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The effect of sampling site on the variability of Umbilical artery PI

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ABSTRACT

Introduction: To test the hypothesis that standardising the site of sampling of umbilical artery Doppler reduces the variability of umbilical artery Pulsatility Index (PI).
Study design: In this prospective study, 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 para-vesical site by the same examiner at the beginning and the end of ultrasound examination in a state of fetal quiescence, generating four measurements per fetus. Variability of the measurements at the two sampling sites was tested using Pitman test of equality of variance for related samples. The difference between the two sets of measurements were plotted against the mean to generate limits of agreement.
Results: A total of 158 women were recruited. Umbilical artery PI was significantly negatively correlated with the gestational age ($r = -0.246$ for free loop and -0.262 for para-vesical site, both $p < 0.005$). The PI at the para-vesical site was significantly higher than in the free loop ($p < 0.001$). Pitman's test showed that the total variability of umbilical artery PI at the two sites was no different ($r = -0.091$, $p = 0.254$).
Conclusion: Measurement site contributes to an insignificant proportion to the total variability of the umbilical artery PI measurements. Umbilical artery PI is significantly lower when measured in the free loop as compared to the para-vesical site. Standardising the site of sampling does not improve the repeatability of umbilical artery PI measurement.

Introduction

Umbilical artery pulsatility index (PI) is of proven value in investigating a fetus with suspected placental insufficiency [1]. Umbilical artery PI is known to be influenced by the site of measurement with the value gradually reducing from the fetal to the placental end [2,3]. Measurement at the fetal end in the para-vesical region standardises the site to within 10 mm. In contrast, the 'free loop' site may be closer to the fetal or placental site, thereby potentially introducing greater variability. The mean length of the umbilical cord is reported to be 350 mm and 550 mm at 24 and 40 weeks respectively [4]. We hypothesised that standardising the site of sampling of umbilical artery Doppler will reduce the variability of umbilical artery PI. Repeatability of measurements refers to the variation in repeat measurements made on the same subject under identical conditions, whereas reproducibility refers to the variation in repeat measurements made on the same subject under changing conditions [5]. By measuring the umbilical artery PI on two occasions each, at two sites, we assessed repeatability and reproducibility of umbilical artery PI.

Methods

This is the first of the two linked manuscripts, and the methods are common to both. In the other manuscript published in this issue of the journal, we assessed of reproducibility and repeatability of cerebro-placental ratio. This prospective study was conducted from January 2017 to June 2018. We invited pregnant women with a singleton pregnancy to participate. Approximately 10 women/week of gestation from 24 weeks till 40 weeks were invited to participate in this study. Inclusion criteria were: gestational age between 24 and 40 weeks; absence of structural malformations or chromosomal abnormalities and normal fetal size (>10th and <90th percentile according to local standards [6]). All pregnancies were dated on CRL between 11–14 weeks, making the dating secure. Informed consent to perform ultrasound and Doppler examination was obtained from each of the participant and documented. The research protocol was approved by the local

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ethics committee. The study was cross sectional. Each participant was included only once in the pregnancy.

Ultrasound examinations were performed for research purpose. Women were requested to be in a semi-recumbent position. After confirming consent, umbilical artery waveforms were obtained using pulsed Doppler at the beginning of the examination from a free loop of the umbilical artery, and from umbilical artery adjacent to the fetal urinary bladder, within 10 mm of the insertion of the umbilical cord in the fetal abdomen, making sure that the fetus is in a state of quiescence. No distinction was made between the left or the right umbilical artery. Gate size was kept large enough to include the entire diameter of the umbilical artery. At least 6 but not more than 10 waveforms were included as recommended, and insonation angle was kept less than 30° [7]. The PI was measured using the automatic trace function (first set of reading). Rest of the ultrasound examination (biometry, assessment of placental location and amniotic fluid volume) was completed. Following this, umbilical artery waveforms were obtained again from the free loop of the umbilical artery, and from umbilical artery adjacent to the fetal urinary bladder (second set of reading).

Each woman was examined by one of the two (ABB, KK) examiners using convex sector probes (2–8 MHz) and standard Obstetric settings. Doppler assessment was performed in keeping with recommended guidelines (ISUOG) [7]. The high-pass filter was set at 50 Hz and energy output levels were lower than 50 mW/cm^2. All pregnancies were followed till delivery, and outcome details were collected either from hospital records, or by contacting the participants on the telephone.

