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ORIGINAL ARTICLE

The risk of preterm birth associated with a low cerebroplacental ratio

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ABSTRACT

Objective: This paper investigated whether a cerebroplacental ratio (CPR) < 10th centile (measured between 23 + 0–36 + 0 weeks gestation) is predictive of any preterm birth, birth within 2 weeks of the ultrasound scan or spontaneous preterm birth.

Methods: This was a retrospective cohort study of 8977 women during 2014 and 2015 at a major tertiary referral hospital. Selection criteria included women who had a nonanomalous, singleton fetus and underwent an ultrasound scan between 23 + 0–36 + 6 weeks gestation.

Results: A low CPR increased the risk of preterm birth or birth within 2 weeks of the scan with the highest odds of birth within 2 weeks seen at 28-week gestation (odds ratio (OR) 3.78, 95%CI 1.63–8.77) – the mode of delivery was most likely emergency caesarean section for nonreassuring fetal status (aOR 2.11, 95%CI 1.69–2.64, $p < .001$). Neonatal outcomes were worse in the low CPR cohort particularly with higher odds of death (aOR 2.30, 95%CI 1.46–3.63) and composite adverse outcome (aOR 1.46, 95%CI 1.24–1.73). The low CPR cohort had a significantly shorter interval to delivery (Cox Proportional Hazard – aHR 1.41, 95%CI 1.33–1.51, $p < .001$) and earlier gestation at birth.

Conclusions: A low CPR is associated with an increased risk of preterm birth and birth within 2 weeks but not spontaneous preterm birth.

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Caesarean section; cerebroplacental ratio; fetal Doppler ultrasound; fetal growth restriction; preterm birth

Introduction

The cerebroplacental ratio (CPR) is the ratio of the MCA Pulsatility Index (MCA PI) to the UA Pulsatility Index (UA PI). It gradually rises until around the 34th week of gestation, and subsequently slowly declines until term [1]. Increased cerebral blood flow is a fetal adaptive response to hypoxia and this is reflected by a reduction in MCA resistance (decreased PI) and thereby a reduction in the CPR. A low CPR is associated with variety of adverse outcomes including an increased risk of stillbirth regardless of fetal weight or gestation [2], poor perinatal outcomes particularly in small for gestational age foetuses [3] and adverse neuro-behaviour sequelae in childhood [4]. We [5] and others [6] have established that the CPR is an independent predictor of intrapartum fetal compromise, acidosis at birth and neonatal unit admission in babies that are not SGA. A low CPR thus is an important marker of whether a fetus is failing to reach its growth potential even within the normal birthweight range (ie non-SGA) [7,8].

The association between cerebral redistribution and/or a low CPR and preterm birth is confounded by the fact that many studies have included fetuses with growth restriction in their study cohorts which often confounds the results because of the higher rate of iatrogenic preterm delivery. Furthermore the evidence for an association between a low CPR and spontaneous preterm birth is very limited with only a small number of studies published in this area [9–11].

The aim of this study therefore was to evaluate firstly the association between a low CPR and the overall risk for preterm birth and secondly the risk for spontaneous preterm birth in an unselected cohort of women attending for care in a tertiary centre.

Materials and methods

This was a retrospective cohort study of 8977 women who birthed at the Mater Mothers' Hospital in Brisbane, Australia between January 2014 and December 2015. Inclusion criteria required a nonanomalous singleton fetus and only patients who underwent an ultrasound scan between 23 + 0–36 + 6 weeks gestation. Recorded data for both the MCA PI and UA PI enabled calculation of the CPR and only cases with

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positive end diastolic flow in the umbilical artery were included. The Mater Mothers' Hospital is a major tertiary centre in the state of Queensland and the largest maternity hospital in Australia. Previous prospectively collected maternal demographic data was cross-referenced against the institution's ultrasound and neonatal databases to correlate outcomes. The study protocol was assessed and approved by the hospital's Human Research Ethics Committee (reference number HREC/14/MHS/37).

Indications for the ultrasound scans were varied and included those for maternal medical conditions (diabetes, hypertension etc.), concerns about fetal size following clinical assessment, previous fetal growth restriction or macrosomia, previous adverse pregnancy outcome, placental site localisation or simply for maternal reassurance.

