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Doppler measurements of both umbilical arteries do not improve predictive value for adverse perinatal outcomes in small-for-gestational age fetuses

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ABSTRACT

Objective: To assess agreement of Doppler ultrasound measurements of the two umbilical arteries in small-for gestational age (SGA) fetuses, and to compare discriminative ability between the two arteries for adverse perinatal outcome.
Study Design: We analysed a prospective cohort of singleton SGA pregnancies, in which the pulsatility index (PI) of both umbilical arteries was standardly measured by Doppler ultrasound in the free-floating umbilical cord. The outcome of interest was a composite adverse outcome, defined as perinatal death, Apgar score <7 at 5 min, cesarean section for fetal distress, and neonatal intensive care unit admission.
Results: A total of 531 measurements were performed in 124 patients. Mean absolute difference between PI measured in the two umbilical arteries was 0.14 (95% CI: 0.12 to 0.15), showing good agreement with an ICC of 0.830 (95% CI: 0.801 to 0.854). Perinatal outcomes were available for 101 patients, of which 48 patients (48%) had a composite adverse perinatal outcome. We found no significant differences between AUCs for prediction of an adverse outcome based on lowest, highest and mean PI values in the two umbilical arteries (AUCs = 0.75, 0.74, 0.75 with p = 0.91). As a comparison, the AUC of a PI value obtained in a single, randomly selected umbilical artery was 0.74.
Conclusion: The two umbilical arteries show good agreement in terms of their PI values in the free-floating umbilical cord, and do not differ in terms of their discriminative ability for adverse perinatal outcome in SGA fetuses. We found no evidence of an added value of standard Doppler measurement of both umbilical arteries.

Introduction

Ultrasonographic Doppler measurements of the umbilical artery (UA) are universally used to assess the fetal condition in pregnancies at risk for placental insufficiency, like in fetal growth restriction (FGR) or hypertensive disorders of pregnancy [1–3]. Multiple observational studies indicate a high prognostic accuracy of UA Doppler for fetal compromise [4,5]. Its clinical value has been described in a Cochrane review of 18 randomized trials, which showed that the use of UA Doppler velocimetry in pregnancies at risk of placental insufficiency reduced the risk of perinatal deaths and resulted in less obstetric interventions [6].

The umbilical cord normally consists of one vein and two arteries. In current practice, only one of the two arteries is assessed in a free-floating loop of the umbilical cord. However, discordance between the two arteries in resistance [7,8] and size [9] has been described. While discordance in size appears to have no impact on perinatal outcome [9], it remains unknown whether discordance in resistance holds any clinical relevance and FGR guidelines do not address this issue.

Lecarpentier et al. [8] found significantly different fetal conditions between discordant and concordant abnormal UA flow and, consequently, concluded that examination of a single UA may miss a large fraction of abnormal flow. However, the authors measured the arteries lateral to both sides of the bladder wall, before they join in the anterior abdominal wall to become part of the umbilical cord. These

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measurements are not at a representative site, since resistance to blood flow is known to be higher at the fetal end of the umbilical cord compared to the placental end [10–14]. Also, differences in Doppler values between the UAs may be lower in the free-floating umbilical cord than lateral to the bladder. Appropriate assessment of the UA is essential in order to make optimal use of this important test. Therefore, we aimed to investigate the agreement of Doppler values in the two UAs in a free-floating loop of the umbilical cord in singleton, small-for-gestational age (SGA) pregnancies, and aimed to compare discriminative ability for adverse perinatal outcome between the two UAs.

Materials and methods

This was a prospective cohort study conducted in a single tertiary referral center between August 2015 and March 2017. This study is described in accordance with STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) Statement [15]. Singleton pregnancies complicated by SGA were included at any gestational age (GA). SGA was defined as an estimated fetal weight (EFW, according to Hadlock-3 formula [16]) below the 10th percentile [17] or abdominal circumference (AC) below the 10th percentile [18], or a decrease in growth of EFW or AC of more than 20 percentiles. Each patient had undergone a first-trimester ultrasound to accurately establish GA, and had undergone a structural anomaly scan around 20 weeks of gestation. Fetuses with suspected chromosomal or structural abnormalities were excluded.

