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Clinical significance of cerebroplacental ratio

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TITLE: Clinical significance of cerebroplacental ratio

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Authors have nothing to disclose.

ABSTRACT

Purpose of review: Two thirds of the pregnancies complicated by stillbirth demonstrate growth restriction. Identification of the fetus at risk of growth restriction is essential in order to reduce the risk of stillbirth. The aim of this review is to critically appraise the current evidence regarding clinical utility of cerebroplacental ratio (CPR) in antenatal surveillance.

Recent findings: The CPR has emerged as an assessment tool for fetuses at increased risk of growth disorders. CPR is a better predictor of adverse events compared to middle-cerebral artery or umbilical artery Doppler alone. The predictive value of CPR for adverse perinatal outcomes is better for suspected small-for-gestational age (SGA) fetuses compared to appropriate-for-gestational age (AGA) fetuses. CPR could be useful for the risk stratification of SGA fetuses to determine the timing of delivery and also to calculate the risk of intrapartum compromise or prolonged admission to the neonatal care unit. Although there are many proposed cut-offs for an abnormal CPR value, evidence is currently lacking to suggest the use of one cut-off over another. CPR appears to be associated with increased risk of intrapartum fetal compromise, abnormal growth velocity and lower birth weight in AGA fetuses as well. Moreover, birthweight differences are better explained with CPR compared to other factors such as ethnicity. However, the role of CPR in predicting adverse perinatal outcomes such as acidosis or low Apgar scores in AGA fetuses is yet to be determined.

Summary: CPR appears to be a useful surrogate of suboptimal fetal growth and intrauterine hypoxia and it is associated with a variety of perinatal adverse events.

Keywords: adverse outcome, morbidity, intrauterine death, neonatal, neurodevelopment

Introduction

Fetal surveillance in order to identify fetal growth abnormalities is an important aspect of antenatal care. Small-for-gestational age (SGA) fetuses are at increased risk of adverse events such as intrauterine death, intrapartum fetal compromise, operative delivery and poor neonatal outcomes [1-7]. Successful antenatal monitoring and identification of SGA prior to delivery can mitigate the negative impact of fetal growth restriction (FGR) [8,9]. In UK, fundal height measurement is the routine method of growth assessment for women deemed to be at low-risk for developing SGA [10]. The basis for this approach lies in the lack of substantial evidence showing ultrasound scans are helpful for preventing perinatal death [11,12]. However, recent evidence suggests that routine ultrasound scans can be helpful for the antenatal diagnosis of SGA and, more importantly, the identification of the subgroup of SGA fetuses at increased risk of adverse outcome [13]. Rather than using a biological basis, SGA is often defined with statistical terminology (percentile) which by default labels 3 to 10% of all pregnant population at risk for adverse perinatal outcomes. However, the actual incidence of adverse events is less than the apparent prevalence of SGA. Moreover, most fetuses who suffer adverse outcomes such as stillbirth or intrapartum fetal compromise are not suspected to be SGA during antenatal follow-up. Autopsy studies demonstrate that the rate of SGA in the pregnancies complicated with stillbirth may be overestimated due to the loss of fetal weight after intrauterine death [14]. The shortcomings of using estimated fetal weight (EFW) alone as a surrogate for adverse outcomes have been outlined in recent publications and it is evident that more refined markers of fetal health are needed [15-17].

The cerebroplacental ratio (CPR) has emerged as an assessment tool for fetuses at increased risk of growth disorders. CPR is calculated as a simple ratio of middle cerebral artery (MCA) pulsatility index (PI) and umbilical artery (UA) PI (Figure 1). A low CPR indicates a redistribution of the cardiac output to the brain. Cerebral redistribution of blood flow is a proxy for hypoxemia and is associated with poor perinatal and long-term

neurodevelopmental impairment [18,19]. Although cerebral redistribution is reflected in MCA Doppler, CPR has been shown to improve the accuracy of predicting adverse outcome compared with MCA or UA Doppler alone and also to have a strong association with intrauterine hypoxia [20,21]. In recent years, there is a surge in studies evaluating CPR in various sub-populations of pregnant women. The aim of this review is to summarize the key evidence regarding the utility of CPR in the antenatal management of SGA and appropriate for gestational age (AGA) fetuses.

