PREDICTIVE ACCURACY OF THE CEREBROPLACENTAL RATIO FOR ADVERSE PERINATAL AND NEURODEVELOPMENTAL OUTCOMES IN SUSPECTED FETAL GROWTH RESTRICTION: A SYSTEMATIC REVIEW AND META-ANALYSIS

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Short title: The cerebroplacental ratio predicts perinatal death in pregnancies with suspected fetal growth restriction

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ABSTRACT

Objective The cerebroplacental ratio (CPR) has been proposed for the routine surveillance of pregnancies with suspected fetal growth restriction (FGR), but the predictive performance of this test is unclear. The aim of this study was to determine the accuracy of the CPR for predicting adverse perinatal and neurodevelopmental outcomes in suspected FGR.

Methods PubMed, EMBASE, CINAHL, and Lilacs (all from inception to July 31, 2017) were searched for cohort or cross-sectional studies that reported on the accuracy of the CPR for predicting adverse perinatal and/or neurodevelopmental outcomes in singleton pregnancies with antenatally suspected FGR based on sonographic parameters. Summary receiver operating characteristic (ROC) curves, pooled sensitivities and specificities, and summary likelihood ratios (LRs) were generated.

Results Twenty-two studies (4301 women) met the inclusion criteria. Summary ROC curves showed that the best predictive accuracy of the CPR was for perinatal death and the worst was for neonatal acidosis, with areas under the summary ROC curves of 0.83 and 0.57, respectively. The predictive accuracy of the CPR was moderate-to-high for perinatal death (pooled sensitivity and specificity of 93% and 76%, respectively, and summary positive and negative LRs of 3.9 and 0.09, respectively), and low for composite of adverse perinatal outcomes, cesarean section for non-reassuring fetal status, Apgar <7 at 5 minutes, admission to the neonatal intensive care unit, neonatal acidosis, and neonatal morbidities with summary positive and negative LRs ranging from 1.1-2.5, and 0.3-0.9, respectively. An abnormal CPR result had moderate accuracy for predicting small for gestational age at birth (summary positive LR of 7.4). The

CPR had a higher predictive accuracy in pregnancies with suspected early-onset FGR. No study provided data for assessing the predictive accuracy of the CPR for adverse neurodevelopmental outcomes.

Conclusion The CPR appears to be useful in predicting perinatal death in pregnancies with suspected FGR. Nevertheless, before incorporating the CPR into the routine clinical management of suspected FGR, randomized controlled trials should assess whether the use of the CPR reduces perinatal death or other adverse perinatal outcomes.

INTRODUCTION

Fetal growth restriction (FGR) is a major clinical and public health challenge around the world[1,2]. Small for gestational age (SGA) at birth, based on different cut-off values, is a commonly used proxy measure of FGR[3]. FGR is associated with an increased risk of short- and long-term morbidity and mortality, as well as impaired neurological and cognitive development[4-11].

Suspected FGR is defined in the antenatal period by sonographic estimation of fetal anthropometric measures using a wide range of seldom validated definitions and cut-off values[12-16]. The clinical management of suspected FGR is challenging and no consensus exists for the best way to monitor fetal well-being in these pregnancies; consequently, clinical practice varies considerably around the world[17-19]. The use of umbilical artery (UA) Doppler velocimetry in high-risk pregnancies, including those with suspected FGR, has been shown to be associated with a significant reduction in perinatal mortality and fewer cesarean deliveries and inductions of labour[20].

In 1987, Arbeille *et al*.[21] reported that the cerebroplacental ratio (CPR), a measure of cerebral centralization of fetal blood flow, appeared to be superior to either the middle cerebral artery (MCA) or UA Doppler indices alone in predicting SGA among women with gestational hypertension. The CPR is calculated by dividing the Doppler indices (pulsatility index [PI], resistance index [RI], or systolic/diastolic ratio [S/D]) of the MCA by the UA. Physiologically, the CPR represents the interaction of alterations in blood flow to the brain as manifest by increased diastolic flow as a result of cerebrovascular dilatation due to hypoxia and increased placental resistance, leading to decreased diastolic flow in the UA[22]. Integrating the CPR into the clinical management of suspected FGR has recently been proposed[22-27], but the test's ability to predict adverse perinatal outcomes in this entity has been questionned[28,29]. Hence, we carried out a systematic review and meta-analysis to assess the accuracy of the CPR to predict adverse perinatal and neurodevelopmental outcomes in antenatally suspected FGR.

