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Liam Dunn, Helen Sherrell, Sailesh Kumar

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Systematic review of the utility of the fetal cerebroplacental ratio measured at term for the prediction of adverse perinatal outcome.

Liam Dunn[1], Helen Sherrell[1], Sailesh Kumar[1,2,3]

1 – Mater Research Institute – University of Queensland, Brisbane

2 – Mater Health Service, Brisbane

3 – School of Medicine, University of Queensland, Brisbane

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Corresponding author:

Professor Sailesh Kumar

Mater Research Institute – University of Queensland

Level 3, Aubigny Place, Raymond Terrace

South Brisbane, Queensland, Australia, 4101

Email: sailesh.kumar@mater.uq.edu.au

Phone: +617 3163 8844

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Abstract

Aim

This systematic review evaluates the utility of the fetal cerebroplacental ratio (CPR) when assessed at term (from 37+0 weeks gestation) as a predictor of adverse obstetric and perinatal outcomes.

Data sources and search strategy

An electronic search of Pubmed and Embase using variations of 'cerebroplacental ratio' and 'cerebroumbilical ratio' was conducted by two independent reviewers. Full text studies written in English that reported on low CPR and its correlation with relevant obstetric and perinatal outcomes were included.

Results

Twenty one studies satisfied inclusion with 13 prospective and eight retrospective analyses. Fetal CPR was predictive of caesarean section for intrapartum fetal compromise, small for gestational age and fetal growth restriction and neonatal intensive care unit admission. Low CPR was also significantly associated with abnormal fetal heart rate pattern, meconium stained liquor, low Apgar score, acidosis at birth and composite adverse perinatal outcome scores. The CPR when taken at term had comparable if not better predictive value than that when taken at pre-term. Most studies included small for gestational age fetuses and postdate pregnancies. Subtle variation existed in the threshold for low CPR.

Conclusion

The CPR at term has a strong association with adverse obstetric and perinatal outcomes. This review suggests the predictive utility of CPR at term is promising however there is insufficient evidence to demonstrate its value as a stand-alone test. Inclusion of CPR as a component of clinical care may

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help better identify fetuses at risk of adverse outcome, and this should be tested with randomised control trials.

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INTRODUCTION

For the majority of pregnancies, the placenta provides adequate metabolic and oxygen supply to the fetus through to birth without any detrimental effects on growth or wellbeing. However, when placental function is suboptimal impaired fetal growth can supervene. In late pregnancy, this is a major risk factor for stillbirth and other adverse obstetric and perinatal outcomes [1-3]. For the neonate, there is also a much greater likelihood of longer term neurological and neurodevelopmental morbidity[4-6], as well as cardiovascular disease and other metabolic conditions later in life[7-10]. There is also evidence that even in a cohort of fetuses that are appropriately grown (AGA) with estimated weights above the 10th centile, some demonstrate circulatory changes consistent to that seen in a fetus with obvious growth restriction. These AGA fetuses are also at increased risk of adverse obstetric and perinatal outcomes[11-14].

The fetal cerebroplacental ratio (CPR) is the ratio of the fetal middle cerebral artery (MCA) pulsatility index (PI) to umbilical artery (UA) PI. It is believed to be a proxy for suboptimal fetal growth[15, 16] given it quantifies both suboptimal placental function and subsequent fetal circulatory adaptations[17]. It is believed that the CPR better predicts adverse perinatal outcomes than its individual components[18-23] and better than conventional anthropometric models[13].

OBJECTIVE

The aim of this systematic review was to evaluate the utility of CPR when assessed at term (≥37+0 weeks) as a predictor for adverse perinatal outcomes.

DATA SOURCES AND METHODOLOGY

An online database search of PubMed and Embase for all relevant publications from the past 30 years was undertaken by the authors and institutional research librarian in September 2016. Search terms were variations of ‘cerebroumbilical ratio’ and ‘cerebroplacental ratio’.

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The population of interest was pregnant women who had a CPR evaluated from 37+0 – 42+0 weeks gestational age compared to those with normal CPR or a control group as described by the authors. Studies were eligible for inclusion if they reported relevant obstetric and perinatal outcomes and their association with the CPR (regardless of blinding).

An initial title and abstract review was conducted on all publications from the search to exclude duplicated and ineligible manuscripts. A revised short-list of full-text manuscripts written in English that were available electronically were then reviewed in detail. A manual search of the reference lists of short-listed articles was also carried out to identify relevant articles not captured in the initial electronic searches. These reviews were conducted independently by authors LD and HS.

