, CPR cut-off at which to diagnose fetal compromise, long-term (not just short-term) morbidity, and which interventions could potentially improve the perinatal outcome. Furthermore, as reported by Sovio et al, the improvement in the detection of SGA neonates using assessment of the fetal growth was associated with an increase in the false positive rate (two false positive diagnoses for every additional SGA neonate detected), and therefore, additional parameters such as the CPR or biochemical markers might be required to optimize the predictive accuracy for the identification of the fetus at risk.[6,48]

Study strengths and limitations

The strengths of our study include the large number of pregnancies, the short interval between third trimester ultrasound and delivery, ascertainment of the outcome data and

adjusting for possible confounding variables including maternal demographics and intrapartum risk factors. Furthermore, neither the difference in AC Z scores nor the CPR values were calculated until the analysis for this study. Therefore, the healthcare professionals providing the intrapartum care were effectively blinded to these values. The retrospective design is a limitation and the data could be biased by selective assessment of a population referred for ultrasound scan in the third trimester, which is not routine practice in the UK. This could explain the higher than expected proportion of SGA in the study cohort. This is mitigated by the relatively large dataset of prospectively collected data and because the majority of women delivered at term and had normal birthweight babies. However, we see this as a strength whereby, despite the bias towards lower birthweight and higher prevalence of SGA, reduced AC growth velocity and low CPR were independently associated with the risk of operative delivery for presumed fetal compromise, and low CPR was also associated with the risk of neonatal unit admission. Another potential limitation is the fact that the results of the ultrasound and Doppler assessment were not blinded, giving rise to the possibility that this knowledge could have influenced subsequent clinical intervention and a 'treatment effect'. However, during the study period, intervention in the form of induction of labor was undertaken only for estimated fetal weight less than the 5th centile or umbilical artery PI above the 95th centile, as per local protocol. Hence, these interventions should be relatively un-influenced by reduced AC growth velocity or low CPR. The study cohort was scanned by a large number of different operators, raising the possibility of inter-observer variability in the measurements. The threshold for the diagnosis of fetal compromise is also likely to have been influenced by changing personnel and attitudes

towards intrapartum management over the 14 year period. Finally, as this was a single center study, there is a potential for selection bias, which might compromise generalizability.

Conclusion

The findings of this study demonstrate that CPR is a marker of impaired fetal AC growth velocity and adverse pregnancy outcome, even in fetuses whose size is considered AGA using conventional biometry.

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Table 1. Maternal demographics, ultrasound parameters and pregnancy outcomes of the study population.

Variable	**Values**
Maternal demographics	
Maternal age in years, median (IQR)	31.0 (27.0-35.0)
Body mass index in kg/m^2, median (IQR)	24.0 (21.6-27.5)
Nulliparous, n (%)	4419 (55.6)
Maternal ethnicity	
Caucasian, n (%)	4974 (62.6)
Afro-Caribbean, n (%)	1257 (15.8)
South Asian, n (%)	1301 (16.4)
East Asian, n (%)	88 (1.1)
Mixed, n (%)	262 (3.3)
Other, n (%)	62 (0.8)
Smoking, n (%)	478 (6.0)
Drug abuse, n (%)	44 (0.6)

Ultrasound parameters	
Gestational age at the second trimester ultrasound in weeks, median (IQR)	21.9 (21.4-22.3)
Abdominal circumference in mm at 20-24 weeks' gestation, median (IQR)	166.7 (160.2-174.4)
Abdominal circumference Z score at 20-24 weeks' gestation, median (IQR)	0.02 (-0.75-0.72)
Gestational age at the third trimester ultrasound in weeks, median (IQR)	40.4 (38.4-41.4)
Abdominal circumference in mm in third trimester, median (IQR)	344.0 (326.6-361.3)
Abdominal circumference Z score in third trimester, median (IQR)	-0.02 (-0.69-0.67)
Estimated fetal weight at the third trimester scan in grams, median (IQR)	3492 (3047-3871)
Umbilical artery pulsatility index (PI), median (IQR)	0.82 (0.71-0.93)
Umbilical artery PI multiple of median (MoM), median (IQR)	1.00 (0.88-1.13)
Middle cerebral artery PI, median (IQR)	1.31 (1.12-1.54)
Middle cerebral artery PI MoM, median (IQR)	1.30 (1.13-1.50)
Cerebroplacental ratio, median (IQR)	1.62 (1.35-1.95)
Cerebroplacental ratio MoM, median (IQR)	0.96 (0.80-1.15)

