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## Assessment of reproducibility and repeatability of cerebro-placental ratio

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## ABSTRACT

*Introduction:* To test the reproducibility and repeatability of the cerebro-placental ratio.*Study design:* Pregnant women with a singleton pregnancy and secure dating were invited to participate after 24 weeks of pregnancy. Using recommended technique, umbilical artery PI was measured from the free loop of the umbilical cord and from the fetal end by one examiner in a state of fetal quiescence, generating four measurements per fetus. Fetal middle cerebral artery PI was also obtained. Cerebro-placental ratio (CPR) was calculated as MCA PI/Umbilical artery PI. Variability of the CPR on the two sampling occasions was tested using Pitman test of equality of variance for related samples. The difference between the two sets of CPR measurements was plotted against the mean to generate 95% limits of agreement.*Results:* A total of 158 women were recruited. The mean CPR was significantly lower when the umbilical artery PI was obtained at the para-vesical site, than when it in obtained from a free loop ( $p < 0.001$ ). No significant correlation was seen between gestational age and CPR, when the umbilical artery PI was measured from the para-vesical site ( $r = -0.079$ ,  $p = 0.323$ ) or the free loop ( $r = -0.103$ ,  $p = 0.198$ ). Total variance of the CPR using the umbilical artery free loop was 0.286, and that using the para-vesical site of the umbilical artery was 0.164. Pitman's test showed that the total variability of CPR at the two sites was significantly different ( $r = 0.254$ ,  $p < 0.001$ ). The variability of CPR was significantly lower if the umbilical artery PI measurement was taken at the fetal end than that in the free loop.*Conclusion:* The mean CPR site was significantly lower when the umbilical artery PI was obtained at the para-vesical than in the free loop. Measurement site for the umbilical artery PI contributes to a significant proportion to the total variability of the cerebro-placental ratio. CPR measurements should include umbilical artery PI measurements at the para-vesical site rather than the free loop of the umbilical cord in order to improve repeatability. Appropriate reference ranges for the interpretation of CPR will be needed.

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### Introduction

Cerebro-placental ratio is calculated as a ratio between middle cerebral artery PI and umbilical artery PI. There are several recent reports of that cerebro-placental ratio (CPR) correlates with adverse pregnancy outcome [1–4], intrapartum fetal distress [5], admission to the neonatal unit [6] and neonatal acid-base balance [7]. The repeatability and reproducibility of cerebro-placental ratio has not been assessed before. This assessment is necessary if CPR is to be used for clinical decision making. In a related manuscript we tested the hypothesis that standardising the site of sampling of

umbilical artery Doppler reduces the variability of umbilical artery Pulsatility Index (PI). In this manuscript, apart from assessing the repeatability and reproducibility [8] of cerebro-placental ratio, we also tested if standardising the site of sampling of umbilical artery Doppler reduces the variability of the CPR.

### Methods

This is the second of the two linked manuscripts, and the methods are common to both. In the other manuscript published in this issue of the journal, we tested the hypothesis that standardising the site of sampling of umbilical artery Doppler reduces the variability of umbilical artery Pulsatility Index (PI). The details of the participants and methods have been described in detail in the accompanying manuscript. After measuring the umbilical artery PI (UmbAD PI), the fetal middle cerebral artery PI was

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measured in the near field using recommended technique [9] (ISUOG guidelines) in a state of fetal quiescence. Two measurements of the middle cerebral artery PI were obtained in the proximal portion of the artery from its origin from the circle of Willis at the beginning and the end of the examination as described previously. Cerebro-placental ratio (CPR) was calculated as a ratio of middle cerebral artery PI to umbilical artery PI. Thus, two CPR values were obtained from each fetus: One where umbilical artery PI was measured in the free loop ( $CPR_{free\ loop}$ ) and the other, where umbilical artery PI was measured in the paravesical part of the umbilical artery ( $CPR_{paravesical}$ ).