Systematic and expert reviews, case series and reports, abstracts, book chapters, opinion pieces and guidelines were excluded. Publications were also excluded if they investigated the influence of an intervention on the CPR. Relevant standards of reporting for each publication type[24] were referenced, as was the Preferred Reporting for Systematic Reviews and Meta-Analyses statement[25].

RESULTS

The flow of identification of relevant studies is shown in Figure 1. Four hundred and seventeen publications were initially retrieved using the abovementioned methodology and 31 full text articles were then reviewed. The final number of eligible manuscripts was 21 and includes 13 prospective observational[11, 14, 16, 23, 26-34] and eight retrospective[12, 13, 15, 35-40] studies.

Data on maternal and fetal characteristics, number of participants that had a CPR evaluated, individual CPR components and abnormal CPR cut off threshold, gestational age at which the CPR was obtained and CPR to delivery interval are presented in Table 1. Obstetric (mode of, and indication for birth, meconium stained liquor (MSL), fetal heart rate (FHR) abnormalities) and perinatal (birthweight, Apgar scores, acidosis at birth, neonatal intensive care unit (NICU) admission)

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outcomes are presented in Table 2. Sensitivities, specificities, negative predictive values (NPV), positive predictive values (PPV) and other predictive ratios for various outcomes are presented in Table 3. Not all outcomes relevant to this review were reported by each publication.

There was lack of uniformity in the Doppler indices used to construct the CPR. Most studies used the MCA-PI/UA-PI ratio[11, 13-16, 26-31, 35, 37], although S/D[23] and RI[36, 38, 39] ratios were also reported, mainly in earlier studies. The threshold that described an abnormal CPR varied between studies including <5th centile[14, 28, 35, 37], <10th centile[11, 14] and values <0.90[37], ≤1[14], <1.05[23, 27], <1.09[30] <1.1[29, 36, 38, 39], <1.3[29] and <0.6765MoM[13, 15, 16, 35]. Not all included studies however reported an abnormal CPR value and there was wide variation in the characteristics of the control group across studies. There was also variation in the terminology used to describe fetal/neonatal size. Some studies defined small for gestational age (SGA) as birthweight (BW) <10th centile[12, 13, 15, 26, 35, 39] whilst others used estimated fetal weight (EFW) <10th centile[16, 28, 30, 32, 33]. Fetal growth restriction (FGR) was variously defined as BW <3rd centile[26] with abnormal fetal Dopplers[15], EFW <3rd centile with abnormal UA-PI[16] and as BW <10th centile with abnormal MCA-PI[40]. Appropriate for gestational age (AGA) was defined as BW[13, 35] or EFW[16] >10th – 90th centiles. Other studies did not clearly define these terms[11, 14, 23, 27, 29, 31, 36, 37].

The CPR-to-delivery interval varied from ≤24 hours[28, 36, 38] to ≤14 days[13-15, 35] and most studies reported clinicians being blinded to CPR data[11, 14, 16, 23, 26, 28-31, 35, 39].

The majority of studies had broadly similar exclusion criteria (e.g. significant maternal conditions, fetal anomalies, intrauterine fetal death and stillbirth) in an attempt to create relatively normal or low risk cohorts. Furthermore, assessment criteria of IFC (e.g. FHR pattern, fetal blood sampling), and neonatal outcomes (e.g. Apgar <7 at one and five minutes, acidosis at birth [UA pH<7.2, base excess (BE) >12mEq/L], NICU admission) was very similar across studies.

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Obstetric Outcomes

Mode of Birth

The association of low CPR and mode of birth was reported in nine studies[11, 12, 14, 16, 27, 28, 33, 36, 40]. An abnormal CPR, as defined in each study, was associated with an overall increased for birth by emergency caesarean (CS)[27, 28, 33, 36, 40]. In particular, the CPR was shown to be an independent predictor of CS for intrapartum fetal compromise (CS-IFC), with an area under the receiver operator characteristic curve (AUROC) of 0.69 [11]. An abnormal CPR had a six- (OR 6.1, 95% CI 3.03-12.75)[11] to 10-fold (OR 10.3 95%CI 3.22-52.8)[28] increased odds of CS-IFC. Khalil et al. 2015[12], also described the association of low CPR with both instrumental delivery for IFC as well as CS-IFC, with the CPR being an independent predictor any operative delivery for IFC, irrespective of fetal size. Conversely, a normal CPR was more likely to be associated with SVD[14, 16, 27]. Birth by SVD was up to three times more likely in the setting of a normal CPR (OR 2.93 95%CI 1.41-6.13)[11].