Interval between the second and third trimester ultrasound scans in weeks, median (IQR)	18.4 (16.6-19.6)
Abdominal circumference growth velocity, median (IQR)	0.01 (-0.74-0.74)
Abdominal circumference growth velocity in the lowest decile, n (%)	795 (10)
Intrapartum factors	
Induction of labor, n (%)	2798 (35.2)
Epidural use, n (%)	2966 (37.3)
Intrapartum pyrexia, n (%)	172 (2.2)
Intrapartum hemorrhage, n (%)	21 (0.3)
Oxytocin used for slow progress, n (%)	2022 (25.5)
Meconium grade 2/3, n (%)	183 (2.3)
Pregnancy outcome	
Birthweight in grams, median (IQR)	3435 (3050-3800)
Birthweight centile, median (IQR)	45.33 (19.28-74.43)
Small for gestational age, n (%)	1151 (14.5)

Stillbirth, n (%)	15 (0.2)
Gestational age at delivery in weeks, median (IQR)	41.1 (39.4-41.9)
Interval between the ultrasound and delivery in weeks, median (IQR)	0.6 (0.3-1.0)

Table 2. Results of the univariable logistic regression analysis of variables associated with the need for operative delivery for presumed fetal compromise.

Risk factors	Total study population			Study population excluding pregnancies resulting in a small for gestational age neonate		
	Unadjusted OR	95% CI	P-value	Unadjusted OR	95% CI	P-value
Maternal age (years)	1.02	1.01-1.03	<0.001	1.02	1.01-1.03	<0.001
Body mass index (kg/m^2)	1.00	0.98-1.01	0.452	0.99	0.98-1.01	0.381
Multiparous	0.25	0.21-0.29	<0.001	0.24	0.21-0.29	<0.001
Ethnicity	0.93	0.88-0.99	0.020	0.92	0.86-0.98	0.012
Smoking	0.65	0.49-0.87	0.004	0.72	0.52-1.00	0.047
Drug abuse	0.62	0.24-1.57	0.313	0.47	0.14-1.54	0.215
Abdominal circumference growth velocity in the lowest decile	1.19	0.98-1.44	0.087	1.30	1.04-1.62	0.022
Low cerebroplacental ratio MoM	1.45	1.20-1.76	<0.001	1.54	1.22-1.93	<0.001
Umbilical artery PI MoM	1.46	1.08-2.00	0.016	1.56	1.09-2.24	0.015
Middle cerebral artery PI MoM	0.87	0.70-1.07	0.195	0.83	0.66-1.04	0.107
Gestational age at delivery (weeks)	1.36	1.29-1.43	<0.001	1.43	1.34-1.51	<0.001
Small for gestational age	1.08	0.91-1.28	0.395	-	-	-
Induction of labor	1.84	1.63-2.08	<0.001	1.84	1.61-2.12	<0.001
Epidural use	5.93	5.15-6.83	<0.001	6.23	5.35-7.32	<0.001
Intrapartum pyrexia	5.64	4.15-7.66	<0.001	5.60	4.08-7.69	<0.001
Intrapartum hemorrhage	4.21	1.79-9.95	0.001	3.29	1.25-8.66	0.016
Oxytocin used for slow progress	3.15	2.78-3.57	<0.001	3.30	2.88-3.78	<0.001
Meconium grade 2/3	2.55	1.86-3.49	<0.001	2.56	1.82-3.60	<0.001

MoM = multiples of median; pulsatility index = PI

Table 3. Results of the multivariable logistic regression analysis of variables associated with the need for operative delivery for presumed fetal compromise.