In patients meeting inclusion criteria, serial ultrasound examinations were conducted to evaluate the fetal condition. All ultrasound examinations were performed by one of six experienced sonographers using a General Electric Voluson^{TM} E6 or E8 (GE Medical Systems, Zipf, Austria) ultrasound machine. According to the local protocol (adhering to standardized, international recommendations [1]), each ultrasound examination was performed at a weekly or bi-weekly basis depending on the severity of the growth restriction. Transabdominal color Doppler ultrasound was used to visualize the two UAs in a free-floating loop of the umbilical cord, not too close to the fetal cord insertion or the placental insertion. In the absence of fetal movements, pulsed-wave Doppler was then used to assess impedance to flow with the angle of insonation as close to 0° as possible; when at least three identical waveforms were obtained, the Pulsatility Index (PI) was measured. We also measured Doppler waveforms of the uterine artery Doppler measurement (at diagnosis) and middle cerebral artery (MCA), and measured amniotic fluid volume. Fetal growth was evaluated at a two-weekly interval. All sonographic findings were available to the obstetrical team, and the lowest PI value measured in the two UAs was always used for clinical management.

The primary outcome was a composite adverse perinatal outcome, which consisted of perinatal death, Apgar score <7 at 5 min, cesarean section for fetal distress, and neonatal intensive care unit (NICU) admission.

Statistical analysis

Because the measurements were made in a free-floating loop of the umbilical cord, it was not possible to allocate the measurements to left or right. A standard Bland-Altman analysis [19] was therefore not possible. As an alternative, we calculated the mean of the absolute within-patient difference between the two measurements together with its 95% confidence interval (CI), and the 95th percentile of these absolute mean differences. The 95th percentile serves as an alternative for the limits of agreements in a standard Bland-Altman analysis as 5 percent of all absolute differences are expected to exceed this threshold. As multiple measurements were done per individual, the mean and its 95% CI were estimated using a mixed model including a random effect for individual and the absolute difference between paired measurements as the dependent variable. To check whether variability increased with increasing UA measurements, an additional mixed model was estimated with a fixed effect for the mean of the two measurements. To check whether the mean absolute difference was associated with GA, a separate mixed model was fitted with a fixed effect for GA. A two-way random effects model was used to determine intraclass correlation coefficient (ICC) for absolute agreement of PI values of different UAs at same measurement.

Associations between last UA measurement before delivery and occurrence of composite adverse perinatal outcome were tested using univariate logistic regression analysis. Separate analyses were performed for UA-low, UA-high and the mean UA (UA-mean). Discriminative ability of the last UA measurement before delivery for composite adverse perinatal outcome was quantified using area under the ROC curve (AUC), and were compared using the DeLong test. AUC for a single measurement was calculated as the mean of 25 AUCs obtained on randomly-generated datasets, where for each patient the highest or lowest PI value was selected with a probability of 50%. The DeLong test was performed in Stata 14 version (StataCorp. 2015. Stata Statistical Software: Release 14. College Station, TX: StataCorp LP). All other statistical analyses were performed with IBM SPPS, Version 22.0. A two-sided significance level of 5% was used for all analyses.

Results

A total of 124 SGA pregnancies could be included during the study period. Table 1 summarizes demographic and pregnancy characteristics of the included patients. Median maternal age was 31.0 years (IQR (interquartile range) 27.0–34.0) and the majority of patients were nulliparous (n = 81, 65%). Hypertensive disorders of pregnancy occurred in 36 patients (29%). Median GA at diagnosis of SGA was 29.1 weeks (IQR 24.2–31.5). Median number of ultrasound examinations per pregnancy was 8 (IQR 3–10). The second UA could be assessed in 531 of 929 measurements (57%).