Abnormal Fetal Heart Rate Pattern

Four studies[11, 16, 36, 39] reported that a low CPR was associated with FHR abnormalities (40.8% v 18.5%[16], 62.3% v 19.0%[36] and 86% v 28.9%[11]; all $p<0.05$) and that the likelihood of the having an abnormal FHR was increased more than two fold with a low CPR[16, 36]. One study also showed that at a CPR threshold of 1.1 had higher sensitivity and NPV for abnormal FHR patterns than either the MCA or UA Doppler indices individually[36].

Meconium Stained Liquor

Meconium stained liquor (MSL) was reported in four studies[11, 16, 30, 36]. Lam et al. 2005[30] did not demonstrate any correlation between a low CPR and MSL, whereas three other studies[11, 16, 36] reported a higher prevalence of MSL amongst the low CPR cohort. In these studies, the rates of MSL ranged from 22.4%[16] to 46.4%[36] and the likelihood of MSL in the setting of a low CPR was nearly two-fold greater (RR1.96, 95% CI 1.12-3.43, p=0.03)[16].

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Perinatal Outcomes

Birthweight

The association of birthweight, SGA and FGR with CPR was reported by 11 studies[11, 13, 15, 16, 26, 30, 32, 33, 35, 36, 40]. Lower median and mean birthweights was associated with low a CPR in six studies[13, 16, 33, 35, 36, 40] though one study reported no difference in mean birthweights across CPR centiles[11]. The latter study along with two others[15, 16] did however report a significant correlation between CPR and birthweight centiles, with higher birthweight centiles reported in the normal CPR cohort[11]. Even amongst AGA cohorts, those with lower birthweights had a significantly lower CPR[13, 15, 16, 35]. A low CPR was consistently reported to correlate with the presence of both SGA[26, 30, 32, 36] and FGR[26, 33] births. Triunfo et al. 2016[26], reported that the CPR z-score was an independent predictor of both SGA (Detection Rate [DR] 13.7, 10% false positive rate[FPR]) and FGR (DR 27.8, 10% FPR), with corresponding AUROC values of 0.56 and 0.65 respectively[26]. However, whilst the CPR performed better than other Doppler indices in this study, it did not out-perform EFW for either SGA or FGR (DR 59.2, 10% FPR and 83.3%, 10% FPR, respectively)[26].

Low Apgar Score

There were four studies[11, 16, 36, 40] that reported the relationship between the CPR and Apgar scores. Prior et al. 2015[16], reported that Apgar scores <7 at both one minute (56.5% v 5.1% $p<0.001$) and five minutes (27.5% v 1.3%, $p<0.001$) were significantly lower with a low pre-labour CPR. Another two studies[11, 16] reported a greater frequency of poor Apgar scores in the low CPR group, but these did not reach significance. In a further study[40], no poor Apgar scores were observed irrespective of the CPR.

Acidosis at Birth

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Ten studies[11, 13, 16, 23, 28, 31, 33, 35, 36, 40] described the results of cord blood analysis. Ropacka-Lesiak et al. 2015[36], reported that neonates born in the low CPR cohort were more likely to have acidosis compared to normal CPR controls. The differences were significant across each parameter: UA pH<7.2 (39.1% v 2.5%), base excess <-12mEq/L (34.8% v 5.1%), pO2 <15mmHg (43.5% v 24.0%) and pCO2 >45mmHg (44.9% v 16.5%) (all p<0.05). Two other studies also reported that low CPR was associated with cord blood acidosis[13, 33] and one reported that the CPR correlated better than birthweight cord blood acidosis[13]. Cruz-Martinez et al. 2011[28], described that SGA fetuses with an abnormal CPR had a five-fold likelihood of cord blood acidaemia (OR 5.0, 95%CI 1.06-46.9). Other studies did not demonstrate a significant relationship between abnormal CPR and abnormal cord blood analysis[11, 16, 31].