Utility of CPR in SGA fetuses: diagnosis and risk stratification

The difficulty in diagnosing late-onset FGR is partly due to the suboptimal performance of EFW alone in identifying the pregnancies with SGA baby. The addition of uterine artery Doppler and placental biomarkers during varying gestational ages marginally improves the detection of SGA in large cohort studies which implies that late-onset FGR is associated with placental dysfunction [22-24]. The degree of placental dysfunction in late-onset FGR is unlikely to produce the characteristic findings found in early-onset cases such as loss of end-diastolic flow or reverse flow in umbilical artery. The lack of characteristics changes in the UA Doppler makes it a poor candidate for improving the detection of late-onset FGR. However, recent evidence suggests that the addition of CPR to EFW may improve the detection of late-onset FGR [25,26]. However, the magnitude of improvement with the addition of CPR was marginal at best (5% increase in detection rate in the third trimester and likelihood ratio of 1.6 in the second trimester). Moreover, larger studies showed limited benefit of adding Doppler assessment (mainly uterine artery) to EFW and biomarkers for predicting SGA at birth [17,27-30]. The utility of CPR in predicting SGA at birth in unselected pregnancies appears to be limited and CPR may be better suited for risk stratification of suspected SGA babies [17,31]. Miranda *et al* have demonstrated prediction models (EFW+CPR or UA, suspected SGA and unselected cohort, respectively) have higher predictive accuracies when used in suspected-SGA fetuses compared to unselected pregnancies (detection rate: 63.0% vs 20.0%) [31]. Veglia *et al* have proposed a risk stratification protocol for suspected-SGA

fetuses which included CPR, uterine artery PI, pregnancy associated plasma protein and presence of hypertension [16]. They compared the outcomes of pre-protocol management in which suspected-SGA fetuses were delivered at 37 weeks' gestation to protocol group where pregnancies were induced at specific times according to their perceived risk. The implementation of risk stratification protocol improved the vaginal delivery rates and lowered neonatal composite adverse outcomes which were mainly due to neonatal care unit admission and ventilation support. Although preliminary evidence suggests that CPR is beneficial for risk stratification of SGA fetuses, more prospective studies are needed to clarify the role of CPR.

Timing and management of labor in suspected SGA

Suspected SGA fetuses are at increased risk of adverse perinatal outcomes compared to AGA fetuses. [32] Numerous studies have evaluated the association of CPR with these adverse outcomes and have shown that the CPR is a useful marker for identifying fetuses at increased risk [1-7,33]. Although intrauterine death is a rare event in late-onset FGR, it is also legitimate concern which prompts most physicians to choose induction of labor at term (beyond 37 weeks' gestation) over expectant management. The ideal time for induction of labor and its association with perinatal outcomes or its interaction with antenatal variables such as parity, EFW and CPR is yet to be determined. Two cohort studies investigated the association of CPR and known antenatal and intrapartum risk factors with the risk of intrapartum fetal compromise and neonatal care unit admission [2,5]. The gestational age at delivery was found to have a significant impact on both outcomes in these studies. Interestingly, the direction of association differed. The risk of intrapartum fetal compromise appeared to increase beyond 39 weeks, while the risk of neonatal care unit admissions appeared to decrease beyond 37 weeks' gestation. As of yet, it is not possible to propose a management algorithm based on high-quality evidence. However, empirical evidence and findings of non-randomized studies suggest that fetuses showing risk of significant compromise due to abnormal CPR or very low EFW should be induced earlier whereas

expectant management up to 39 weeks' gestation may be feasible for a subgroup of SGA fetuses (Figure 2) [2,5,16]. The benefit of prolonging gestation beyond 39 weeks' gestation appears to be limited even in low-risk pregnancies, and therefore, suspected SGA fetuses should not be expectantly managed beyond this point [34].

Labor management of suspected SGA fetuses is also complicated due to varying risk of intrapartum compromise. A multivariable prediction model including CPR, gestational age at delivery, parity and intrapartum risk factors was able to discriminate the fetuses who will need operative delivery for presumed compromise with modest accuracy (AUC: area under the curve: 0.76, 95% CI: 0.72 – 0.80) [5]. In this cohort, the CPR showed a linear association with the risk of operative delivery and the strength of association was similar to that of intrapartum risk factors such as labor induction and augmentation or epidural analgesia. An external validation study is currently ongoing which could verify the utility of the prediction model in clinical practice (Kalafat E, Morales-Rosello J, Scarinci E, Thilaganathan B, Khalil A. under review). Although studies on CPR commonly use a predefined threshold (<10th centile, 0.6765 MoM, <1.1 etc.), some values above these thresholds may be falsely reassuring. Prior *et al* suggested a CPR above >90th centile for gestational age is a protective factor against intrapartum fetal compromise [35]. Findings from these two studies imply that CPR have a dose-response relationship with the risk of intrapartum fetal compromise and using crude cut-offs may be less efficient for predicting adverse outcomes [5,35]. However, the clinical applicability of CPR greatly diminishes when we use cut-offs (as a binary variable) instead of using it as a continuous measure. A mobile app is also developed to overcome this problem and calculate the individualized risk of operative delivery with ease using the multivariable model suggested by Kalafat *et al* (IRIS tool for SGA babies, https://itunes.apple.com/us/app/iris-tool-for-sga-babies/id1371991518?ls=1&mt=8) [5].