Demographic data collected included maternal age, parity, body mass index (BMI), ethnicity (Caucasian, Asian, Indigenous, Indian or other), smoking status and maternal medical conditions (diabetes, thyroid disease, hypertension). Indigenous ethnicity refers to patients identifying as being of Aboriginal or Torres Strait Islander origin. Gestational age was calculated using the last menstrual period or earliest ultrasound examination or by correlation with both. Doppler parameters were recorded in the absence of fetal breathing movements. An automated tracing method incorporating at least three waveforms was employed and repeated three times to obtain the mean PI. The angle of insonation was maintained at $<30^{\circ}$. The MCA, either right or left, depending on waveform quality, was imaged using colour Doppler and its waveform recorded from the proximal third of the vessel, distal to its origin at the circle of Willis. The UA Doppler waveforms were recorded from a free loop of cord. The CPR was calculated by dividing the MCA PI by the UA PI. A low CPR was defined as <10th centile for gestation.

Outcomes analysed included any preterm birth (defined as birth <37 weeks gestation), birth within 2 weeks of the ultrasound scan and spontaneous preterm birth. Other outcomes included the gestation at birth, mode of, and indication for delivery and proportion of pregnancies induced. Neonatal outcomes included birth weight, admission to the Neonatal Intensive Care Unit (NICU), respiratory distress, Apgar score <7 at 5 minutes, severe acidosis (defined as pH $\leq$7.0 or lactate $\geq$6 mmol/L or base excess < -12 mmol/L) and death. A composite adverse neonatal outcome was defined as a composite measure of any of death or admission to the neonatal intensive care unit (NICU) or Apgar score <7 at 5 minutes or severe acidosis.

Statistical analysis

Wilcoxon Rank Sum tests were used for comparisons of medians where data showed a skewed distribution and t test was used for comparisons of means between groups for parametric data. Proportions were compared using chi-square test or z test for two proportions. Spearman's rank correlation coefficients were used to assess for correlations between continuous variables. Statistics are reported as mean (SD) or median (interquartile range (IQR)) for normally and non-normally distributed variables respectively or as the number of observations with the percentage of total. Univariate analysis was performed using logistic regression with odds ratio (OR) and Cox proportional hazards with hazard ratios and 95% confidence intervals reported. Multivariate analysis was performed adjusting for estimated fetal weight and gestation at birth where appropriate. Data were analysed using Stata v14 (StataCorp. 2015. *Stata Statistical Software: Release 14*. College Station, TX: Stata Corp LP). Statistical significance was defined as $p < .05$.

Results

During the study period, 8977 women met the inclusion criteria. Of these 17.9% (1609/8977) of women had preterm births. Women that had spontaneous preterm birth comprised 19.8% (479/1609), whilst those that had iatrogenic preterm delivery for various indications consisted of the remaining 70.2% (1130/1609) preterm cohort. Of the total study cohort, 14.1% (1266/8977) of women had a fetal CPR <10th centile. Maternal demographics of the entire study cohort are reported in Table 1. Spearman's Rho showed that the CPR was correlated with estimated fetal weight and gestational age at birth (Figure 1a and 1b). The CPR

Table 1. Maternal Demographics.

	CPR <10th Centile ($n = 1,266$)	CPR ≥10th Centile ($n = 7,711$)	p Value
Age[a]	Mean =31.3 (± 5.8)	31.4 (± 5.7)	.90
BMI[b]	23.6 (20.6–28.6)	24.0 (20.8–29.3)	.04
Ethnicity			
Caucasian[§]	59.1% (748/1266)	56.4% (4352/7711)	.08
ASTI[§]	3.5% (44/1266)	3.3% (253/7711)	.72
Indian[§]	7.4% (93/1266)	7.0% (543/7711)	.70
Asian[§]	13.0% (165/1266)	14.9% (1149/7711)	.08
Other[§]	17.0% (215/1266)	18.3% (1411/7711)	.26
Nulliparous[§]	49.1% (621/1265)	39.9% (3077/7709)	<.001
Diabetes[§]	23.9% (302/1266)	27.7% (2133/7711)	.01
Thyroid disease[§]	9.2% (117/1266)	7.5% (577/7711)	.03
Smoking[§]	17.0% (215/1266)	14.8% (1144/7711)	.048
Hypertension[§]	9.9% (125/1266)	10.9% (842/7711)	.27
Preterm birth (<37 weeks)			

CPR: Cerebro–Placental Ratio; BMI: body Mass Index; ATSI: Aboriginal and Torres Strait Islander.
[a]t-test; [b]Wilcoxon Rank Sum; [§]Chi square.