Admission to Neonatal Intensive Care Unit

Admission to NICU was reported in five studies[11, 12, 16, 33, 40]. Between 21.9%[40] and 37.1%[33] of fetuses with an EFW<10th centile and an abnormal CPR required admission to NICU – rates significantly higher compared to normal CPR cohorts (11.1%[40] to 21.3%[33]). Irrespective of fetal size, a low CPR was independently associated with NICU admission (aOR 0.55, 95%CI 0.33-0.92, p<0.021), outperforming that of birthweight centile (aOR 1.00, 95%CI 0.99-1.00, p0.794)[12]. Two further studies reported higher NICU admission rates amongst abnormal CPR cohorts but these did not reach significance[11, 16].

Composite Adverse Perinatal Outcome

Composite adverse perinatal outcomes and their association with CPR were reported in 11 studies[11, 16, 23, 26, 27, 29, 32-34, 36, 37]. Outcome variables included in the composite included CS-IFC, cord blood acidosis, poor Apgar scores and NICU admission. Low CPR resulted in a more than two-fold increase in the likelihood of adverse perinatal outcomes (OR 2.43, 95%CI 1.28-4.59)[33] and had better sensitivity (87.8%) and NPV (93.7%) than MCA and UA Dopplers[36] as well as other tests

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including amniotic fluid index, biophysical profile and non-stress test[23]. Triunfo et al. 2016[26], reported that the CPR had a detection rate of 23.1% (10% FPR) for composite adverse perinatal outcome which was more reliable than EFW (DR 19.2%), umbilical venous blood flow (DR 16.9%) and uterine artery Dopplers (DR 9.2%). The AUROC for CPR predicting adverse perinatal outcomes was 0.52 (0.44-0.59)[27]. In two studies[32, 33] more than half of the low CPR fetuses had adverse perinatal outcomes (50.7% v 6.3%[36]; 57.3% v 34.7%[33] respectively, $p<0.05$) and in another study more than one third (37.5% v 19.1%, $p<0.05$)[32] had poor outcomes. The CPR was shown to be lower in cohorts with adverse perinatal outcomes compared to controls[29, 37] with two of these reaching significance[23, 27]. Four studies however did not demonstrate a significant association between low CPR and composite adverse perinatal outcome[11, 16, 29, 37].

Perinatal Mortality

There were limited data reported for perinatal mortality. Morales-Rosello et al. 2014[15], reported six (0.05%) early neonatal deaths and six (0.05%) late neonatal deaths. The CPR data corresponding to these deaths however were not obtainable. Perinatal mortality was a component of one composite outcome score however no CPR data or mortality rates were obtainable from that study either[34].

DISCUSSION

This systematic review clearly demonstrates that a low CPR when detected at term is associated with a number of adverse obstetric and perinatal outcomes, regardless of birthweight. A low CPR is independently predictive of CS-IFC, SGA and FGR and NICU admission. Furthermore, a low CPR correlates significantly with pregnancies complicated by intrapartum events like MSL and FHR pattern abnormalities, as well as adverse neonatal outcomes, such as low Apgar scores and acidosis. Composite adverse perinatal outcomes were also significantly higher in low CPR cohorts. There were however no data related to the risk of perinatal mortality. This is probably because this is such a rare

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event at term and the studies included in this systematic review were not powered to detect this outcome. The results of this systematic review as well as other studies strongly support the incorporation of the CPR as a component in an antenatal screening test for adverse perinatal outcomes.

There is considerable difficulty identifying pregnancies in which placental function is inadequate to support fetal growth potential and where greater risk of adverse perinatal outcomes exists. This clinical dilemma is particularly difficult in late pregnancy[41]. Current practices vary considerably but include symphysis-fundal height measurements, risk-based ultrasound assessment and routine third-trimester ultrasound scan[42-45]. The conventional anthropometric model of EFW has high sensitivity for growth restriction, using the 10^{th} centile as an arbitrary threshold. This biometric proxy for placental insufficiency however has a high false positive rate as it also includes healthy fetuses that may just be constitutionally small without being growth restricted[46]. Data also suggest this approach fails to identify AGA fetuses that, whilst above the 10^{th} centile for EFW, have not reached their growth potential as a consequence of suboptimal placental function[15]. This cohort of pregnancies has been shown to have poorer perinatal outcomes than fetuses that have reached their growth potential[13]. Additionally, SGA fetuses may have subtle cardiovascular redistribution that is not appreciable with UA Doppler alone[28]. Other antenatal fetal surveillance tests in use like cardiotocography, amniotic fluid index and biophysical profile have not been shown to improve perinatal outcomes[47-51]. Thus, these limitations have largely prompted the renewed relevance of CPR as a potentially important clinical tool.