Statistical analysis - Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS 20, IBM Inc. USA). Pitman's test [10] was used to explore if the variability of  $CPR_{free\ loop}$  and  $CPR_{paravesical}$  were different. Paired 't' test was used to compare  $CPR_{free\ loop}$  and  $CPR_{paravesical}$ . Intra-class correlation coefficients were calculated to explore the repeatability of measurements of  $CPR_{free\ loop}$  and  $CPR_{paravesical}$ . Bland-Altman plots [11] were constructed to assess the 95% limits of agreement.

**Results**

A total of 158 women were recruited. Please see the accompanying manuscript for maternal demographics. The mean  $CPR_{paravesical}$  was significantly lower, than  $CPR_{free\ loop}$  ( $p < 0.001$ , Table 1). No significant correlation was seen between gestational age  $CPR_{paravesical}$  ( $r = -0.079$ ,  $p = 0.323$ , Fig. 1) or  $CPR_{free\ loop}$  ( $r = -0.103$ ,  $p = 0.198$ , Fig. 2). Total variance of the  $CPR_{free\ loop}$  was 0.286, and that of  $CPR_{paravesical}$  was 0.164. Pitman's test showed that the total variability of  $CPR_{free\ loop}$  compared to  $CPR_{paravesical}$  was significantly different ( $r = 0.254$ ,  $p < 0.001$ ). Therefore, variability of  $CPR_{paravesical}$  was significantly lower than  $CPR_{free\ loop}$ . The intra-class correlation coefficients (ICC) for  $CPR_{free\ loop}$  and  $CPR_{paravesical}$  were 0.569 (95% CI: 0.410 – 0.685) and 0.719 (95% CI: 0.616 – 0.795) respectively (Table 1). Bland-Altman plots for CPR measurements using two techniques are shown in Figs. 3 and 4.

**Discussion**

The data from this study show that the mean  $CPR_{paravesical}$  was significantly lower than  $CPR_{free\ loop}$ . Measurement site for the umbilical artery PI contributes to a significant proportion to the total variability of the cerebro-placental ratio. CPR measurements should include umbilical artery PI measurements at the paravesical site rather than the free loop of the umbilical cord in order to improve repeatability.

Although there are multiple reports linking CPR and adverse pregnancy outcome [12–14], not all authors agree that it can be used for decision making in individual cases [15,16]. Satisfactory repeatability is necessary for clinical use. ICC values less than 0.5, between 0.5 and 0.75, between 0.75 and 0.9, and greater than 0.90 are indicative of poor, moderate, good, and excellent reliability, respectively [17]. We report a moderate reliability both for  $CPR_{paravesical}$  and  $CPR_{free\ loop}$ , but the ICC was higher for

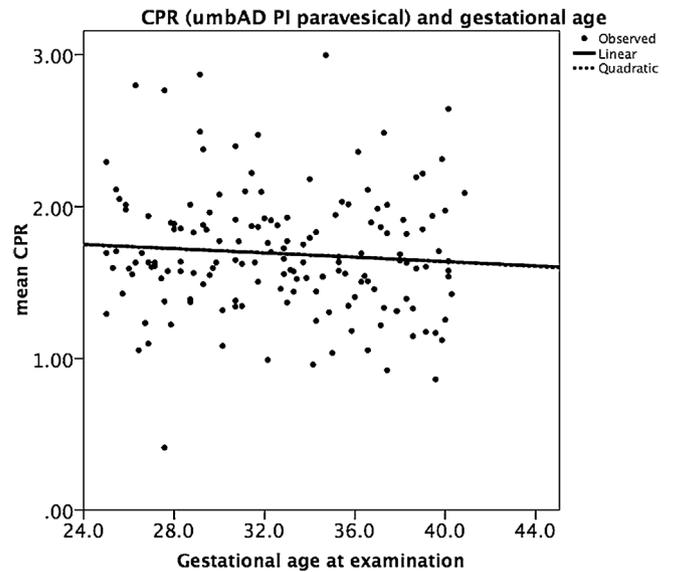


Fig. 1. Cerebro-placental ratio plotted against gestational age (when the measurement of umbilical artery PI is at the para-vesical site( $CPR_{paravesical}$ )).