Agreement of PI values measured in the two UAs

The differences between the average PI values of UA-low and PI values of UA-high are visualized for each patient in Fig. 1. The overall mean (±standard deviation SD) PI value of UA-low was 1.11 ± 0.31, while overall mean (±SD) PI value of UA-high was 1.25 ± 0.39. Mean absolute difference of PI values between the two UAs was 0.14 (95% CI 0.12–0.15), 95% of the absolute differences were below 0.40. In Fig. 1 it can also be observed that the mean absolute difference increased by 0.02 with each 0.10 increase in magnitude of mean PI ($P < 0.001$). Measurements made in the two different UAs showed good agreement with an ICC of 0.830 (95% CI: 0.801–0.854). No association was found between the absolute differences and GA ($P = 0.249$). Discordant PI (i.e. < 95th percentile

Table 1
Demographics and pregnancy characteristics of all 124 included patients. Continuous data are presented as median (interquartile range), categorical data are presented as n (%).

Characteristics	n = 124
Age, y	31.0 (27.0–34.0)
BMI, kg/m^2 (n = 79)	22.8 (19.8–25.5)
Smokers (n = 93)	7 (8%)
Nulliparous	81 (65%)
Diabetes	4 (3%)
Chronic hypertension	4 (3%)
Hypertensive disorders of pregnancy	36 (29%)
GA at diagnosis SGA, weeks	29.1 (24.2–31.5)
Number of ultrasound measurements	8 (3–10)

Abbreviations: BMI = body mass index, GA = gestational age, SGA = small-for-gestational age.

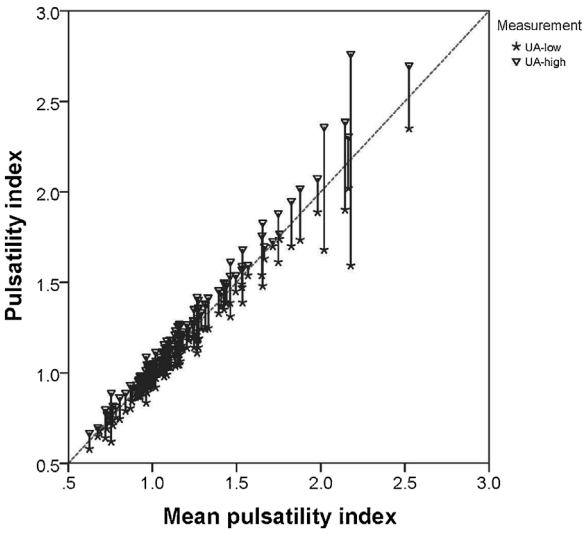

Fig. 1. Difference plot comparing the UA with the mean of the lower PI values (UA-low) with the mean of the higher PI values (UA-high) for each individual (n = 124). Connected dots refer to PI values of the same individual.

[20] in one artery, and ≥95th percentile in the other artery) occurred in 72/531 measurements (14%) in 46/124 patients. In 11 of these patients the discordant PI occurred in the final measurement before delivery, in 19 patients it transitioned into concordant ≥95th percentile, while in 16 patients it returned to concordant <95th percentile. The numbers were too small to perform subgroup analyses. Discordant end-diastolic flow (EDF) (i.e. positive in one artery, and absent or reversed in the other artery) occurred in 9/531 measurements (2%) in 6/124 patients. In 3 of these 6 patients the discordant EDF occurred in the last measurement for delivery, in one patient it transitioned into concordant abnormal EDF, and in two patients it returned to concordant normal EDF.

Prognostic accuracy of measures based on PI values from both UAs

Perinatal outcomes were available for the 101 patients that delivered in our hospital, after exclusion of two cases with early termination of pregnancy (<24 weeks of gestation for fetal and maternal indication). Obstetric and neonatal data are described in Table 2. Median gestational age at delivery was 37.4 weeks (IQR 32.9–38.9). Median interval between final ultrasound examination and delivery was 5.0 days (IQR 2.0–11.5). Birth weight of most neonates was less than the 5th percentile based on Dutch reference curves [21] (n = 91, 90%). There was one case of intra uterine fetal death, and one case of neonatal death. There were 48 cases (48%) with a composite adverse outcome.

Odds ratios (ORs) of UA-low, UA-high and UA-mean were very similar for the association with the composite adverse perinatal outcome (UA-low OR = 1.35 per 0.1 increase, UA-high OR = 1.32, UA-mean OR = 1.34) (Table 3). Discriminative ability as quantified by the AUCs for ROC curves (Fig. 2, Table 3) was 0.75, 0.74 and 0.75 for UA-low, UA-high, and UA-mean, respectively, and were not statistically different (p = 0.910). As a comparison, the AUC of a PI value obtained for a single randomly selected UA was found to be 0.74.