The CPR was initially described in the 1980s[52] and assesses both placental function and fetal response by its evaluation of the UA and MCA Dopplers[52]. Current data suggest that it predicts adverse perinatal outcomes better than UA and MCA Dopplers on their own[18-23] and outperforms uterine artery Dopplers[53]. Conventional EFW by ultrasound performs relatively poorly at identifying at risk fetuses at term[54-59] and the CPR has been shown to better identify pregnancies

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with adverse perinatal outcome than anthropometric models[13] and biophysical profile[19, 60]. The evaluation of CPR, particularly amongst SGA and FGR pregnancies, provides a strong predictor of adverse obstetric and perinatal outcomes: caesarean for intrapartum fetal compromise (CS-IFC) at term and acidaemia at birth[11, 17, 21, 32, 52, 61-64]. Furthermore, a low CPR has been associated with neurological morbidity in both growth restricted and AGA cohorts[12, 64-67].

However, the majority of published studies report on the CPR evaluated in the **mid and late trimesters pregnancy rather than at ≥37 weeks.** Given that the majority of most pregnancies regardless of setting, proceed to term[68] and the difficulties in identifying late-pregnancy growth restriction and placental insufficiency, there is a clear need to improve the reliability of fetal surveillance techniques to predict adverse perinatal outcomes in this large cohort. Whilst the CPR has been suggested as a component of antepartum testing[69] there is a dearth of robust evidence from randomised clinical trials.

Currently, there is increasing evidence from published studies as well as anecdotally that the CPR has been adopted into clinical decision making at term[41, 70, 71] despite the lack of good evidence supporting its use. One reason for this is that the optimal gestation at which to measure the CPR is not entirely apparent from the current evidence and some clinicians have extrapolated the data from preterm pregnancies to a term cohort. Most of the data available regarding the predictive ability of the CPR relate to cohorts of pre-term pregnancies complicated by growth restriction[61, 72]. In a large prospective study of preterm SGA pregnancies, Flood et al. 2014[61], reported the sensitivity and specificity of CPR for adverse perinatal outcomes as 80-85% and 41-60% respectively. In other studies, despite the clear association with adverse obstetric and perinatal outcomes, detection rates are still relatively poor when measured <37 weeks[73, 74].

In our view, incorporation of the CPR into routine clinical practice as a stand-alone measure of risk assessment is inappropriate for the following reasons. Firstly, the optimal discriminatory threshold has not been definitively described and this will clearly impact upon detection rates for various

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adverse outcomes. Although the CPR is significantly lower in pregnancies complicated by a number of adverse intrapartum and perinatal outcomes, there is substantial overlap between groups. The reported false positive rates in many of the studies are also unacceptably high and consideration needs to be given to the maternal and healthcare provider anxiety, a screen positive result would engender, in an otherwise "normal" pregnancy. Secondly, the optimal CPR-to-delivery interval is uncertain. Prior et al 2013[11] demonstrated an abnormal CPR measured within 72 hours of labour amongst an AGA cohort increased the likelihood of CS-IFC six-fold and conversely, a CPR >90th centile had a 100% NPV. The logistics of performing an ultrasound scan within this narrow window are largely impractical. More recent data though suggest that abnormal CPR measured up to two weeks remote from delivery yielded a 'fair' prediction for CS-IFC (AUROC 0.71), but not for an adverse neonatal composite outcome (AUROC 0.56)[14]. This time frame may be much more achievable particularly when aligned with a routine antenatal appointment.

The ability of the CPR to identify the 'at risk' fetus might also be improved by combining it with other parameters. Addition of the CPR to the EFW improves the detection of FGR compared to EFW alone (DR 88.6% v 83.3%, 10% FPR) and the CPR, EFW and umbilical vein blood flow improved detection of adverse perinatal outcome compared to EFW alone (DR 29.2% v 19.2%, 10% FPR)[26] although overall detection rates are still poor. A number of maternal biochemical markers such as placental growth factor (PlGF) and soluble fms-like tyrosine kinase 1 have been linked to sequelae of placental dysfunction[75, 76]. There is evidence that PlGF is significantly lower in the final month of pregnancy in term, AGA pregnancies that went on to require emergency delivery for IFC and had poorer neonatal outcomes[77]. The inclusion of biochemical markers might therefore further strengthen the predictive utility of CPR.