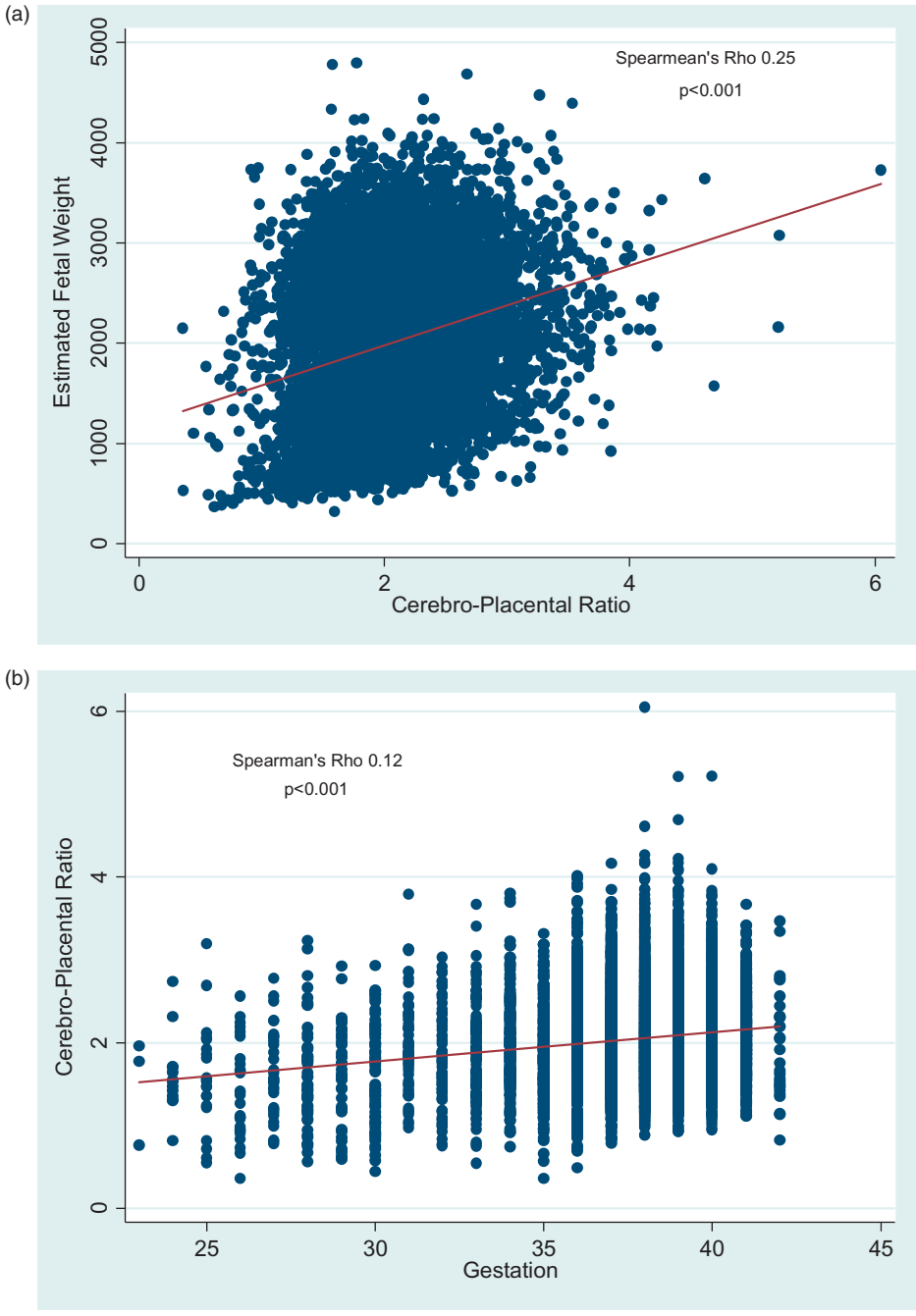

Figure 1 (a) Relationship between Cerebroplacental Ratio and Estimated Fetal Weight, (b) Relationship between Cerebroplacental Ratio and Gestation.