METHODS

The systematic review was conducted following a prospectively prepared protocol and reported in accordance with recommended methods for systematic reviews of diagnostic test accuracy[30,31]. The protocol was registered with PROSPERO on March 2016 (CRD42016036488; available from: http://www.crd.york.ac.uk/PROSPERO/display_record.php?ID=CRD42016036488).

Literature search

We searched PubMed, EMBASE, CINAHL, and Lilacs (all from inception to July 31, 2017) using a combination of keywords and text words related to *cerebroplacental ratio* and *fetal growth restriction* without language restrictions (Appendix S1).

Eligibility criteria

We included cohort or cross-sectional studies that reported on the accuracy of the CPR for predicting adverse perinatal and/or neurodevelopmental outcomes in singleton pregnancies with antenatally suspected FGR based on sonographic parameters, and provided the necessary information to generate 2x2 tables. Studies were excluded if they: (1) assessed retrospectively the predictive accuracy of the CPR in infants categorized as SGA or FGR based on postnatal parameters such as birthweight or other anthropometric measures, and/or placental histopathology; (2) assessed the CPR in a mix of high-risk pregnancies but did not report results separately for pregnancies with suspected FGR; (3) assessed the CPR in the general population as a screening tool; (4) were case-control studies without complete information for cases with suspected FGR, case series or reports, editorials, comments, reviews, or letters without original data; (5) reported data for the CPR only as mean or median values; (6) did not publish accuracy test estimates or sufficient information to calculate them could not be retrieved.

One reviewer (A.C.-A.) screened titles and abstracts of all identified citations and selected potentially eligible studies. Then, these studies were retrieved and assessed by the same reviewer for inclusion and data extraction, and a 10% sample of the papers was examined by a second independent reviewer (J.V.). Disagreements were resolved through consensus. In cases of duplicate publication, we included only the most recent or complete version.

Reference standard outcomes

The reference standard outcomes included the following: perinatal death; any composite of adverse perinatal outcomes (as defined in the original study and regardless of its individual components); cesarean delivery for fetal distress/non-reassuring fetal status; Apgar <7 at 5 minutes; admission to the neonatal intensive care unit (NICU); neonatal acidosis; neonatal brain lesions; neonatal morbidities other than brain lesions; use of mechanical ventilation; SGA at birth (birthweight <10th, <5th or <3rd perpercentile or <2 standard deviations of mean adjusted for gestational age and based on local population values), and adverse neurodevelopmental outcomes (suspected or diagnosed developmental delay, cerebral palsy, intellectual disabilities, vision impairment, hearing loss, cognitive and behavioral impairments, and motor, communication and learning disorders at any age in childhood).

Assessment of risk of bias

The risk of bias in each included study was evaluated by at least one investigator using a modified version of the QUADAS (Quality Assessment of Diagnostic Accuracy Studies)-2 tool[32]. The following domains were assessed: study design, description of the test, selection of test cut-off value, blinding of clinicians to the CPR results, inclusion of participants recruited into the study in the analysis, and use of interventions aimed to prevent adverse perinatal outcomes based on the CPR results. Each domain was scored as “low risk”, “high risk”, or “unclear risk” of bias (Appendix S2). We did not calculate a summary score estimating the overall quality of each study because of the well-known problems associated with such scores[33].

Data extraction

Data were extracted from each article using a specially designed form for capturing information on study characteristics (authors, setting, year of publication, method of recruiting women, design, prospective or retrospective data collection, blinding of test results, flow diagram, completeness of follow-up and reporting of withdrawals, and use of interventions after performing the test), patient characteristics (inclusion and exclusion criteria, sample size, and demographic characteristics), how the test was carried out (gestational age at testing, frequency of test, method of performance of test, type of Doppler and route, site of measurement, plane in which images were obtained, Doppler index used [PI, RI, or S/D], cut-off value used, and interval from Doppler examination to delivery), and reference standard outcomes assessed and their prevalences.

For each study and for all cut-off values defining an abnormal CPR result, we extracted the number of true positive, false positive, true negative, and false negative test results. When predictive accuracy data were not available, we recalculated them from the reported results including scatterplot and bar graphs. The corresponding authors of primary studies were contacted to obtain additional information on methods used and/or unpublished relevant data. Only three authors supplied additional data.