Risk factors	Total study population			Study population excluding pregnancies resulting in a small for gestational age neonate		
	Unadjusted OR	95% CI	P-value	Unadjusted OR	95% CI	P-value
Maternal age (years)	1.04	1.02-1.05	<0.001	1.04	1.02-1.05	<0.001
Body mass index (kg/m^2)	1.01	0.99-1.02	0.440	1.01	0.99-1.02	0.455
Multiparous	0.38	0.31-0.46	<0.001	0.38	0.31-0.47	<0.001
Ethnicity	1.10	1.03-1.18	0.006	1.10	1.02-1.19	0.010
Smoking	0.90	0.64-1.25	0.525	0.98	0.67-1.42	0.905
Drug abuse	0.83	0.31-2.25	0.721	0.53	0.15-1.81	0.309
Abdominal circumference growth velocity in the lowest decile	1.21	0.96-1.53	0.101	1.38	1.06-1.79	0.016
Low cerebroplacental ratio MoM	1.30	1.04-1.64	0.023	1.36	1.04-1.77	0.026
Gestational age at delivery (weeks)	1.20	1.13-1.28	<0.001	1.20	1.12-1.28	<0.001
Small for gestational age	1.58	1.27-1.96	<0.001	-	-	-
Induction of labor	1.22	1.05-1.42	0.008	1.23	1.05-1.45	0.012
Epidural use	4.05	3.39-4.84	<0.001	4.08	3.35-4.98	<0.001
Intrapartum pyrexia	2.62	1.85-3.70	<0.001	2.61	1.82-3.75	<0.001
Intrapartum hemorrhage	7.33	2.52-21.32	<0.001	5.91	1.72-20.25	0.005
Oxytocin used for slow progress	0.98	0.83-1.15	0.767	0.98	0.82-1.18	0.844
Meconium grade 2/3	3.17	2.16-4.66	<0.001	2.84	1.87-4.31	<0.001

MoM = multiples of median. Each variable included in the list of risk factors has been included in the multivariable logistic regression analysis.

Table 4. Results of the univariable and multivariable logistic regression analysis of variables associated with admission to the neonatal unit.

Risk factor	Unadjusted OR	95% CI	P-value	Adjusted OR	95% CI	P-value
Maternal age (years)	0.98	0.96-1.00	0.052	0.98	0.96-1.01	0.201
Body mass index (kg/m^2)	1.02	1.00-1.05	0.048	1.03	1.00-1.05	0.051
Multiparous	0.64	0.50-0.81	<0.001	0.83	0.59-1.17	0.279
Ethnicity	1.04	0.94-1.15	0.463	1.06	0.93-1.20	0.370
Smoking	1.28	0.82-2.00	0.278	1.19	0.64-1.96	0.694
Drug abuse	0.60	0.08-4.39	0.617	0.67	0.09-5.00	0.697
Abdominal circumference growth velocity in the lowest decile	1.06	0.73-1.55	0.752	0.67	0.40-1.15	0.147
Low cerebroplacental ratio MoM	1.71	1.23-2.38	0.001	0.85	0.49-1.47	0.554
Umbilical artery PI MoM	2.46	1.42-4.29	0.001	2.33	1.05-5.20	0.039
Middle cerebral artery PI MoM	0.62	0.40-0.94	0.025	0.66	0.37-1.18	0.159
Gestational age at delivery (weeks)	0.96	0.89-1.03	0.233	0.99	0.89-1.10	0.814
Small for gestational age	1.41	1.05-1.90	0.024	1.23	0.82-1.85	0.312
Induction of labor	1.10	0.86-1.40	0.467	1.07	0.80-1.43	0.656
Epidural use	1.99	1.54-2.57	<0.001	1.56	1.11-2.20	0.011
Intrapartum pyrexia	6.14	4.03-9.36	<0.001	4.45	2.73-7.26	<0.001
Intrapartum hemorrhage	4.56	1.34-15.60	0.015	4.47	1.00-19.93	0.050
Oxytocin used for slow progress	1.54	1.20-1.96	0.001	1.04	0.74-1.47	0.804
Meconium grade 2/3	5.03	3.31-7.64	<0.001	4.63	2.79-7.68	<0.001