<10th centile cohort was more likely to be nulliparous, have thyroid disease and be smokers, and less likely to have diabetes mellitus. Table 2 details the maternal demographics of women who birthed within 2 weeks of the ultrasound scan in the <10th centile cohort. In this group, there was a higher proportion of women who were nulliparous (55.5 versus 46.6%, OR 1.43, 95%CI 1.12–1.83, $p = .01$) and who had hypertension (15.1 versus 7.8%, OR 2.09, 95%CI 1.44–3.05, $p < .001$).

Table 3 shows the gestation at ultrasound stratified for CPR threshold and the odds for preterm birth or birth within 2 weeks of the ultrasound scan. A low CPR was clearly associated with increased odds of preterm birth from 24-week gestation onwards. After adjusting for estimated fetal weight, the greatest odds of birth within 2 weeks of ultrasound scan was at 28-week gestation (aOR 3.78, 95%CI 1.63–8.77) and a clear association from 32-week onwards.

Table 4 demonstrates the odds of spontaneous preterm birth according to the CPR. There was no difference in the risk of spontaneous preterm birth between both cohorts. After adjusting for estimated fetal

Table 2. Odds Ratio of being born preterm if CPR <10th centile by gestation at ultrasound scan.

Gestation at USS	CPR <10th centile	CPR ≥10th centile	OR (95%CI)	*p* Value	OR of birth within 2 weeks of USS (95%CI)	*p* Value	Adjusted OR of birth within 2 weeks of USS (95%CI)[a]	*p* Value
23 weeks	33.3% (7/21)	29.0% (54/186)	1.22 (0.47–3.20)	.68	2.34 (0.46–11.84)	.30	1.49 (0.26–8.38)	.65
24 weeks	32.3% (21/65)	19.4% (94/485)	1.98 (1.13–3.50)	.02	2.98 (1.12–7.92)	.03	1.80 (0.59–5.54)	.30
25 weeks	62.2% (23/37)	36.0% (54/150)	2.92 (1.39–6.14)	.01	3.17 (1.19–8.45)	.02	0.68 (0.16–2.88)	.61
26 weeks	65.8% (25/38)	35.0% (48/137)	3.57 (1.67–7.60)	.001	3.93 (1.68–9.19)	.002	1.64 (0.49–5.51)	.42
27 weeks	41.8% (23/55)	29.5% (83/281)	1.71 (0.95–3.11)	.08	2.55 (1.09–5.95)	.03	1.31 (0.47–3.64)	.60
28 weeks	31.7% (38/120)	18.2% (131/719)	2.08 (1.35–3.19)	<.001	8.76 (4.47–17.17)	<.001	3.78 (1.63–8.77)	.002
29 weeks	37.5% (24/64)	21.1% (63/299)	2.25 (1.26–4.00)	.01	4.51 (2.05–9.94)	<.001	2.52 (0.82–7.70)	.11
30 weeks	41.5% (22/53)	20.9% (82/392)	2.68 (1.48–4.88)	.001	4.20 (1.91–9.22)	<.001	2.51 (0.99–6.34)	.052
31 weeks	30.4% (24/79)	19.8% (86/435)	1.77 (1.04–3.02)	.04	2.18 (1.05–4.56)	.04	1.39 (0.58–3.35)	.46
32 weeks	23.6% (35/148)	13.4% (130/968)	2.00 (1.31–3.04)	.001	4.27 (2.50–7.29)	<.001	2.75 (1.46–5.18)	.002
33 weeks	37.8% (37/98)	18.1% (98/541)	2.74 (1.73–4.36)	<.001	3.87 (2.23–6.70)	<.001	2.38 (1.21–4.67)	.01
34 weeks	27.9% (41/147)	13.5% (126/931)	2.47 (1.65–3.71)	<.001	2.89 (1.87–4.45)	<.001	2.66 (1.65–4.28)	<.001
35 weeks	31.9% (44/138)	15.0% (119/792)	2.65 (1.76–3.98)	<.001	2.48 (1.72–3.59)	<.001	1.89 (1.25–2.88)	.003
36 weeks	12.3% (25/203)	3.7% (52/1395)	3.63 (2.20–5.99)	<.001	2.07 (1.53–2.78)	<.001	2.15 (1.57–2.94)	<.001