Short-term and long-term neonatal outcomes of SGA fetuses

CPR has been shown to be a predictor of short- and long-term adverse perinatal outcomes in SGA fetuses [3,36]. Suspected SGA fetuses with low CPR are at increased risk of perinatal death, neonatal acidosis, low Apgar scores, and composite adverse outcomes (Table 1) [37]. CPR also shows better accuracy for predicting adverse outcomes compared to MCA assessment (Table 1) [38]. CPR is also associated with the risk of long-term cognitive impairment in suspected SGA fetuses [39,40]. Although signs of overt neurological damage could not be demonstrated via biomarkers, these findings suggest that cerebral autoregulation is not entirely a protective mechanism but merely a salvage pathway in response to inadequate oxygenation [41]. The short- and long-term outcomes of fetuses with abnormal CPR suggests that prolonging the gestation when there is evidence of cerebral involvement may not be beneficial for the fetus.

Changing CPR values with gestation: role of longitudinal assessment in SGA fetuses

Abnormal growth velocity was suggested as an adjunct marker for diagnosing late-onset FGR in a recent Delphi consensus [42]. Some studies suggest that models accounting for the longitudinal changes in Doppler parameters are superior to cross-sectional assessment for the prediction of adverse outcomes [43-45]. Studies investigating the association of longitudinal changes in fetal biometry and Doppler parameters with the risk of adverse pregnancy outcome have reported conflicting results [7,46-49]. Despite the fact that assessment of the fetal growth velocity is likely to be useful in identifying FGR, the complex nature of its calculation and lack of standardization of its assessment limits its potential use in routine clinical practice. More studies are needed to demonstrate whether the change in CPR with advancing gestation improves the prediction of the fetus at risk of adverse pregnancy outcome, compared to its assessment at a single point.

Role of CPR in early-onset FGR

The role of CPR in early-onset FGR has been scarcely evaluated. Current decision-making protocol for early-onset FGR relies on venous Doppler and computerized cardiotocography leaving little room for CPR in the management of these fetuses. However, the TRUFFLE investigators have reported that higher MCA PI z-scores and lower umbilicocerebral ratio were associated with better neonatal survival and normal neurodevelopmental outcome at 2-years [50]. Post-hoc analyses of randomized trials such as TRUFFLE could be beneficial for discerning the role of CPR in the management of early-onset FGR.

Utility of CPR in AGA fetuses: failing to reach growth potential and stillbirth

EFW is a poor indicator of fetal well-being and most stillbirth cases are not suspected to be SGA during the antenatal period [51]. In a recent cohort study, Binder *et al* have demonstrated that episodes of reduced fetal movements are associated with lower CPR values, with women reporting recurrent episodes having even lower CPR values compared to women with a single episode of reduced fetal movement [51]. It is important to note that none of the stillbirth cases in this cohort were suspected to be SGA during the antenatal follow-up. CPR showed an independent association with both reduced fetal movements and stillbirth in this relatively high-risk cohort. In a similar study, Monaghan *et al* have suggested that the utility of CPR may be limited in low-risk pregnancies in which the uterine artery Doppler and EFW showed significant association with stillbirth [52]. However, the estimated effect for all three variables (CPR, uterine artery PI and EFW) were marked by large confidence intervals due to the low number of stillbirth cases (n=12) in the cohort. CPR still had a positive but insignificant association with stillbirth (OR: 1.97) due to wide confidence intervals which may very well be due to low number of cases included in the study. These findings are in line with previous reports suggesting that placental dysfunction may be better predicted by Doppler studies compared to EFW [1,7]. CPR appears to be beneficial for identifying fetuses who fail to reach their growth potential while still remaining within normal EFW ranges.

Birth weight is known to be associated with maternal characteristics, including ethnicity. Customized growth charts were developed to account for ethnic differences with the aim of improving the detection of SGA fetuses at risk. A recent study by Morales-Rosello *et al* used a different approach to address this issue and has shown that CPR is better in explaining birth weight differences, when compared to ethnicity [53]. Furthermore, racial/ethnic standard proposed by the National Institute of Child Health and Human development failed to better identify fetuses at risk for neonatal adverse outcomes compared to Hadlock chart [54]. Similar results were reported for customized charts proposed by Gardosi *et al* which also uses maternal ethnicity as a modifier [55]. These findings suggest that birth weight differences may be better explained in a context of placental function rather than ethnic/genetic influence.