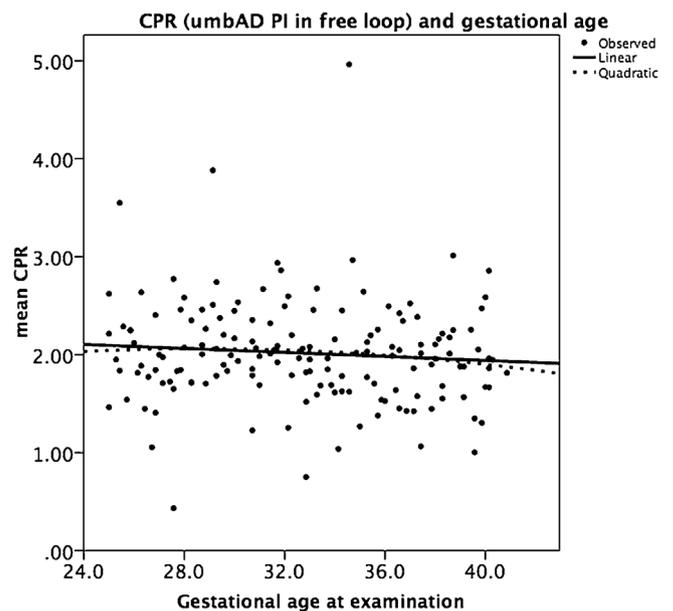


Fig. 2. Cerebro-placental ratio plotted against gestational age (when the measurement of umbilical artery PI in the free loop ( $CPR_{free\ loop}$ )).

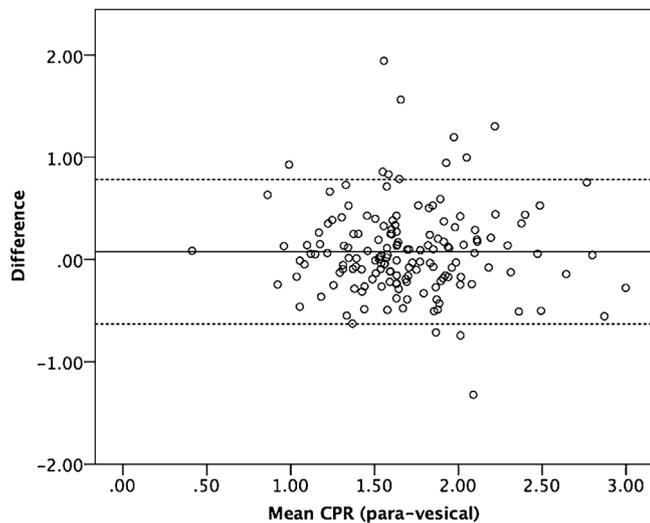
$CPR_{paravesical}$ . Bland-Altman plots show that the 95%limits of agreement for CPR are wide. Mean CPR is reported to be 2.05 at 27 weeks [18]. However, the 95% limits of agreement show that it

**Table 1**

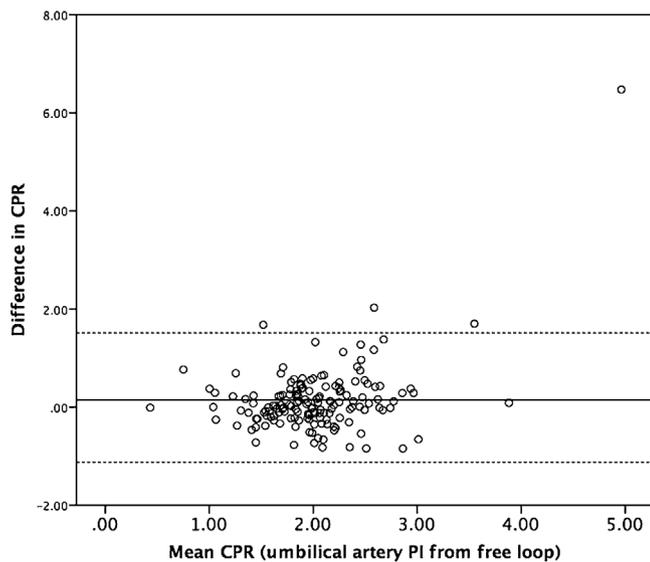
Comparison of CPR measurements taken on two occasions, and with the umbilical artery PI measurement at the two sites.