OR: Odds Ratio; CI: Confidence Interval; USS: Ultra Sound Scan; CPR: cerebroplacental ratio.
[a]Adjusted for Estimated Fetal Weight.

Table 3. Neonatal outcomes.

	CPR <10th Centile (*n* = 1266)	CPR >10th Centile (*n* = 7711)	OR (95%CI)	*p* Value	Adjusted OR (95%CI)[a]	*p* Value
Method of birth						
SVD	44.5% (563/1266)	48.8% (3765/7711)	0.84 (0.74–0.95)	.004	0.95 (0.84–1.08)	.45
Instrumental	9.9% (125/1266)	11.4% (880/7711)	0.85 (0.70–1.04)	.11	1.00 (0.81–1.23)	.99
Elective CS	17.1% (216/1266)	19.9% (1537/7711)	0.83 (0.71–0.97)	.02	0.83 (0.71–0.98)	.03
Em CS	28.6% (362/1266)	19.8% (1529/7711)	1.62 (1.42–1.85)	<.001	1.26 (1.08–1.46)	.003
Em CS NRFS	10.7% (135/1266)	4.9% (375/7711)	2.34 (1.90–2.87)	<.001	2.11 (1.69–2.64)	<.001
Em CS "other"	17.9% (227/1266)	15.0% (1154/7711)	1.24 (1.06–1.45)	.01	0.92 (0.77–1.10)	.38
IOL	59.9% (518/865)	54.3% (3110/5724)	1.25 (1.08–1.45)	.002	1.23 (1.06–1.44)	.01
NICU	25.5% (323/1266)	14.4% (1113/7711)	2.03 (1.76–2.34)	<.001	1.36 (1.14–1.63)	.001
Respiratory Distress	26.5% (336/1266)	16.5% (1271/7711)	1.83 (1.59–2.10)	<.001	1.17 (0.98–1.39)	.09
Apgar <7 at 5 minutes	6.3% (78/1248)	3.2% (245/7651)	2.02 (1.55–2.62)	<.001	1.49 (1.10–2.01)	.01
Acidosis	2.8% (35/1266)	2.0% (152/7711)	1.41 (0.97–2.05)	.07	1.37 (0.92–2.05)	.12
Death	3.2% (40/1266)	0.9% (70/7711)	3.56 (2.40–5.28)	<.001	2.30 (1.46–3.63)	<.001
Composite neonatal outcome	29.9% (378/1266)	16.7% (1288/7711)	2.12 (1.86–2.43)	<.001	1.46 (1.24–1.73)	<.001

SVD: Spontaneous Vaginal Delivery; Em: Emergency; CS: Caesarean; NRFS: NonReassuring Fetal Status; NICU: Neonatal Intensive Care Unit; IOL: Induction of Labour; CPR: cerebroplacental ratio; OR: odds ratio.
[a]Adjusted for Estimated Fetal Weight and Gestation.
Composite neonatal outcome: Acidosis, NICU Admission, Death, Apgar score <7 at 5 Minutes.

Table 4. Spontaneous preterm birth if CUR <10th centile by gestation at ultrasound scan.