Association of CPR with adverse outcomes in AGA fetuses

In recent years, an increasing number of studies investigate the association of CPR with adverse outcome in low-risk and/or AGA pregnancies [56-69]. Initially, it may appear unconventional to associate CPR with adverse outcome in apparently healthy pregnancies. However, as stated previously, EFW is a poor predictor of fetal well-being and most stillbirth cases are not suspected to be SGA during the antenatal assessment. Moreover, AGA stillbirth cases contribute to the majority of perinatal deaths even though they are classified as low risk compared to SGA babies. Therefore, it is more beneficial to investigate better markers of fetal well-being in apparently low-risk pregnancies. Current literature reports conflicting results regarding the value of CPR in AGA pregnancies. Most studies suggest an increased risk of intrapartum fetal compromise and operative delivery due to presumed compromise in AGA fetuses with low CPR (Table 2). Three most commonly reported associations of low CPR in AGA babies were increased risk of presumed fetal compromise, lower birth weight and lower gestational age at delivery. The estimated effects are relatively similar in the various published studies and are also consistent between blinded prospective studies and retrospective studies. However, the strength of association between CPR and

these outcomes is not strong enough to suggest preemptive cesarean section over a trial of labor, mainly due to the strong influence of intrapartum risk factors which are unknown antenatally. However, the association implies that CPR is beneficial in identifying a subgroup of AGA pregnancies at greater risk of fetal compromise and would merit closer intrapartum surveillance. Neonatal outcome measures such as admission to the neonatal unit or abnormal umbilical cord pH were inconsistently reported to be associated with low CPR in contrast to SGA babies. This heterogeneity in the reported association between CPR and short-term perintal outcomes could be explained by the confounding effect of intrapartum risk factors, variable diagnostic criteria of intrapartum fetal compromise and different intrapartum management protocols across centres. It is also plausible that the lower association of CPR with adverse neonatal outcomes in AGA than SGA fetuses could be explained by the fact that AGA fetuses are more resilient to metabolic stress compared to SGA fetuses. High-quality large prospective studies with consistent intrapartum protocols are needed to determine the place of CPR in the management of AGA fetuses. In the meantime, close intrapartum surveillance may be prudent in AGA fetuses with low CPR. Figure 3 summarizes the utility of CPR in SGA and AGA fetuses.

Conclusion

CPR appears to be a useful surrogate for suboptimal fetal growth and intrauterine hypoxia in suspected SGA fetuses. A low CPR value should prompt delivery at term (≥37 weeks' gestation) in suspected SGA fetuses and a close intrapartum surveillance in AGA fetuses. Although there are many proposed cut-offs for abnormal CPR, most of these cut-offs are associated with similar risk estimates as long as the used cut-off adjusts for gestational age (i.e. percentile or MoM). Future large randomized trials should help with discerning the role of CPR in the management late-onset FGR.

Key points

- A low cerebroplacental ratio (CPR) is associated with poor perinatal outcomes including stillbirth, perinatal death, low Apgar score, neonatal acidosis, admission to the neonatal care unit, intrapartum compromise, cesarean delivery and long-term neurocognitive impairment in suspected small-for-gestational age (SGA) fetuses.
- In fetuses deemed to be appropriate for gestational age (AGA), CPR is still associated with abnormal growth velocity, lower birth weight and increased rate of intrapartum fetal compromise.
- The stand-alone predictive value of CPR is unlikely to be sufficient for clinical use without using other antenatal and intrapartum variables in both SGA and AGA fetuses.

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Table 1. Cerebroplacental ratio as a marker of adverse perinatal outcomes in suspected small-for-gestational age (SGA) fetuses