Of the publications included in this review, there were no randomised control trials and a substantial proportion of the data came from retrospective studies. Furthermore some of the outcomes reported in this systematic review may be considered "soft" endpoints that are not entirely relevant

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in terms of longer term outcomes such as cerebral palsy. Hard outcomes such as perinatal death, meconium aspiration syndrome, hypoxic ischaemic encephalopathy and extended NICU admission however whilst perhaps more reflective of neonatal morbidity, require adequately powered and larger cohort studies. Whilst some studies did report these outcomes, the data were insufficient to establish an association with a low CPR.

Nonetheless, despite these limitations the results presented in this systematic review strongly suggest that a low CPR is associated with a higher risk of obstetric intervention for intrapartum fetal compromise and poorer perinatal outcomes at term. In our view these results emphasise the need for randomised controlled trials to assess its value.

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Table 2 – Association between low cerebroplacental ratio and obstetric and perinatal outcomes

CPR – cerebroplacental ratio. *-p<0.05. NS – p>0.05. CS-IFC – caesarean for intrapartum fetal compromise. OP-IFC operative delivery for IFC. CS – caesarean. SVD spontaneous vaginal delivery. FHR fetal heart rate. MSL meconium stained liquor. BW- birthweight. NICU neonatal intensive care unit. CAPO composite adverse perinatal outcome.<5th centile. <10th centile. MoM Multiples of the median. [a] - 0.8095 MoM. [b] - 0.98.

Outcome	Bligh 2016	Bellido-Gonzalez 2016	Triunfo 2016	Figueras 2015	Garcia-Simon 2015	Khalil 2015	Morales-Rosello 2015	Morales-Rosello 2015	Prior 2015	Ropacka-Lesiak 2015	Maged 2014	Morales-Rosello 2014	Prior 2013	D'Antonio 2013	Cruz-Martinez 2011	El-Sokkary 2011	Murata 2011	Gupta 2006	Lam 2005	Figueras 2004	Devine 1994
Low CPR	≤1; <5th; <10th	<5th	z-score	<5th	<5th	<0.6765 MoM	<5th [a]; <0.6765 MoM	<0.6765 MoM	<0.6765 MoM	<1.1	≤1.05	<0.6765 MoM	<10th	≤5th [b]; ≤0.90	<5th	<0.85	<1.1	<1.1; <1.3	≤1.09		<1.05
CS-IFC	Yes*				Yes 31.5% v 16.0%*				Yes 36.7% v 11.3%*		Yes 50.0% v 12.1%*		Yes 36.4% v 9.5% v 0%*		Yes 46.7% v 22.0%*						
OP-IFC						Yes 13.1% v 9.4%*															
CS		Yes 21.9% v 11.1%*			Yes 46.1% v 28%*					Yes 24.6% v 7.6%*					Yes 58.3% v 29.3%*						
Less SVD									Yes 16.3% v 37.9%*		Yes 32.4% v 55%*		Yes (CPR >90$^{\%}$) 22.7% v 44.9% v 57.5%*								
Abnormal FHR Pattern									Yes 40.8% v 18.5%*	Yes 62.3% v 19.0%*			Yes 86% v 31% v 12.5%*				Yes 1.05±0.2 v 1.23±0.2*				
MSL									Yes 22.4% v 11.4%*	Yes 46.4% v 24.1%*			Yes 22.7% v 10.1% v 2.5%*						NS		
Lower BW or BW centile		Yes*	Yes*		Yes*; FGR 49.4% v 33.3%*		Yes*	Yes*	Yes*	Yes*; SGA 5.8% v 0%*		Yes*	NS (BW); Yes* (centile)						Yes*		
Apgar Score <7		No							NS 1min (26.1% v 8.1%); 5min (2.0% v 1.2%)	Yes 1min 56.5% v 5.1%*; 5min 27.5% v 1.3%*			NS 5min 2.3% v 0.9% v 0%								
Acidosis at birth (arterial or venous)		No			Yes (arterial <7.15 11.2% v 6.7%*)		Yes* (venous pH)	Yes* (arterial and venous pH)	No	Yes (arterial pH 39.1% v 2.5%* & BE 34.8% v 5.1%*)			NS pH<7.2: 29.5% v 28.5% v 27.55%		Yes*					NS	Yes* (arterial pO2)
NICU		Yes 21.9% v 11.1%*			Yes 37.1% v 21.3%*	Yes 14.3% v 9.7%*			NS 2.0% v 1.8%				NS 4.5% v 1% v 2.5%								
CAPO				Yes	Yes 57.3%				NS	Yes 50.7% v	Yes		No					NS			Yes