Gestation at USS	<10th centile	>10th centile	OR (95%CI)	*p* Value	Adjusted OR[a]	*p* Value
23 weeks	28.6% (2/7)	25.0% (15/60)	1.20 (0.21–6.84)	.84	1.19 (0.21–6.87)	.84
24 weeks	12.5% (2/16)	22.4% (36/161)	0.50 (0.11–2.28)	.37	0.48 (0.11–2.25)	.36
25 weeks	36.4% (4/11)	41.1% (23/56)	0.82 (0.21–3.13)	.77	0.63 (0.15–2.72)	.54
26 weeks	62.5% (5/8)	40.0% (18/45)	2.50 (0.53–11.79)	.25	2.36 (0.46–12.19)	.31
27 weeks	50.0% (7/14)	30.4% (24/79)	2.29 (0.72–7.25)	.16	2.07 (0.62–6.89)	.23
28 weeks	21.4% (6/28)	19.8% (51/258)	1.11 (0.43–2.87)	.84	0.93 (0.34–2.59)	.89
29 weeks	21.1% (4/19)	20.4% (21/103)	1.04 (0.31–3.47)	.95	1.11 (0.28–4.36)	.88
30 weeks	33.3% (6/18)	19.9% (26/131)	2.02 (0.69–5.89)	.20	1.47 (0.48–4.51)	.50
31 weeks	21.7% (5/23)	17.5% (25/143)	1.31 (0.44–3.86)	.62	1.23 (0.40–3.78)	.72
32 weeks	10.3% (4/39)	14.7% (51/347)	0.66 (0.23–1.95)	.46	0.63 (0.21–1.87)	.41
33 weeks	35.7% (10/28)	19.8% (38/192)	2.25 (0.96–5.27)	.06	1.45 (0.53–3.95)	.47
34 weeks	10.9% (5/46)	11.2% (38/340)	0.97 (0.36–2.60)	.95	1.08 (0.40–2.93)	.89
35 weeks	24.3% (9/37)	12.8% (33/258)	2.19 (0.95–5.05)	.07	1.46 (0.56–3.85)	.44
36 weeks	1.9% (1/53)	2.3% (10/441)	0.83 (0.10–6.61)	.86	0.65 (0.08–5.25)	.68
Total	20.2% (70/347)	15.6% (409/2614)	1.36 (1.03–1.81)	.03	1.15 (0.85–1.57)	.37

OR: Odds Ratio; 95%CI: 95% Confidence Interval; USS: Ultrasound Scan.
[a]Adjusted for Estimated Fetal Weight.

weight there was no difference in the odds ratio between the CPR cohorts. Table 5 details the intrapartum and neonatal outcomes stratified for CPR. After controlling for gestation at birth and estimated fetal weight, the CPR <10th centile cohort had higher odds for emergency caesarean section (aOR 1.26, 95%CI 1.08–1.46, $p = .003$) and particularly for emergency caesarean section for nonreassuring fetal status (aOR

Table 5. Maternal demographics of CPR <10th centile cohort delivering within 2 weeks of ultrasound scan.

	Birth ≤2 weeks of USS ($n = 358$)	Birth ≥2 weeks of USS ($n = 908$)	OR (95% C.I.)	p Value
Age	31.1 ± 5.8	31.4 ± 5.8	0.99 (0.97–1.01)	.35
BMI	23.9 (20.8–29.0)	23.4 (20.6–28.3)	1.00 (0.99–1.02)	.51
Ethnicity				
Caucasian	60.1% (215/358)	58.7% (533/908)	1.06 (0.82–1.36)	.66
ASTI	3.1% (11/358)	3.6% (33/908)	0.84 (0.42–1.68)	.62
Indian	8.9% (32/358)	6.7% (61/908)	1.36 (0.87–2.13)	.17
Asian	12.0% (43/358)	13.4% (122/908)	0.88 (0.61–1.27)	.50
Other	15.6% (56/358)	17.5% (159/908)	0.87 (0.63–1.22)	.43
Nulliparous	55.5% (198/357)	46.6% (423/908)	1.43 (1.12–1.83)	.01
Diabetes	22.1% (79/358)	24.6% (223/908)	0.87 (0.65–1.16)	.35
Thyroid disease	8.9% (32/358)	9.4% (85/908)	0.95 (0.62–1.46)	.82
Smoking	18.2% (65/358)	16.5% (150/908)	1.12 (0.81–1.55)	.49
Hypertension	15.1% (54/358)	7.8% (71/908)	2.09 (1.44–3.05)	<.001
Labour Induced	65.0% (119/183)	58.5% (399/682)	1.32 (0.94–1.85)	.11

CPR: Cerebro–Placental Ratio; BMI: body Mass Index; ATSI: Aboriginal and Torres Strait Islander; USS: Ultrasound Scan; OR: Odds Ratio; CI: Confidence interval.