Short-term adverse outcomes*	
Significant associations	**Non-significant associations**
- Perinatal death † (LR+: 3.9, 95 CI: 3.4-4.5)	Neonatal brain lesions (LR+: 1.1, 95% CI: 0.8-1.4)
NICU admission (LR+: 2.2, 95% CI: 1.9-2.5)	
Neonatal acidosis (LR+: 1.6, 95% CI: 1.3-2.0)	
Ventilation support (LR+: 1.5, 95% CI: 1.2-1.7)	
SGA at birth (LR+: 7.4, 95% CI: 2.5-22.4)	
Low Apgar score (<7) at 5th minute † (LR+: 1.9, 95% CI: 1.5-2.4)	
Cesarean section for presumed fetal compromise † (LR+: 2.3, 95% CI: 2.0-2.6)	
Composite adverse perinatal outcome † (LR+: 2.5, 95% CI: 2.3-2.8)	
Long-term adverse outcomes¶	
- Risk of motor and state organizational problems on Neonatal Behavioral Assessment Scale - Lower mean percentile scores in communication and problem solving at 2 years of age on the Ages and Stages Questionnaire - Lower cognitive functioning at 6-8 years regarding the following domains; verbal comprehension, perceptual reasoning, processing speed indices, full scale IQ, broad reading, written language and mathematics scores.	

*Adapted from meta-analyses of Conde-Agudelo *et al* and Vollgraff *et al* [41,42].

†Superior predictive accuracy compared to assessment with middle-cerebral artery Doppler alone according to Vollgraff *et al* [42].

¶Adapted from meta-analysis of Meher et al. and study of Bellido-Gonzalez *et al* [43,44].

IQ: intelligence quotient, NICU: neonatal intensive care unit, LR+: positive likelihood ratio

Table 2. Review of recent publications evaluating the utility of cerebroplacental ratio (CPR) in appropriate for gestational age (AGA) fetuses.

Author	Size of the study	Scan-delivery interval	Study type, CPR cut-off used	Significant findings between groups	Non-significant findings between groups
Chainarong *et al* [56].	384	~1 day (Prelabor)	Prospective cohort, blinded‡, <5th centile	Abnormal fetal heart traces (OR*: 2.99, 95% CI: 1.58-5.69), lower birth weight in grams (MD: -159 grams, 95% CI: -288.4 to -31 grams†)	Operative delivery, meconium stained liquor, NICU admission, low Apgar (<7 at 5th minute), SGA at birth
Dall'asta *et al* [57].	562	~1 day (Prelabor)	Prospective cohort, blinded, CPR MoM <10th centile	Operative delivery for fetal distress (OR: 3.42, 95% CI: 1.33-8.04), lower birth weight in grams (MD: -137 grams, 95% CI: -249.2 to -24.6 grams), cord arterial pH <7.10 (OR: 4.20, 95% CI: 1.11-13.48), composite adverse neonatal outcome (OR: 3.21, 95% CI: 1.00-8.86) and gestational age at delivery (MD: -5 days, 95% CI: -7 to -3 days)	Operative delivery due to dystocia, labor length, birth weight percentile, SGA at birth, low Apgar (<7 at 5th minute), cord arterial base excess>8, NICU admission or need for resuscitation
Atabay *et al* [61].	311	~1 day (Prelabor)	Prospective cohort, blinded, CPR<1.22	Operative delivery due to fetal distress (OR: 4.18, 95% CI: 1.32-12.18)	Not reported
Fratelli *et al* [59].	151	~1 day (Prelabor)	Prospective cohort, blinded, Continuous CPR without a cut-off	Not reported	Operative delivery due to distress, cord arterial pH <7.00
Morales-Rosello *et*	569	<4 weeks	Prospective cohort, CPR	Intrapartum fetal compromise (OR: 4.88, 95% CI: 2.59-9.16)	Not reported

al [60].			MoM <0.6765		
Khalil *et al* [6].	6793	<2 weeks	Retrospective cohort, CPR MoM <0.6765	Operative delivery due to fetal distress (OR: 1.54, 95% CI: 1.22-1.93)	Not reported
Flatley *et al* [58].	2093	<4 weeks	Retrospective cohort, CPR <10th centile	Delivery above 40 weeks' gestation (aOR: 0.53, 95% CI: 0.31–0.91), cesarean section for fetal distress (aOR: 2.42 ,95% CI: 1.52–3.85)	Instrumental delivery, neonatal acidosis Low Apgar (<3 at 1st minute), NICU admission, perinatal death, serious composite neonatal outcome
Bligh *et al* [63].	207	~1 to 2 weeks	Prospective cohort, blinded, CPR<20th centile	Serious composite neonatal outcome (PLR: 1.80, 95% CI: 1.16-2.80), cesarean section for fetal distress (PLR: 3.84, 95% CI: 3.04-4.86)	Not reported
Bligh *et al* [62].	437	<2 weeks	Prospective cohort, blinded, CPR<10th centile	Abnormal fetal heart rate trace (OR: 2.98 , 95% CI: 1.69-5.31), instrumental delivery due to fetal compromise (OR: 2.64, 95% CCI: 1.33-5.11), cesarean section due to fetal compromise (OR: 8.04, 95% CI: 2.73-24.53), gestational age at delivery, birthweight (median: -3 days), birth weight centile (median: -22 centile), composite adverse neonatal outcome (OR: 2.80, 95% CI: 1.48-5.21), cord blood gas abnormality (OR: 2.46, 95% CI: 1.05-6.47)	Meconium stained liquor, labor, duration, low Apgar (<7 at 5th minute) , NICU admission
Morales-Rosello *et al* [64].	2340	Variable	Retrospective cohort, continuous CPR without a cut-off	Not reported	Preterm birth
Ropacka-Lesiak *et al* [65].	148	2 weeks	Prospective, case-control, CPR<1.1	Abnormal fetal heart rate traces (OR: 6.95, 95% CI: 3.16-15.98), meconium stained liquor (OR: 2.71, 95% CI: 1.28-5.86), arterial cord pH (mean: -0.1, 95% CI: -0.15 to -0.05), arterial cord pH <7.2 (OR: 24.27, 95% CI: 5.64-219.81), adverse neonatal	SGA at birth