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				37.5% v 19.1%*	v 34.7%*					6.3%*	1.04±0.19 v 1.83±0.37 *							1.23±0.13 v 1.39±0.26			1.00 v 1.20*

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Table 3 – Predictive values of cerebroplacental ratio taken from 37+0 weeks gestational age

CS-IFC caesarean for intrapartum fetal compromise. FHR fetal heart rate. MSL meconium stained liquor. NICU neonatal intensive care admission. CAPO composite adverse perinatal outcome. CPR – cerebroplacental ratio. MoM multiples of median. <10th centile. <5th centile. PPV positive predictive value. NPV negative predictive value. OD odds ratio. RR relative risk. LR likelihood ratio. DR detection rate. (95% CI) 95% confidence interval. aOR adjusted odds ratio. AUROC area under receiver operator characteristic curve.

Outcome	Low CPR Threshold	Sensitivity	Specificity	PPV	NPV	OR/RR/LR/DR (95% CI)	AUROC	Reference
CS-IFC	<0.6765 MoM (10th centile)	18.0%	95.4%	36.7%	88.7%	RR 3.25 (2.14-4.95)		Prior 2015
	<10th	32.5%	93.2%	36.4%	91.6%	OR 6.1 (3.03-12.75)	0.69	Prior 2013
	<5th					OR 10.3, (3.22-52.8) DR 45.9% (21.5% FPR)		Cruz-Martinez 2011
	<5th					OR 2.54 (1.18-5.61)		Garcia-Simon 2015
	MoM					aOR 0.67 (0.52-0.87)* aOR 0.68 (0.52-0.91)†		Khalil 2015
Abnormal FHR pattern	<1.1	74.1%	71.1%	62.3%	81.0%	LR 2.6		Ropacka-Lesiak 2015
	<1.1	62.5%	74.5%	45.5%	85.4%			Murata 2011
	<0.6765 MoM (10th)					RR 2.21 (1.53-3.20)		Prior 2015
MSL	<0.6765 MoM (10th)					RR 1.96 (1.12-3.43		Prior 2015
Birthweight	z-score					DR (10% FPR) SGA: 13.7, FGR: 27.8 DR (20%)	SGA: 0.56, FGR: 0.65	Triunfo 2015
Acidosis at birth	<5th					OR 5.0 (1.06-46.9) DR 37.5% (27.8% FPR)		Cruz-Martinez 2011
NICU	MoM					aOR 0.55 (0.33-0.92)		Khalil 2015
CAPO	<1.1	87.8%	68.5%	51.4%	93.7%	LR 2.8		Ropacka-Lesiak 2015
	z-score					DR 23.1 (10% FPR)	0.52	Triunfo 2016
	<1.05	80.0%	94.9%	80.0%	94.9%			Devine 1994
	<0.85	80.0%	72.0%	62.5%	77.0%			El-Sokkary 2011
						2.43 (1.28-4.59)		Garcia-Simon 2015
	<1.1	40.0%	77.0%	25.0%	87.0%			Gupta 2006
	<1.3	80.0%	53.8%	25.0%	93.3%			Gupta 2006
	≤1.05	75.0%	98.2%	97.1%	83.3%		0.963	Maged 2014
							0.53	D'Antonio 2013

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Table 1 – Study characteristics

AO adverse outcome. GA gestational age. CPR cerebroplacental ratio. Y Yes. P prospective. AGA appropriately grown. PI Pulsatility Index. <5th centile. <10th centile. R Retrospective. IUGR – Intrauterine growth restricted. SGA small for gestational age. NR not reported. LGA large for gestational age. MoM multiples of the median. [a] - 0.8095 MoM. RI resistance index. [b] - 0.98 MoM.