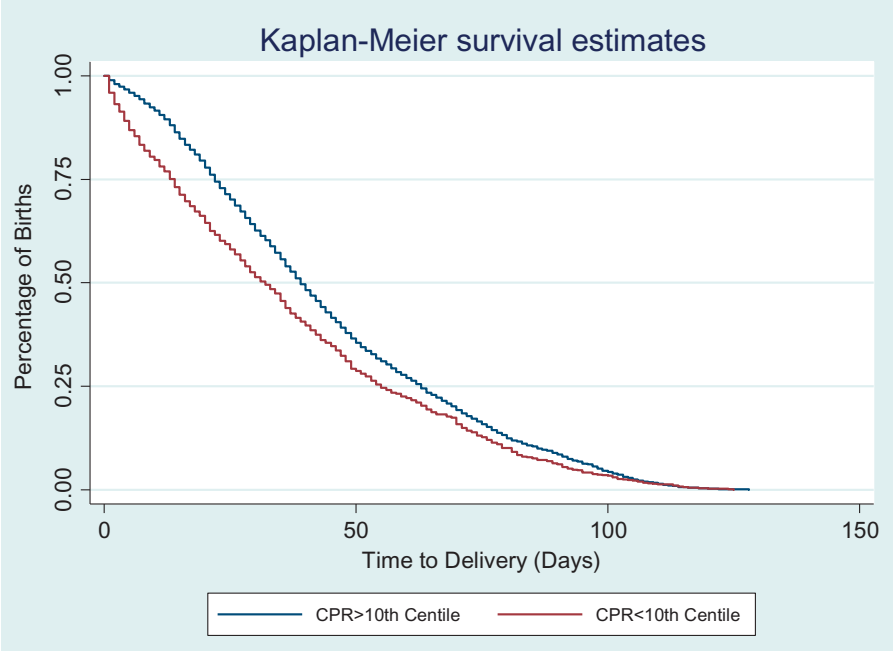

Figure 2. Kaplan–Meier survival curve depicting latency to delivery. Cox Proportional Hazard - HR 1.41, 95%CI 1.33–1.51, $p < .001$.

2.11, 95%CI 1.69–2.64, $p < .001$). The odds for induction of labour (IOL) was also increased in the <10th centile cohort (aOR1.23, 95%CI 1.06–1.44). Neonatal outcomes were worse in the low CPR cohort particularly with higher odds of death (aOR 2.30, 95%CI 1.46–3.63) and composite adverse outcome (aOR 1.46, 95%CI 1.24–1.73).

Kaplan-Meier survival curve analysis revealed a significantly shorter interval to delivery in the CPR <10th centile cohort compared to the CPR ≥10th centile group (Cox Proportional Hazard – aHR 1.41, 95%CI 1.33–1.51, $p < .001$) (Figure 2) and earlier gestation at birth after adjusting for estimated fetal weight (Cox Proportional Hazard – aHR 1.21, 95% C.I. 1.13–1.28, $p < .001$) (Figure 3).

Discussion

Our results demonstrate a correlation between the CPR and gestational age at birth and further show that the overall risk of preterm birth or birth within 2 weeks of the CPR measurement is increased in fetuses with a CPR <10th centile after controlling for EFW. We also found that in the cohort with a low CPR that delivered within 2 weeks, there was an increased prevalence of hypertension as well as an increased rate of IOL. However, in contrast to other publications [9] our results indicate that there is no increased risk of spontaneous preterm birth in the low CPR cohort. Consistent with other publications [1,12,13] we found an increased risk of emergency caesarean section for