				outcome, low Apgar (<7 at 5th minute), birth weight (mean: -329 grams, 95% CI: -520 to -137 grams)	
Prior *et al* [66].	775	<3 days	Prospective cohort, blinded, CPR MoM <0.6765	Abnormal fetal heart rate traces (OR: 3.04, 95% CI: 1.58-5.76), cesarean section due to fetal compromise (4.54, 95% CI: 2.29-8.82), meconium stained liquor (OR: 2.24, 95% CI: 0.99-4.69), fetal compromise diagnosed at any time during labor (OR: 3.29, 95% CI: 1.75-6.27), birth weight in grams (mean: -181 grams), birth weight centile (median: -9.2 centile)	Low Apgar score (<7 at 1 and 5 minute), arterial cord pH <7.20, base excess <8 mmol/L, neonatal unit admission
Prior *et al* [35].	400	<3 days	Prospective cohort, blinded, CPR <10th centile	Abnormal fetal heart rate traces (OR: 15.44, 95% CI: 6.22-46.05), cesarean section due to fetal compromise (6.16, 95% CI: 2.79-13.39), meconium stained liquor (OR: 2.86, 95% CI: 1.16-6.63), fetal compromise diagnosed at any time during labor (OR: 5.22, 95% CI: 2.59-10.86), birth weight percentile (mean: -7 centile)	Birth weight, Low Apgar score (<7 at 1 and 5 minute), arterial cord pH <7.20, neonatal unit admission, composite neonatal outcome score
Morales-Rosello *et al* [4].	9939	<2 weeks	Retrospective cohort, continuous CPR without a cut-off	Lower birth weight centile	Not reported
Midga *et al* [67].	446	<2 weeks	Retrospective cohort, continuous CPR without a cut-off	Not reported	Low Apgar score (<7 at 5 minute), operative delivery
MacDonald *et al* [68].	308	~1 month	Prospective cohort, blinded, CPR<5th centile	Lower estimated fetal weight growth velocity (OR: 1.02, 95% CI: 1.01-1.04)	Lower abdominal circumference growth velocity
Bardien *et al* [69].	48	~1 month	Prospective cohort,	Change in customized estimated fetal weight centile between 28 weeks' gestation and birth	Not reported

			blinded, continuous CPR without a cut-off		

*Unadjusted odds ratios are reported for most studies.

†Confidence intervals for continuous outcomes were bootstrapped using statistics reported in respective articles

‡Blinding indicates attending physician and/or labor management team were blinded to the Doppler findings

MoM: multiple of median, MD: mean difference, OR: odds ratio, PLR: positive likelihood ratio, aOR: adjusted odds ratio, NICU: neonatal intensive care unit, SGA: small-for-gestational age, CI: confidence intervals