Parameter	Sampling site of umbilical artery PI		Mean difference (95% CI)	P <sup>a</sup>
	Free loop ( $CPR_{free\ loop}$ ) Mean(SD)	Para-vesical ( $CPR_{paravesical}$ ) Mean(SD)		
CPR (measurement 1)	2.09 (0.753)	1.73 (0.452)	0.359 (0.257- 0.461)	<0.001
CPR (measurement 2)	1.94 (0.502)	1.65 (0.464)	0.293 (0.240 – 0.346)	<0.001
ICC	0.569 (0.410 – 0.685)	0.719 (0.616 – 0.795)		

<sup>a</sup> Paired 't' test.



**Fig. 3.** Bland-Altman plot of 95% limits of agreement for Cerebro-placental ratio when the measurement of umbilical artery PI is at the para-vesical site ( $CPR_{para-vesical}$ ).



**Fig. 4.** Bland-Altman plot of 95% limits of agreement for Cerebro-placental ratio when the measurement of umbilical artery PI in the free loop ( $CPR_{free\ loop}$ ).

could be 0.902 (<2.5<sup>th</sup> centile) to 3.198 (>97.5<sup>th</sup> centile). Therefore, the measurement is too imprecise for clinical use.

Reference ranges of the cerebro-placental ratio have been published on cross sectional [19] and longitudinal [18] data. A quadratic relationship between CPR and gestational age was reported by both these reports. The findings of the current study did not show a statistically significant quadratic relationship between gestational age and CPR. The proportion of variability attributed to the gestational age in the current study was small ( $R^2=0.006$ ) and was not statistically significant ( $p=0.614$ ). It is possible that this was related to the number of participants. In the study of Baschat & Gembruch [19], 306 participants were included. In the study of Ebbing et al. [18], 566 observations in 161 pregnancies were used. Although 316 observations of CPR were available from 158 pregnancies in the current study, each pregnancy was included only once. The purpose of the current study was not to construct a reference range, but to assess repeatability. In the present study gestational age showed a

significant negative correlation with umbilical artery PI, and a quadratic relation with MCA PI as reported in previous publications [18,20–22].

All the studies reporting reference range of CPR obtained umbilical artery PI in the free loop. In this study we have showed that CPR is less variable if umbilical artery PI is obtained from the para-vesical portion of the umbilical artery. We recommend that umbilical artery PI should be obtained from para-vesical region for calculation of CPR. We also show that  $CPR_{para-vesical}$  is significantly lower than  $CPR_{free\ loop}$ . Therefore, appropriate reference range for CPR (constructed with umbilical artery PI from para-vesical site) will be necessary to interpret the CPR values.

#### Strengths and weaknesses

This is a prospective study specifically designed to test the repeatability of CPR measurements. We also tested if standardising the site of sampling of umbilical artery Doppler reduces the variability of the CPR. This was a low-risk group and pregnancies with abnormal fetal Dopplers were not encountered. We are unable to comment if the variability of CPR is lesser in the subgroup of fetuses with abnormal results. In fact, Figs. 3 or 4 show no evidence that the variability is related to the CPR value.

Each fetus was examined twice, but by the same examiner (either ABB or DW). Therefore, we were not able to assess inter-observer variability. However, when an ultrasound scan is being performed on a pregnant woman, it is performed usually only by a single operator. In this manuscript we describe and report within-operator variability. We show that a reduction of within-operator variability of CPR is possible by obtaining umbilical artery PI at the fetal end rather than the free loop.

#### Conclusion

The mean  $CPR_{para-vesical}$  was significantly lower than  $CPR_{free\ loop}$ . Measurement site for the umbilical artery PI contributes to a significant proportion to the total variability of the cerebro-placental ratio. CPR measurements should include umbilical artery PI measurements at the para-vesical site rather than the free loop of the umbilical cord in order to improve repeatability. Appropriate reference ranges for the interpretation of CPR will be needed.

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