Comment

The results of this study show good agreement between PI values of the two UAs measured by Doppler ultrasound in the free-floating umbilical cord of singleton SGA pregnancies. Discriminative ability for the composite adverse perinatal outcome did also not differ between PI values measured in both UAs. The AUC based on a single, randomly selected UA Doppler measurement was found to be very similar.

Importantly, it was not possible to reliably measure the second UA in almost half of the cases, while all measurements were

Table 2
Obstetric and neonatal data of the 101/124 patients with outcome data available (after exclusion of two cases with early termination of pregnancy). Continuous data are presented as median (interquartile range), categorical data are presented as n (%).

Obstetric and neonatal data	n = 101
GA at delivery, weeks	37.4 (32.9–38.9)
Antenatal corticosteroids	27 (27%)
Mode of delivery	
Vaginal	47 (47%)
Cesarean section	54 (53%)
Indication for cesarean section	
Non-reassuring fetal heart rate	19 (19%)
Maternal	13 (13%)
Placental abruption	2 (2%)
Other	20 (20%)
Birth weight, kg	2.30 (1.34–2.67)
Birth weight <5th percentile	91 (90%)
Apgar score <7 at 5 min	8 (8%)
Arterial cord pH (n = 41)	7.28 (7.25–7.30)
NICU admission	43 (43%)
IUFD	1 (1%)
Neonatal death	1 (1%)
Composite adverse perinatal outcome	48 (48%)

Abbreviations: GA = gestational age, NICU = neonatal intensive care unit, IUFD = intra uterine fetal death, Composite adverse perinatal outcome = perinatal death, Apgar score <7 at 5 min, cesarean section for fetal distress, and neonatal intensive care unit (NICU) admission.

Table 3
Comparison of odds ratios and area under the curves between the UA with the lower PI (UA-low), the UA with the higher PI (UA-high), and the mean UA Doppler (UA-mean) for prediction of the composite adverse perinatal outcome.

Test	Odds ratio	95% CI of odds ratio	AUC	95% CI of AUC
UA-low (per 0.1 PI)	1.35	1.16–1.58	0.75	0.65–0.85
UA-high (per 0.1 PI)	1.32	1.15–1.53	0.74	0.64–0.84
UA-mean (per 0.1 PI)	1.34	1.16–1.56	0.75	0.65–0.84

Abbreviations: UA = umbilical artery, PI = pulsatility index, CI = confidence interval, AUC = area under the curve.

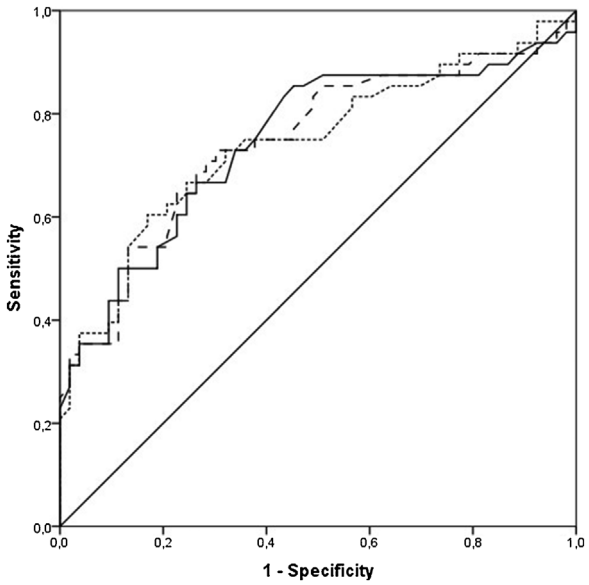

Fig. 2. Receiver operating characteristics curves for prediction of composite adverse perinatal outcome by UA-low ( ), UA-high (. . . ..) and UA-mean (– – –).

performed by dedicated obstetric sonographers. This was most often the result of a very active fetus, and sometimes of suboptimal imaging quality. The sonographers were allowed to decide against measuring the second UA, if this was not feasible in view of the time limit of the ultrasound. This suggests that standard Doppler measurement of both UAs is practically difficult to achieve.