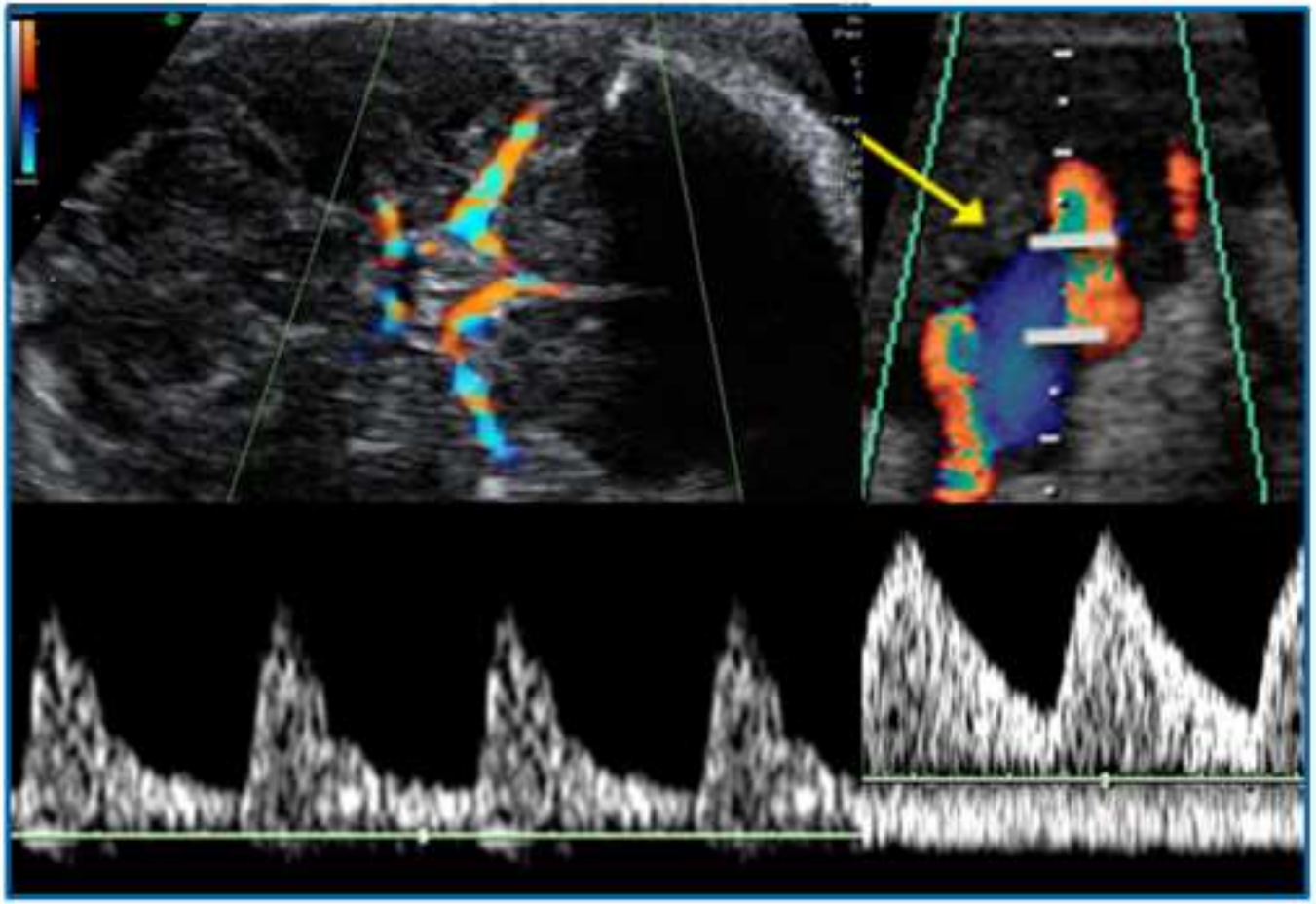
Figure legends

Figure 1. Ultrasound image demonstrating the umbilical artery and middle cerebral artery Doppler