Statistical analysis - Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS 20, IBM Inc. USA). Umbilical artery PI readings from two sites in the same fetus are clearly correlated. The correct procedure for testing the equality of variance between correlated samples is credited to Pitman [8]. If S = sum of the two measurements from the two sites, and D = difference between the same two measurements, the statistical equality of variance of measurements from the two sites is tested by the sample correlation between S and D with n - 2 degrees of freedom (where n = number of subjects in a matched sample). A statistically significant correlation indicates significant difference between variances [8]. Paired '*t*' test was used to compare the two PI measurements from the same site, and for comparison between the two sites. Intra-class correlation coefficients were calculated to explore the repeatability of measurements of umbilical artery PI from each of the two sites. Bland-Altman plots were constructed to assess the 95% limits of agreement.

Results

A total of 158 women were recruited. Demographics of the participants can be seen in Table 1. Satisfactory flow velocity waveforms were obtained successfully from each fetus at each sampling site in every case.

Umbilical artery PI was significantly negatively correlated with the gestational age ($r = -0.246$ for free loop and -0.262 for para-vesical site, both $p < 0.005$). The PI at the para-vesical site was significantly ($p < 0.001$) higher than in the free loop (Table 2). Pitman's test showed that the sample correlation between the sum and differences of mean PI of free loop and mean PI of para-vesical umbilical cord was not statistically significant ($r = -0.091$, $p = 0.254$), demonstrating no significant difference in the variance of measurement of umbilical artery PI from each of the two sites. The difference between the two recordings of umbilical artery PI in the free loop were significantly correlated with the mean ($r = 0.264$, $p = 0.001$). Therefore, coefficient of variation (cv) was calculated in percentage as cv = difference/mean*100. The coefficient of variation was not related to mean PI (free loop) ($r = -0.96$, $p = 0.23$). The cv was also unrelated to mean PI from the para-vesical site ($r = -0.111$, $p = 0.163$). Therefore, cv was used to construct Bland-Altman plots for both the sites. Figs. 1 and 2 show the Bland-Altman plots for umbilical artery PI from the free loop and para-vesical region. The intra-class correlation coefficients for the free loop and para-vesical sites were 0.884 (95% CI: 0.814 to 0.915) and 0.896 (95% CI: 0.858 to 0.924) respectively.

Table 1
Demographics of women participating in the study.

Parameter	Mean/Median (SD/range)
Median gestational age at scan (weeks)	32^{+6} (28^{+6} to 36^{+5})
Median gestational age at delivery (weeks)	39^{+1} (37^{+4} to 41^{+0})
Birthweight (g)	2851 (582)
Birthweight z-score	−0.226 (−1.07 to 1.29)

Discussion

In this study we found that restricting the target of sampling to a specific site does not improve the variability of umbilical artery PI. Therefore, the contribution of sampling site to the variability of umbilical artery PI measurements is insignificant.

There are several sources of variability in the assessment of umbilical artery PI using pulsed wave Doppler: Gestational age, fetal heart rate, site of the sampling along the length of the umbilical cord, laterality of the umbilical artery, sampling error, and finally true biological variability. Baseline fetal heart rate is related to the gestational age [9], and the gestational age is taken into account in construction of the reference ranges for umbilical artery PI [10–12].

The two fixed sites of insertion of the umbilical cord are the placental and the fetal end. 'Free loop' constitutes the remaining portion of the umbilical cord. Previous research has shown that the umbilical artery PI is highest at the fetal end, gradually decreasing to the placental end, where it is the lowest [2,3]. The fixed sampling site could either be the fetal end or the placental end of the umbilical cord. In a previous unpublished study, we found that, although umbilical artery PI in the free loop could be obtained in each of the fetuses examined, the placental end could be interrogated in only 63%, and fetal end in 87% (unpublished data). Therefore, fetal end of the umbilical cord was chosen as the fixed standardises site to compare against free loop in this study. We did not differentiate between the left or the right umbilical artery while insonating the para-vesical segment. It is possible that some variability is introduced due to the laterality of the umbilical artery. Previous work has shown that differences between left and right Doppler indices exist in 98% of cases [13]. These differences were greater than 20% in at least one-third [13]. While insonating the free loop of the umbilical cord, the distinction between the left and the right umbilical artery is not possible. In order to maintain consistency, the para-vesical region was insonated without distinction to laterality in the current study.

Maulik et al. [14] examined the components of variability of umbilical arterial Doppler velocimetry. They reported that gestational age and fetal heart rate contributed to 33–46%, and 15–18% of the variance respectively. The location of the Doppler measurement contributed to 29–46% of the error variance. The study was performed using continuous wave Doppler, and range gating and selecting the sample volume was not possible. Scherjon et al [15] also reported on reliability of pulsatility index measurement of the umbilical artery. They reported an intra-class correlation coefficient for umbilical artery of 0.91, which is similar to that observed in the current study. A high ICC indicates high reliability and values above 0.75 show an acceptable level of concordance [16]. Although high ICCs were found at each of the two sites, Bland Altman plots show

Table 2
Comparison of Umbilical artery PI measurements at the two sites.