Data synthesis

Data extracted from each study were used to construct 2x2 contingency tables. When any single cell in these tables contained a zero, we added 0.5 to each cell to enable calculation of predictive values[34]. Sensitivity and specificity with 95% confidence intervals (CIs) were calculated separately for all Doppler indices and cut-off values used, and reference standard outcomes reported. Then, we constructed summary receiver-operating characteristic (ROC) curves for each predefined reference standard outcome using the hierarchal summary ROC model, regardless of Doppler indices and cut-off values used to define abnormality[35]. Variation in cut-off values across studies is taken into account by using this model. Pooled estimates and 95% Cis of sensitivity and specificity were generated using random-effects bivariate meta-regression models[36]. For studies that reported results for more than one Doppler index and/or cut-off value, we selected the most commonly used. We also calculated area under the summary ROC curves with their corresponding 95% CIs, which allowed for comparison of the predictive accuracy of the CPR for different outcomes[37].

Thereafter, summary likelihood ratios (LRs) with 95% CIs were calculated from the pooled sensitivities and specificities[38]. A guide for the interpretation of

LRs suggests that LRs >10 for a positive test result and LRs <0.1 for a negative test result generate large changes from pretest to post-test probabilities of disease; LRs of 5 to 10 and 0.1 to 0.2 generate moderate changes in probability; LRs of 2 to 5 and 0.2 to 0.5 generate small (but sometimes important) changes in probability; and LRs of 1 to 2 and 0.5 to 1 generate minimal (and rarely important) changes in probability[39]. Finally, we planned to calculate the post-test probabilities of the most important reference standard outcomes by combining summary LRs obtained from meta-analyses for positive and negative test results and a global prevalence (pretest probability) of these reference standard outcomes across the studies[39].

Prespecified subgroup analyses were carried out to assess the predictive accuracy of the CPR for any composite of adverse perinatal outcomes according to gestational age (GA) at diagnosis or delivery (early-onset [<32 or <34 weeks] and late-onset [≥32 or ≥34 weeks], as defined by the authors), definition of abnormal CPR result (MCA-PI/UA-PI ≤1.08, MCA-PI/UA-PI <5th percentile, and MCA-RI/UA-RI <1 or <1.05), interval from CPR to delivery (≤7 and >7 days), and definition of suspected FGR used (estimated fetal weight [EFW] <10th percentile for GA and EFW <10th percentile for GA and abnormal UA Doppler). In addition, a post-hoc subgroup analysis according to the use or non-use of the CPR results for managing pregnancies with suspected FGR was performed. We also assessed the effect of risk of bias of the included studies on the predictive accuracy of the CPR by performing a sensitivity analysis, including only studies with a low risk of bias in at least five of the six domains evaluated.

As it is common in diagnostic accuracy studies, we anticipated that there would be substantial between-study variation in reported pairs of sensitivity and specificity values. As forest plots, which display both sensitivity and specificity, depict estimates with associated CIs it is possible to discern the presence of high levels of heterogeneity where there is little overlap in the CIs from different studies. In order to formally investigate potential sources of heterogeneity, we used subgroup analysis and meta-regression by including covariates defined *a priori* (Doppler indices and cut-off values used, definition of suspected FGR used, GA at diagnosis or delivery, interval from CPR to delivery, and study's risk of bias) in the bivariate model, which enabled us to assess the effect of various factors on the predictive accuracy of the CPR[40,41]. If there were at least 10 studies included in a meta-analysis, we assessed publication and related biases by examining the symmetry of the funnel plots with the Deeks' test[42]. A value of $P < 0.1$ for the slope coefficient indicated significant asymmetry of the funnel plot.

We used SAS version 9.2 (SAS Institute Inc, Cary, NC) for the analyses and Review Manager 5.3.5 (The Nordic Cochrane Centre, Copenhagen, Denmark) to generate forest plots and summary ROC curves.

RESULTS

Selection, characteristics and quality of studies

Of 1191 citations initially identified, 22 studies[43-64] including a total of 4301 women/fetuses met the inclusion criteria (Figure 1). Two studies were performed using the same cohort[60,61], one reporting results for all cases of suspected FGR[60] and the other for cases of suspected early-onset FGR[61]. We included results of this last study only in the subgroup analysis according to GA at diagnosis or delivery.

The main characteristics of the included studies are displayed in Table 1. All studies but two[44,52] were performed in European or North American countries.