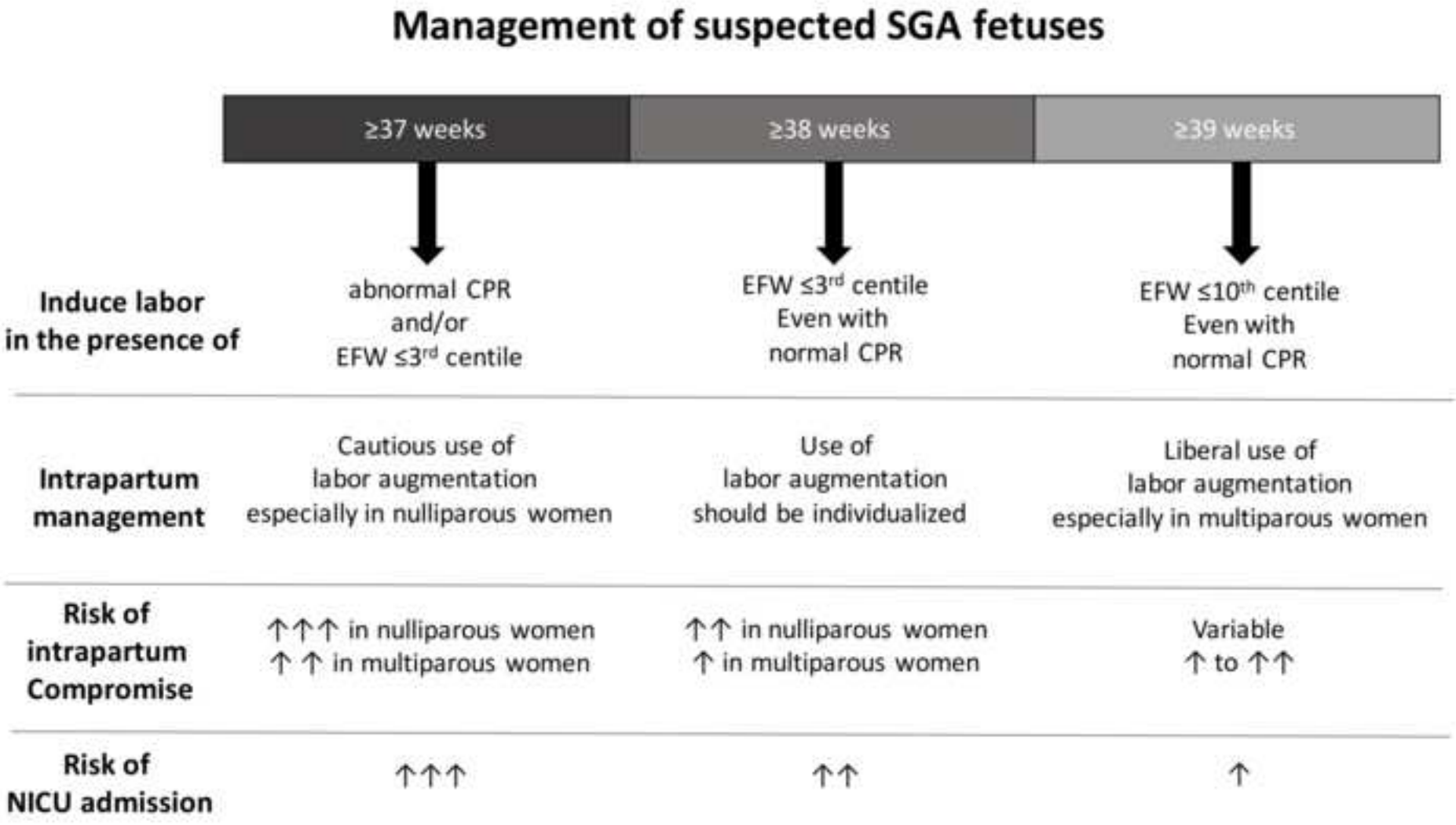
Figure 2. Management algorithm for suspected small-for-gestational age fetuses according to apparent peripartum risk

Figure 3. Infographic summarizing the utility of cerebroplacental ratio in appropriate-for-gestational age and small-for-gestational age fetuses

Ultrasound image demonstrating the umbilical artery and middle cerebral artery Doppler



Management algorithm for suspected small-for-gestational age fetuses according to apparent peripartum risk



Infographic summarizing the utility of cerebroplacental ratio in appropriate-for-gestational age and small-for-gestational age

AGA fetuses

Utility of CPR

- Studies consistently report an association with increased rates of operative delivery due to presumed fetal compromise and abnormal FHR traces during labor.

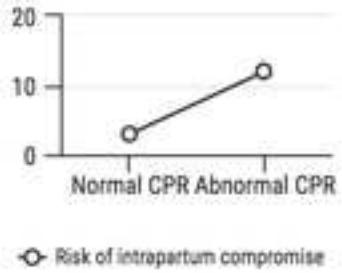
-Lower CPR values correspond to lower birth weight percentiles albeit within ranges considered to be normal (>10%).

-A weak predictor of adverse outcomes in unselected populations.

Fetuses with low CPR are at increased risk of

~10%

lower birth-weight centile



intrapartum compromise

SGA fetuses

Utility of CPR

- Better predictor for adverse outcome in late-FGR fetuses compared to other Doppler indices.

- Risk stratification is probable to determine the timing of delivery.

- Associated with adverse outcomes including abnormal FHR traces, operative delivery, admission to NICU, long-term neurocognitive impairment.

-Randomized trials are planned to determine clinical utility.

Fetuses with low CPR are at increased risk of

perinatal death

+

intrapartum compromise and NICU admission

long-term neurocognitive impairment

Kalafat E, Khalil A. Clinical significance of cerebroplacental ratio. Curr Opin Obstet Gynecol. 2018