Outcome	**Bligh 2016**	**Bellido-Gonzalez 2016**	**Triunfo 2016**	**Figueras 2015**	**Garcia -Simon 2015**	**Khalil 2015**	**Morales-Rosello 2015**	**Morales-Rosello 2015**	**Prior 2015**	**Ropacka -Lesiak 2015**	**Maged 2014**	**Morales-Rosello 2014**	**Prior 2013**	**D'Antonio 2013**	**Cruz-Martinez 2011**	**El-Sokkary 2011**	**Murata 2011**	**Gupta 2006**	**Lam 2005**	**Figueras 2004**	**Devine 1994**
Significant association with AO	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	N	Y	N	Y
Study Type	P	R	P	P	P	R	R	R	P	R	P	R	P	R	P	P	R	P	P	P	P
GA	36+0-41+6	≥37+0	37+1	≥37+0	≥37+0	≥37+0	37+0-41+6	37+0-41+6	37+0-41+6	40+0-42+0	40+0-42+0	37+0-41+6	37+0-42+1	≥41+3	≥37+0	≥40+0	37+0-41+6	≥40+0	≥41+0	41+0-42+6	≥41+0
Cohort	AGA	IUGR	All	SGA	SGA	All	All	All	AGA	Post-dates	Post-dates	All	AGA	Post-dates	SGA	Post-dates	SGA	Post-dates	Post-dates	Post-dates	Post-dates
n=	364	120	946	509	164	9772	1059	2927	775	148	100	11576	400	320	410	100	309	31	118	56	49
Abnormal CPR cohort size	58	32	NR	200	89	837; 908	NR	284	49	69	34	63	44	14; 4	60	NR	63	NR	NR	NR	10
CPR Doppler Index	PI	PI	PI	PI	PI	PI	PI	PI	PI	RI	PI	PI	PI	PI	PI	PI	RI	PI	PI	PI	S/D
Low CPR	≤1; <5th; <10th	<5th	z-score	<5th	<5th	<0.6765 MoM	<5th [a]; <0.6765 MoM	<0.6765 MoM	<0.6765 MoM	<1.1	≤1.05	<0.6765 MoM	<10th	≤5th [b]; ≤0.90	<5th	<0.85	<1.1	<1.1; <1.3	≤1.09	NR	<1.05
CPR-Delivery interval	≤14 days	≤7 days	NR	≤7 days	≤24 hours	≤14 days	≤14 days	≤14 days	≤72 hours	≤24 hours	≤7 days	≤14 days	≤72 hours	≤10 days	≤24 hours	NR	≤7 days	≤7 days	≤48 hours	≤48 hours	≤7 days
Blinded	Yes	NR	Yes	Yes	Yes	NR	Yes	NR	Yes	NR	NR	NR	Yes	NR	Yes	NR	Yes	Yes	Yes	Yes	Yes

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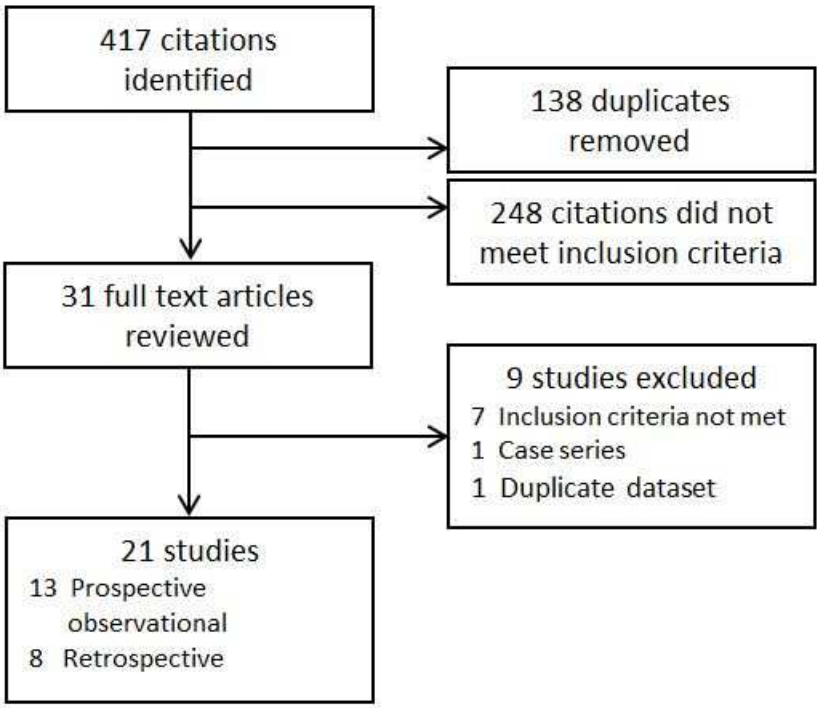
Figure 1 – Selection of studies



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Highlights

- The cerebroplacental ratio (CPR) assesses both fetal and placental circulation
- Low CPR at term is associated with adverse obstetric and perinatal outcomes
- Predictive utility is inadequate as a stand-alone antenatal screening tool at term

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