Parameter	Sampling site		Mean difference (95% CI)	p[a]
	Free loop	Para-vesical		
Umbilical artery PI (measurement 1)	0.942 (0.296)	1.105 (0.280)	−0.163 (−0.196 to −0.131)	<0.0001
Umbilical artery PI (measurement 2)	0.952 (0.252)	1.127 (0.299)	−0.175 (−0.212 to −0.138)	<0.0001
Mean coefficient of variation in % (SD)	−2.035 (19.28)	−1.573 (15.253)	−0.462 (−0.467 to 3.144)	0.801
ICC	0.884 (0.814 to 0.915)	0.896 (0.858 to 0.924)		

[a] = Paired '*t*' test.

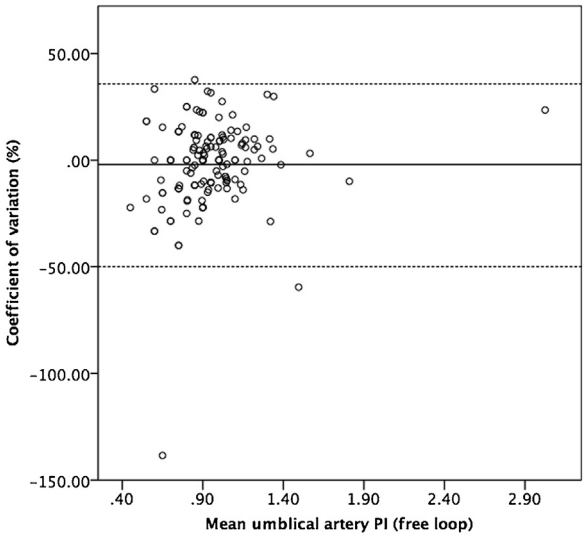

Fig. 1. Bland-Altman plot of 95% limits of agreement for the coefficient of variation of umbilical artery PI at the free loop.

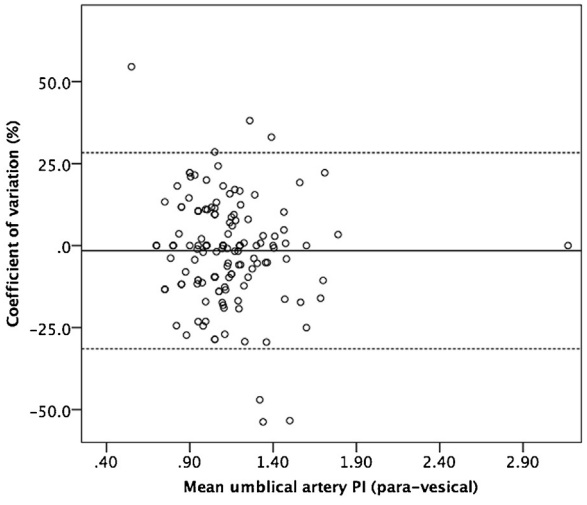

Fig. 2. Bland-Altman plot of 95% limits of agreement for the coefficient of variation of umbilical artery PI at the para-vesical site.

that the extent of variation in repeat measurements does not give clinical discrimination. For example, for a reading of umbilical artery PI of 1.0, the 95% limits of agreement for a repeat measurement are 0.6 (<5th centile) to 1.36 (95th centile) for free loop. In this study we show that it is not possible to reduce the variability by selecting the site of insonation of the umbilical cord for assessment of the pulsatility index. Repeating a measurement of the umbilical artery PI is more likely to yield a result closer to the true value (regression towards the mean). Therefore, repeating the PI measurement, particularly for values at the extreme ends of the centiles, are more likely to yield the real value if they are persistently away from the mean. Spencer & Price [17] reported a mean coefficient of variation of 8.5% indicating good reproducibility for umbilical artery PI. However, this report may be too optimistic. It was based on only 20 women in late pregnancy (exact gestational age range is not reported) using continuous wave Doppler. The findings of the current study are in keeping with previous publications of limited reproducibility [14,15].

Strengths and weaknesses – This is a prospective study and measurements of PI of fetal vessels were performed specifically and systematically for research purposes. Doppler measurements in an individual woman was obtained only by one observer. Therefore, assessment of inter-observer variability was not possible from this study design.

Conclusion

Measurement site contributes to an insignificant proportion to the total variability of the umbilical artery PI measurements. Umbilical artery PI is significantly lower when measured in the free loop as compared to the para-vesical site. Standardising the site of sampling does not improve the repeatability of umbilical artery PI measurement.

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