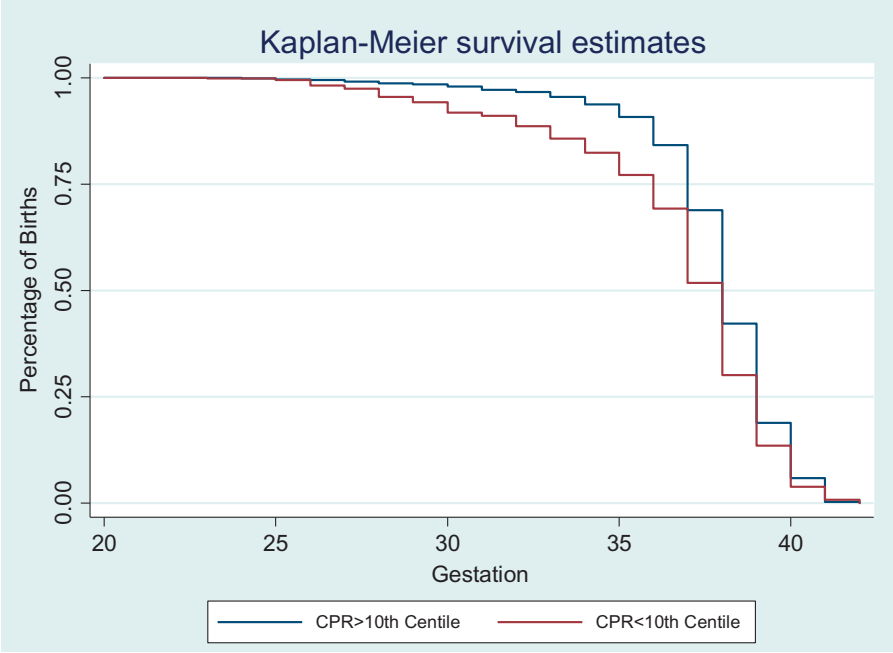

Figure 3. Kaplan–Meier survival curve depicting gestation at birth. Cox Proportional Hazard – HR 1.21, 95%CI 1.13–1.28, $p < .001$.

fetal compromise as well as poorer neonatal outcomes in this group.

Warshak et al. [14] showed that in a cohort of fetuses with suspected growth restriction, a low CPR was not only associated with a higher risk of delivery before 32 weeks (aOR 5.2, 95%CI 2.85–9.48) but also birth within 2 weeks of the ultrasound (aOR 4.76, 95% CI 2.32–9.76). These investigators suggest that the CPR is useful in discriminating between fetuses with suspected growth restriction most at risk earlier delivery from those with a longer latency before delivery. Our results also support these findings and conclusions.

The lack of association between a low CPR and spontaneous preterm birth suggest that the reason for preterm birth in the majority of cases is iatrogenic, probably as a consequence of either a fetal (deterioration in fetal condition) or maternal indication (eg worsening hypertension). Furthermore, after adjusting for the confounding effects of gestation at birth and fetal weight, a low CPR remained associated with an increased odds of poor neonatal outcomes. Karslen et al. [15] in a smaller study of 227 women at risk of fetal growth restriction showed that the risk of preterm birth was increased following a low CPR (defined as <5th centile or <10th centile) measured from 24-week gestation. In their study, using a threshold of <10th centile (based on either conventional or conditional centiles) resulted in an increased risk for preterm birth (RR 5.7, 95%CI 3.3–9.9 for conventional centiles and RR 7.1, 95%CI 4.2–12.2 for conditional centiles).

We have previously shown that a greater magnitude of change of the CPR from 30–37 weeks gestation was associated with an increased risk of preterm birth [1]. The results of our current study extend this finding to a much earlier gestation. Knowledge of the risk of preterm birth can assist in clinical management particularly when deciding the need for in-patient care, transfer to a tertiary centre or timing of antenatal corticosteroid administration.

The strengths of our study include the large number of cases with comprehensive ultrasound and pregnancy outcome data. We also analysed the risk of preterm birth according to the CPR measured at the final ultrasound scan before birth stratified by weekly scan intervals thus making our results clinically relevant. For clinicians the risk of spontaneous preterm birth is an obvious consideration in obstetric management and our findings of the lack of association between a low CPR and spontaneous preterm delivery will influence clinical management. The limitations of this study include those inherent to its retrospective nature. The study cohort was clearly not an unselected population with ultrasound scans performed for various clinical indications including previous obstetric history, maternal medical conditions such as diabetes or hypertension, suboptimal fetal growth or concerns about fetal size.

In conclusion, our results demonstrate that a CUR <10th centile is predictive of preterm birth (but not spontaneous preterm delivery), emergency caesarean section for nonreassuring fetal status and adverse neonatal outcome.

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