MoM = multiples of median; pulsatility index = PI

FIGURE LEGENDS

Figure 1. The proportion of pregnancies with abdominal circumference growth velocity in the lowest decile in the four study groups according to a combination of a birthweight cut-off of the 10th centile and a cerebroplacental ratio (CPR) cut-off of 0.6568 MoM. (SGA = small for gestational age; AGA = appropriate for gestational age).

Figure 2. Box and whisker plots of the abdominal circumference (AC) growth velocity in the four study groups according to a combination of a birthweight cut-off of the 10th centile and a cerebroplacental ratio (CPR) cut-off of 0.6568 MoM. (SGA = small for gestational age; AGA = appropriate for gestational age). The horizontal line in the box represents the median, the box represents the interquartile range and the whiskers indicate the minimum and maximum values.

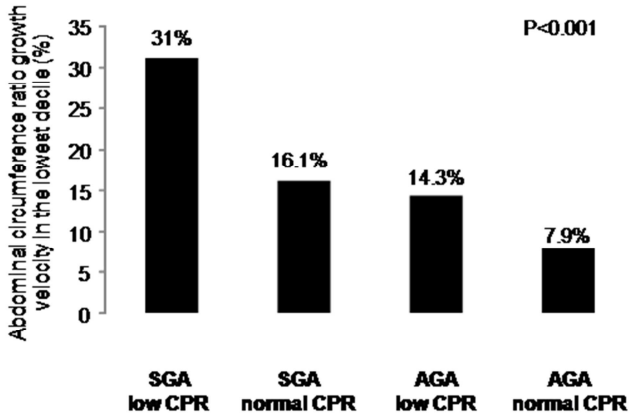

Figure 1. SGA: Small for gestational age; CPR: Cerebroplacental ratio; AGA: Appropriate for gestational age

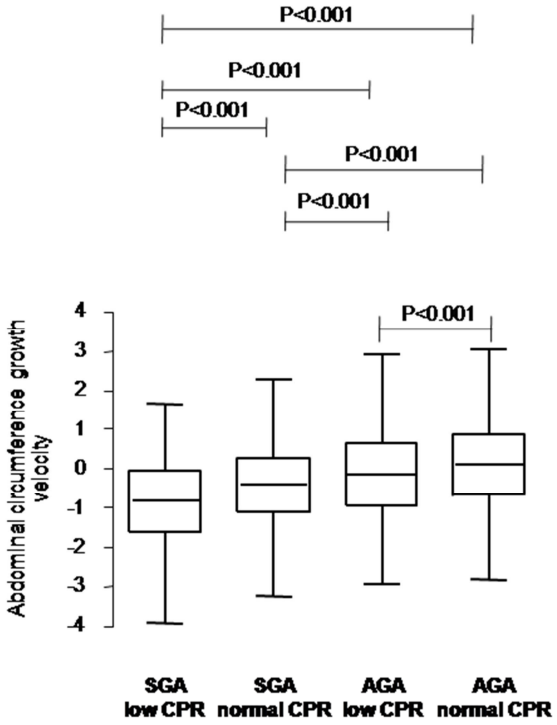

Figure 2. SGA: Small for gestational age; CPR: Cerebroplacental ratio; AGA: Appropriate for gestational age