This is the first study that assessed agreement of PI values measured in both UAs and investigated whether discriminative ability can be improved when both UAs in the free-floating umbilical cord are measured. This provides important information for optimal use of the UA Doppler in assessment of fetal well-being. However, we mostly included mildly affected SGA fetuses, and the results of this study therefore cannot be extrapolated for fetuses with more severe hemodynamic changes. Other limitations were the study's sample size, which was not sufficient to perform subgroup analyses, and the missing follow-up data of several patients that had delivered in another hospital. Over the past years, the cerebroplacental ratio (CPR) has gained increasing interest as a potential indicator of fetal well-being [22]. The findings of this study directly apply to the CPR, given that the CPR is calculated as the ratio of MCA PI to UA PI.

Predanic et al. [7] found significantly different systolic-diastolic ratio (S/D) values between the two UAs in the free-floating umbilical cord in singleton pregnancies. However, it is now common to use the PI value instead of the S/D ratio in clinical practice. The different mathematical properties of S/D ratio and PI may account for the fact that we found smaller differences of PI values between the two UAs. Janeczek et al. [23] found much smaller differences of PI than of S/D values between the two UAs in singleton pregnancies. Moreover, both differences were not significant in the SGA subgroup. Their study measured the left and right UAs lateral to both sides of the bladder wall of the fetus, which had the advantage that laterality of the arteries could be determined. Lecarpentier et al. [8] investigated PI values measured at the same site in singleton pregnancies and found significantly different PI values and concluded that bilateral absent or reverse end-diastolic (ARED) flow in the two UAs indicated more severe hemodynamic compromise and worse fetal conditions than unilateral ARED flow. Contrastingly, in dichorionic twin pregnancies a recent study found the opposite, concluding that routine measurement of both UAs was not relevant [24].

All these studies however are not representative, since in clinical practice Doppler measurements are not performed lateral to both sides of the bladder wall within the fetus, but in the free-floating umbilical cord as recommended in current guidelines [25]. Reasoning for this is the relative simplicity and need for consistency in clinical practice. Our study therefore assessed the free-floating umbilical cord and found only small differences with good agreement. That Lecarpentier et al. [8] found more cases with abnormal flow, could partly be explained by the fact that vascular resistance is higher in the fetus than in the umbilical cord [10–14]. Nonetheless, Lecarpentier et al. [8] did include a more severely affected cohort than our study, and more research is needed to investigate the impact of possible differences between the UAs in case of abnormal flow in the free-floating umbilical cord. Additionally, the ideal sampling site could be further investigated in order to improve accuracy of UA Doppler measurements.

Another possible explanation for the findings in our study is the Hyrtl anastomosis, a communication between the two arteries near the placental end of the cord. This anastomosis is believed to equalize the blood pressure in the umbilical arteries, helping to equalize the area of placental coverage between the two arteries [26]. Thus, the fact that the difference in vascular resistance becomes lower towards the placental end of the umbilical cord may be due to Hyrtl anastomoses. In line with this theory, our study showed smaller differences between the two arteries in the free-floating umbilical cord than those found by Lecarpentier et al. [8] and Janeczek et al. [23], who measured the UAs alongside the bladder within the fetus. Furthermore, the rare extreme discrepancies found in our study may be explained by anatomical variation of the Hyrtl anastomosis, as described in a case series showing a relation between discordant UA Doppler measurements and absence of Hyrtl anastomosis [27]. However, postpartum assessment of the placenta was not part of this study, which is why we were not able to confirm this theory.

In conclusion, in singleton SGA pregnancies, we found a good agreement between PI values of the two UAs measured by Doppler ultrasound in the free-floating umbilical cord. Also, we found no differences between the two arteries in discriminative ability for adverse perinatal outcome. Therefore, standard measurement of both UAs would appear not to improve prognostic accuracy for adverse perinatal outcome. More research is needed to investigate the impact of possible differences between the UAs in fetuses with severe hemodynamic changes.

Disclosure of interests

The authors did not report any potential conflicts of interest.

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