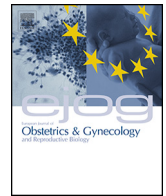




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Full length article

## A low fetal cerebroplacental ratio confers a greater risk of intrapartum fetal compromise and adverse neonatal outcomes in low risk multiparous women at term<sup>☆</sup>

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## ABSTRACT

**Background:** A low fetal cerebroplacental ratio (CPR) and nulliparity have independently been shown to be associated with adverse obstetric and perinatal outcomes.

**Objectives:** To assess the effect of parity on the CPR and investigate the utility of a CPR threshold of <10<sup>th</sup> centile for predicting adverse outcomes. We hypothesised that nulliparous women would have a lower CPR than multiparous women, impacting the diagnostic performance of the <10<sup>th</sup> centile threshold. This is an important consideration for interpretation of a low CPR in clinical practice.

**Study Design:** This was a retrospective cohort study of low risk, singleton pregnancies delivering at term in Australia's largest maternity hospital. The primary outcome was emergency caesarean section for intrapartum fetal compromise (EmCS IFC). Data was dichotomised according to parity and further by CPR <10<sup>th</sup> centile. Multiple logistic regression was performed.

**Results:** 4737 women were included for analysis, 2333 were nulliparous and 2404 were multiparous. Overall the z-score (mean [SD])(CPR standardised for gestation) was lower in nulliparous compared to multiparous women (−0.16 [−1.73 – 1.42] vs 0.04 [−1.63 – 1.69], p < 0.001). Multiparous women had a non-significantly lower mean z-score for those who delivered by EmCS IFC than nulliparous women (−0.52 [−2.23 – 2.02] vs −0.45 [−2.22 – 1.1]).

Nulliparous women had greater odds of having a CPR <10<sup>th</sup> centile compared to the multiparous cohort (OR 1.24, 95% CI 1.02–1.5 vs. OR 0.81, 95% CI 0.7–0.98, p < 0.001). A CPR threshold <10<sup>th</sup> centile in nulliparous women was associated with increased odds of intrapartum fetal compromise (IFC), EmCS IFC (aOR 1.72, 95% CI 1.2–2.6, p < 0.05) and birthweight <10<sup>th</sup> centile. A low CPR in multiparous women was associated with increased odds of all adverse perinatal outcomes measured: IFC, meconium stained liquor, EmCS IFC (aOR 4.99, 95% CI 2.5–9.9, p < 0.001), birthweight <10<sup>th</sup> centile, acidosis, neonatal intensive care admission and severe composite neonatal outcome. These aORs were associated with specificities of >90% and false positive rates of <10% for all outcomes in multiparous women.

**Conclusions:** A CPR <10<sup>th</sup> centile in multiparous women confers greater odds of adverse perinatal outcomes and as such of the influence of parity should be taken into account when decisions regarding clinical management are made because of a low CPR.

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### Introduction

Uterine contractions in labour are associated with a 60% reduction in placental blood flow and whilst the majority of fetuses are able to cope with this lower perfusion, those that are unable to do so are at risk of intrapartum hypoxia [1,2]. Although fetal growth restriction is a major risk factor for intrapartum compromise, there is now good evidence to suggest that some apparently normally grown fetuses are also at increased risk. These fetuses have evidence of cerebral redistribution, similar to that seen in their growth restricted

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counterparts rendering them vulnerable to adverse obstetric and perinatal outcomes [3–7]. Cerebral redistribution in these fetuses is reflected by a low cerebroplacental ratio (CPR) [ratio of the fetal Middle Cerebral Artery Pulsatility index (MCA PI) to the Umbilical Artery Pulsatility Index (UA PI)], which is now believed to be a reliable surrogate marker of suboptimal fetal growth [8–10].

A low CPR is associated with a number of adverse outcomes including operative birth for intrapartum fetal compromise (IFC), low birth weight, Neonatal Intensive Care Unit (NICU) admission [11,12], meconium-stained liquor, non-reassuring fetal heart rate patterns, low Apgar scores, acidosis and perinatal mortality [13].

Concurrent with studies demonstrating an association between aberrant fetoplacental Doppler changes and adverse outcomes there are also considerable data showing that nulliparity is strongly associated with complications related to placental dysfunction including pre-eclampsia [14], stillbirth [15], fetal growth restriction [16] as well as emergency operative delivery for IFC [17] and adverse neonatal outcomes [18–20].

The aim of this study thus was to, firstly, assess the influence of parity on the CPR and secondly, ascertain if the utility of a low CPR (CPR <10<sup>th</sup> centile) for predicting emergency caesarean for IFC and adverse neonatal outcomes differed in nulliparous compared to multiparous women.

## Methods

Data from low risk women with singleton pregnancies, delivering at term, between 2010 and 2017 at the Mater Mothers' Hospital, Brisbane were analysed. This is Australia's largest maternity hospital with an annual birth rate of approximately 10,500 births. This study was approved by the hospital's Human Research Ethics Committee (Ref no. HREC/14/MHS/37). Low risk pregnancy was defined as the absence of the following: multiple pregnancy, known genetic syndromes or congenital fetal malformations, small for gestational age/intrauterine growth restriction (defined as estimated fetal weight <10<sup>th</sup> centile on ultrasound scan, with or without fetal Doppler changes), pre-existing or gestational diabetes mellitus, renal disorders, hypertension, smoking, maternal age <18 or >40 years or BMI > 40 kg/m<sup>2</sup>. These variables are known to confer a greater risk of intrapartum fetal compromise. Women were excluded from the study if they did not have recorded ultrasound data for both the MCA PI and UA PI measured at ≥32 weeks gestation. Gestational age was calculated from either the last menstrual period or the earliest obstetric ultrasound scan. If a woman underwent >1 ultrasound scan, the last Doppler indices prior to delivery was used.