The sample size ranged from 29[48] to 881[56] (median, 159). The definitions of suspected FGR used in the studies were as follows: EFW <10th percentile for GA (11 studies)[44,45,47,50,54,56-59,62,64], EFW <10th percentile for GA and/or abdominal circumference (AC) <5th percentile (two studies)[60,61], EFW <10th percentile for GA and abnormal UA Doppler indices (two studies)[53,63], AC <5th percentile for GA and abnormal UA Doppler indices (two studies)[46,49], AC <10th percentile for GA (one study)[43], AC <10th percentile for GA on at least two consecutive measurements, two weeks apart (one study)[55], EFW <10th percentile for GA with growth rate slower than normal and abnormal UA Doppler indices (one study)[48], EFW or AC <10th percentile for GA and abnormal UA Doppler indices (one study)[52], and EFW below the GA-adjusted mean value minus 2 SD (2.3rd percentile), or a fall of ≥10% weight deviation from the mean weight between two ultrasound examinations (one study)[51]. Ten studies reported results for suspected late-onset FGR[47,50,51,54,56-59,62,63], four for suspected early-onset FGR[47,56,58,61], and 13 for suspected FGR at all GAs[43-49,52,53,55,56,58,60].

The most common definitions of an abnormal CPR result were MCA-PI/UA-PI ≤1.08 (eight studies[43,47,51-53,56,60,61]) and MCA-PI/UA-PI <5th percentile for GA (six studies[47,50,54,56,58,62]). The mean or median interval between the CPR and delivery was <48 hours in five studies[46,48,50,51,62], <7 days in six studies[49,53,56,57,59,64], 7 to 14 days in three studies[44,47,58], >14 days in five studies[45,54,55,60,61], and unreported in three studies[43,52,63]. Most studies (N=16) used the last CPR result before delivery in analyses[44,46-55,57-59,62,64]. Sixteen studies reported that the CPR results were not used to manage the pregnancies[43-45,47,48,50-53,56,58-63], one reported that the CPR results were used to manage the pregnancies[54], and the remaining five studies did not report on this issue[46,49,55,57,64]. Eleven studies provided data on the predictive accuracy of the CPR for a composite of adverse perinatal outcomes[43,44,47,53,54,56-60,62], nine on admission to the NICU[43-45,51,56,58-60,62], seven on cesarean delivery for non-reassuring fetal status[43,45,50,58-60,62], six each on perinatal death[45,52,55,56,58,60] and Apgar <7 at 5 minutes[43,44,51,58,59,64], five each on neonatal acidosis[50,51,59,62,64] and neonatal brain lesions[45,48,52,55,63], four on neonatal morbidities other than brain lesions[43,45,46,49], two on SGA at birth[43,59], and one on use of mechanical ventilation[55]. No study provided data on adverse neurodevelopmental outcomes.

The risk of bias in each included study is shown in Figure 2. Eight studies (36%) fulfilled ≥5 criteria, whereas the remaining 14 studies (64%) had ≥2 methodological flaws. The most common deficiencies were related to blinding of clinicians to the CPR results and inclusion of participants recruited into the study in the analyses.

Predictive accuracy for adverse perinatal outcomes

Summary ROC curves of the CPR for predicting adverse perinatal outcomes in pregnancies with suspected FGR are shown in Figure 3. The best predictive accuracy was for perinatal death and the worst was for neonatal acidosis, with areas under the summary ROC curves of 0.83 (95% CI, 0.74-0.92) and 0.57 (95% CI, 0.51-0.63), respectively. Similar summary ROC curves were obtained for the prediction of any composite of adverse perinatal outcomes, cesarean delivery for non-reassuring fetal status, and admission to the NICU (areas under the summary ROC curves between 0.71 and 0.74). The sensitivity and specificity of the CPR ratio to predict adverse perinatal outcomes in suspected fetal growth restriction in the individual studies are shown in Figure S1.

Table 2 presents the pooled estimates of the predictive accuracy of the CPR for adverse perinatal outcomes. Overall, the CPR showed a moderate-to-high predictive ability for perinatal death with pooled sensitivity and specificity of 93% and 76%, respectively, and summary positive and negative LRs of 3.9 and 0.09, respectively (six studies, 1495 fetuses, 29 perinatal deaths). The CPR had a low predictive performance for any composite of adverse perinatal outcomes, cesarean delivery for non-reassuring fetal status, Apgar <7 at 5 minutes, admission to the NICU, neonatal acidosis, neonatal brain lesions, neonatal morbidities other than brain lesions, and use of mechanical ventilation with summary positive and negative LRs that varied between 1.1 and 2.5, and 0.3 and 0.9, respectively. An abnormal CPR result had moderate accuracy for predicting SGA at birth (summary positive LR of 7.4; two studies, 554 fetuses). Based on all included studies, we estimated that fetuses with suspected growth restriction had a prevalence rate (pretest probability) of 25% for the composite of adverse perinatal outcomes, 2.0% for perinatal death, and 90% for SGA at birth (birthweight <10th percentile for GA). Then, based on estimated pretest probabilities and summary positive and negative LRs, we calculated that an abnormal CPR result would increase the pretest probability of the composite of adverse perinatal outcomes, perinatal death, and SGA at birth from 25% to 45%, 2% to 7.4%, and 90% to 98.5%, respectively, whereas a normal CPR result would decrease the pretest probability to 17%, 0.2%, and 84%, respectively.

Visual assessment of both forest plots (Figure S1) and summary ROC curves (Figure 3) suggested substantial between-study heterogeneity, mainly for perinatal death, any composite of adverse perinatal outcomes, cesarean delivery for non-reassuring fetal status, and admission to the NICU. Meta-regression analyses showed that none of the prespecified covariates explained the heterogeneity (Table S1). Sensitivity analyses revealed that pooled predictive accuracy estimates obtained from studies with low risk of bias in ≥5 domains did not differ significantly from those obtained in the overall analysis (data not shown). The funnel plot of the meta-analysis that included at least ten studies showed no significant asymmetry (P = 0.19, by Deeks' test).

Subgroup analyses

Subgroup analyses of the accuracy of the CPR to predict any composite of adverse perinatal outcomes are depicted in Table 3. The CPR had a significantly higher predictive accuracy for any composite of adverse perinatal outcomes among pregnancies with suspected early-onset FGR than among those with suspected late-onset FGR. Moreover, the accuracy of the CPR for predicting any composite of adverse perinatal outcomes was lower when using a MCA-PI/UA-PI <5th percentile as the abnormal result and when the CPR results were used to manage pregnancies. There were no differences in the predictive ability of the CPR between studies in which the interval from CPR to delivery was ≤7 days or >days, and between studies using an EFW <10th percentile for GA as definition of suspected FGR and that using an EFW <10th percentile for GA and abnormal UA Doppler as definition of suspected FGR.

DISCUSSION

Main findings

The results of this systematic review indicate that the CPR had a moderate-to-high predictive accuracy for perinatal death, the most important outcome measure in relation with utero-placental insufficiency in suspected FGR. In particular, a normal CPR result had high accuracy to identify which fetuses with suspected growth restriction are at low risk of dying in the perinatal period, decreasing the pretest probability of perinatal death from 2% to 0.2%. Overall, the CPR had a low predictive accuracy for the other adverse perinatal outcomes considered, several of which are less correlated with utero-placental insufficiency in suspected FGR. Notwithstanding, the presence of an abnormal CPR result increased the pretest probability of having an adverse perinatal outcome from 25% to 45%. In addition, subgroup analyses suggest that the predictive accuracy of the CPR is higher in pregnancies with suspected early-onset FGR and when a MCA-PI/UA-PI ≤1.08 or a MCA-RI/UA-RI <1 or <1.05 is used as the definition of an abnormal CPR.

Previously, it has been suggested that the CPR is a stronger predictor of adverse perinatal outcomes in suspected late-onset FGR than suspected early-onset FGR[23,25-27]. Unexpectedly, our subgroup analysis showed the opposite: a higher predictive accuracy for adverse perinatal outcomes in pregnancies with suspected early-onset FGR. Usually, suspected late-onset FGR is characterized by abnormal Doppler indices involving the MCA, with a normal or minimally elevated resistance of the UA[22]. In contrast, suspected early-onset FGR is characterized by abnormal Doppler indices of both the UA and MCA[22]. Abnormality in both vessels included in the calculation of the CPR, in particular high values of UA indices, could explain the better predictive accuracy of the CPR in suspected early-onset FGR in comparison with suspected late-onset FGR in which there are abnormal indices in only one vessel.

It was noteworthy that no included study provided data to assess the predictive ability of the CPR for adverse neurodevelopmental outcomes in pregnancies with suspected FGR. A secondary analysis of the TRUFFLE study[65] reported that the CPR was not associated with neurodevelopmental impairment at 2 years' corrected age in fetuses with suspected early-onset growth restriction[66]. Two studies reported similar results for a decreased MCA-PI in suspected FGR[67,68]. A systematic review reported that SGA or growth-restricted fetuses with cerebral redistribution may be at higher risk of adverse neurodevelopmental outcomes[69]. However, none of the studies included in this review used the CPR for defining cerebral redistribution.