The fetal MCA was first imaged using colour Doppler and the waveform then recorded from the proximal third of the vessel, distal to its origin at the circle of Willis [21]. 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. The gestation specific 10<sup>th</sup> centile CPR threshold was defined according to previously published data [7,22,23]. Intrapartum fetal heart rate patterns were classified by the treating birth suite obstetric team according to criteria detailed in the Royal Australian and New Zealand College of Obstetricians and Gynaecologists' guidelines [24]. These are not dissimilar to those used in the United Kingdom [25] and North America [26]. The diagnosis of IFC was made contemporaneously by the treating Obstetrician based on abnormal fetal heart rate patterns and/or high fetal scalp lactate levels (>4 mmol/L). The primary outcome measure was Emergency caesarean section for IFC (EmCS IFC). Secondary outcomes included IFC, meconium stained liquor (MSL), birthweight, gestation specific birthweight <10<sup>th</sup> centile, [27], neonatal sex, severe acidosis (defined as umbilical artery pH ≤ 7.0 or Base Excess ≤ -12 mmol/L, or lactate ≥ 6 mmol/L), Apgar score ≤ 3 at 5 min, admission to NICU and perinatal death (neonatal death and

stillbirth). Serious composite neonatal outcome (SCNO) was defined as a composite of admission to NICU, severe acidosis, Apgar score ≤ 3 at 5 min and perinatal death. Data was dichotomised according to parity (P0 vs ≥ P1) and further by CPR (<10<sup>th</sup> vs. ≥10<sup>th</sup> centile).

## Statistical analysis

Generalized Estimating Equations (GEE) were used to adjust for the correlation between women who birthed more than once within the study period. Multiple GEE regression adjusting for birthweight, gestation at delivery and maternal age was used to generate adjusted odds ratios (aOR), false positive rates (FPR), positive likelihood ratios (PLR), sensitivity and specificity as well as the area under the receiver operating characteristic curves (AUROC) for the outcomes of interest.

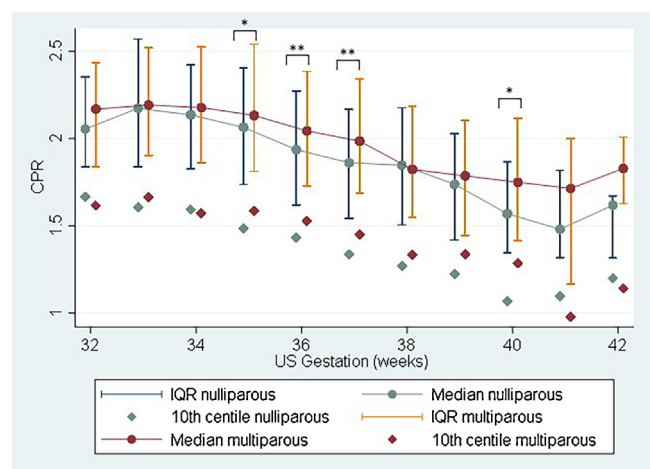
Individual CPR values were standardised by calculating z-scores against previously published gestation-specific reference centiles [23]. This allowed for comparison, using the students t-test, of z-score between those who had an adverse outcome compared to those who did not (mean, [SD]) as well as a comparison between nulliparous and multiparous women.

Statistical analysis was performed using Stata SE<sup>®</sup>, Release 15, for Windows (StataCorp LP, College Station, TX, USA) and R versions 3.1.1 (R core team 2014) R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria, URL <http://www.R-project.org/>). Statistical significance was defined as  $p < 0.05$ .

## Results

A total of 4737 women were included in the analysis – 2333 were nulliparous (P0) and 2404 were multiparous (≥P1). The CPR 10<sup>th</sup> centile values were significantly different at all gestation points ( $p < 0.001$ ) between nulliparous and multiparous women. (Table 3) (Fig. 1)

Of these, 284 (12.2%) nulliparous women and 223 (9.3%) multiparous women had a CPR <10<sup>th</sup> centile. Median maternal age, BMI and birthweight were different between the two cohorts according to parity (30 years vs. 32 years, 21.8 kg/m<sup>2</sup> vs. 22.9 kg/m<sup>2</sup> and 3240 g vs. 3370 g respectively,  $p < 0.001$ ). For nulliparous



**Fig. 1.** CPR median, IQR and 10<sup>th</sup> centile threshold by ultrasound gestation and parity.

This figure demonstrates the differences in CPR values between nulliparous and multiparous women at different ultrasound gestations ( $p < 0.05$  at 35, 36, 37 and 40 weeks gestation) and the differences in 10<sup>th</sup> centile threshold at each gestation ( $p < 0.001$  at every gestation).

CPR, cerebroplacental ratio; US gestation, ultrasound gestation; IQR, interquartile range. \*  $p < 0.05$ ; \*\*  $p < 0.001$ .

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