Strengths and limitations

The reliability and robustness of our systematic review are supported by the: (1) adherence to guidelines for the conduct and reporting of systematic reviews of predictive test accuracy; (2) use of a prospective protocol designed to address a highly specific research question; (3) comprehensive literature search without language restrictions; (4) inclusion of a relatively large number of studies, mostly published in recent years; (5) strict study quality assessment; (6) quantitative synthesis of the evidence; (7) use of contemporary statistical methods to obtain summary measures of predictive accuracy including subgroup and sensitivity analyses; and (8) exploration of potential sources of heterogeneity.

Limitations include the lack of blinding of the CPR results or omission of information on this subject in approximately two-thirds of the included studies. Although most studies reported that the CPR results were not used to manage pregnancies with suspected FGR, it is possible that women with abnormal CPR results were followed-up more closely or received interventions, which could have introduced bias in the assessment of the test's predictive accuracy. However, sensitivity analyses that were restricted to studies at low risk of blinding bias showed no significant differences in the results obtained with overall meta-analyses.

There were considerable differences among studies in the definition of suspected FGR and Doppler indices/cut-off values used for defining an abnormal CPR, which limit the generalisability of our findings. Moreover, prespecified variables did not explain substantial heterogeneity and therefore, pooled estimates of predictive accuracy should be interpreted cautiously. Finally, the statistical power of some of our meta-analyses was limited by the small number of studies within each subgroup and the relatively small number of outcome events in some included studies.

Interpretation in the light of previous systematic reviews

We identified three systematic reviews on the predictive accuracy of the CPR for adverse perinatal outcomes[70-72]. Nassr et al [70] included seven studies, and reported that an abnormal CPR in pregnancies at high risk for FGR or with diagnosis of FGR increased the risk for adverse perinatal outcomes. Summary ROC curves showed that the CPR had a better predictive accuracy for neonatal complications and NICU admission. Dunn et al [71] reported that the CPR was predictive of cesarean section for intrapartum fetal compromise, SGA, and NICU admission in pregnancies at term. These reviews did not report pooled estimates of predictive accuracy. Finally, Vollgraff Heidweiller-Schreurs *et al*.[72] assessed the accuracy of the CPR to predict adverse perinatal outcomes in singleton pregnancies of all risk profiles. The CPR was significantly superior to UA and MCA Doppler in predicting a composite of adverse perinatal outcomes and emergency delivery for fetal distress. No differences were found between the CPR and either UA Doppler or MCA Doppler in the prediction of perinatal death, low Apgar score, or NICU admission. Overall, our estimates of the predictive accuracy of the CPR for adverse perinatal outcomes among pregnancies with suspected FGR were lower than those reported in this review among pregnancies of all risk profiles.

The CPR has been hypothesized to be a more accurate test for predicting adverse perinatal outcomes than its individual components UA and MCA Doppler. When comparing the estimates obtained in our study with those reported in two meta-analyses that assessed the accuracy of UA Doppler[73] and MCA Doppler[74] to predict adverse perinatal outcomes in high-risk pregnancies, the CPR had better predictive accuracy for perinatal death (summary positive and negative LRs of 3.9 and 0.09, respectively) than both UA Doppler (summary positive and negative LRs of 2.5 and 0.3, respectively) and MCA Doppler (summary positive and negative LRs of 1.4 and 0.5, respectively). In general, the predictive accuracy of the CPR for other adverse perinatal outcomes appeared to be comparable to those of UA Doppler and MCA Doppler.

Conclusions

The CPR appears to be useful in predicting perinatal death in pregnancies with suspected FGR. Nevertheless, before incorporating the CPR into the routine clinical management of suspected FGR, randomized controlled trials –ideally blinded- should assess whether the use of the CPR reduces perinatal death or other adverse perinatal outcomes. Studies are required to assess the predictive accuracy of the CPR for adverse neurodevelopmental outcomes in fetuses with antenatally suspected growth restriction.

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FIGURE LEGENDS

Legend for Figure 1: Study selection process

Legend for Figure 2: Risk of bias of included studies

Legend for Figure 3: Summary ROC curves of the cerebroplacental ratio to predict adverse perinatal outcomes in suspected fetal growth restriction

Legend for Figure S1: Forest plots of the cerebroplacental ratio to predict adverse perinatal outcomes in suspected fetal growth restriction