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Uterine artery blood flow volume in pregnant women with an abnormal pulsatility index of the uterine arteries delivering normal or intrauterine growth restricted newborns☆

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ABSTRACT

The aim of this study was to assess and compare uterine artery (UtA) blood flow volume in pregnant patients with an abnormal uterine Doppler pulsatility index (PI) who delivered fetuses with an appropriate weight for gestational age (AGA) or with intrauterine growth restricted (IUGR).

We prospectively recruited singleton pregnancies with abnormal uterine arteries P.I. between 18 and 38 weeks of gestation regardless of estimated fetal weight (EFW). Vessel diameter and blood flow velocity were measured along the UtA upstream to the vessel bifurcation in both the right and left UtAs. Uterine blood flow volumes measured in these pregnancies were compared to historical Control-pregnancies. Forty-three patients delivered at term a normal weight newborn (AGA-pregnancies). Thirty patients delivered growth restricted newborns at 32 weeks (i.r. 29–36w) with a median weight of 1160 gr (i.r. 1000–2065 gr) (IUGR-pregnancies).

At mid-gestation (18 + 0 – 25 + 6 weeks + days of gestation) a significantly lower uterine blood flow volume per unit weight was observed between the two study groups and compared to controls: 142 ml/min/kg in IUGR-pregnancies, 217 ml/min/kg in AGA-pregnancies and 538 ml/min/kg in Control-pregnancies. These striking differences in blood flow volume were already present at mid-gestation, at a time when EFW was still normal. In late gestation (27 + 0 – 37 + 6 weeks + days of gestation), pregnancies with an abnormal uterine P.I. showed persistently low UtA flow (<50% of controls) even when corrected for fetal weight: 81 ml/min/kg in IUGR-pregnancies, 105 ml/min/kg in AGA-pregnancies, and 193 ml/min/kg in Control-pregnancies; $p < 0.0001$.

Our findings are consistent with other recent studies regarding the association between reduced uterine blood flow volume and fetal growth restriction. However, the study brings new insight into the finding of abnormal uterine P.I. in normally grown fetuses typically dismissed as "falsely abnormal" or "false positive" findings. Our study suggests that blood flow volume measurement may serve as a new tool to assess this group of patients and possibly those with ischemic placental diseases that may provide some basis for therapeutic interventions.

1. Introduction

Doppler waveform analysis of uterine artery (UtA) velocimetry is widely used as a screening test for early identification of placental damage in pregnancies at risk for severe intrauterine (fetal and placental growth restriction; IUGR), gestational hypertension (GH), and preeclampsia (PE). In 2000, Chien [1] reviewed almost 13,000 low risk patients showing that an abnormal uterine waveform value had positive and negative likelihood ratios (LR) for severe preeclampsia of 15.6 and 0.4, respectively. This important finding together with other significant LRs both for severe early PE and fetal growth restriction [5] are considered significant clinical achievements as they identify a large proportion of patients at risk early in pregnancy prior to the development of clinical disease. The combination of uterine Doppler velocimetry with biochemical markers of placental damage may further improve its predictive

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value as a possible screening test at mid-trimester and possibly even in the first trimester for low risk pregnancies [2–6]. These studies may eventually lead clinicians to provide early intervention in screen-positive patients [7].

However, a recent and extensive review [8] still defined uterine Doppler velocimetry, as a research tool. According to this review, the poor specificity of this test is one of the primary reasons why this potential diagnostic test remains questionable. This lack of specificity raises a fundamental question on the significance of an abnormal and notched Doppler waveform of the uterine artery. In fact, a commonly accepted interpretation of the high pulsatility of the Doppler waveform associated with abnormal placentas [9,10] is that poor trophoblastic invasion of spiral arteries fails to reduce the normally high impedance and limits the amount of flow delivered to the intervilluos space with each cardiac cycle. This recently was directly observed in human placenta with contrast enhanced NMR [11]. The reduced delivery of flow to the intervillous space due to a reduced number and extension of funneled spiral arteries may induce upstream a poor uterine vessels development, and thus poor placental perfusion. Additional criticism might be raised toward simplistic Doppler velocimetry waveform interpretation in these vessels in the light of low P.I. values induced simply by fibroids [12], or the persistence of low P.I. values even in the postpartum period [13,14] and in the puerperium [15] when subplacental spiral arteries are securely closed.

Recently our group reported [16] a novel methodology to measure uterine volume blood flow and established reference values in normal pregnancies. The data also reflected a significant correlation of UtA volume flow with UtA Doppler P.I. (UtA PI). Blood flow volume measurements of uterine vessels are subject to many limitations that include, but are not limited to anatomic issues on the sampling site, indeterminate collateral flow contributions from uterine-ovarian arteries, variations in fetal and placental weight, and in metabolic variations. Additional technical challenges include different Doppler technologies, vessel diameter measurements and flow volume calculations. However, the robust fluid dynamic model based on experimental 3D angio-Doppler imaging and high-resolution sonographic imaging collectively [17] compares favorably with the precision of steady state diffusion techniques adopted in experimental animal models for uterine blood flow volume measurements [18].

As one would expect, Doppler blood flow volume measurements calculated by different methodologies result in systematic differences in values and reference values. However, even then these measurements are still able to detect adaptive physiological differences between extreme conditions such as that seen in Andean and Caucasian pregnant women at high and low altitude [19], or even minor differences in uterine arteries of non-pregnant uterus under the influence of sildenafil [20].

We hypothesize that pregnancies with abnormal uterine artery velocimetry, but normal newborn size, will have normal volume blood flow measurements. The aim of this study was to assess and compare uterine volume blood flow in pregnant patients with an abnormal UtA PI who delivered newborns with a normal birth weight (appropriate for gestational age—AGA) and in pregnant patients who delivered newborns who suffered from IUGR.

2. Materials and methods

2.1. Study population

From September 2007 to September 2009, we prospectively recruited singleton pregnancies with abnormal uterine arteries mean P.I. between 18 and 37 completed weeks of gestation at the Department of Clinical Sciences and Department Maternal and Pediatric Sciences. Recruitment of patients with abnormal uterine artery (UtA) PI came from our own outpatient obstetric ultrasound unit as well as from referring providers who normally refer patients to our center both for pregnancy complications or for abnormal Doppler velocimetry findings. Eligible patients were divided into cases collected between 18 + 0 to 25 + 6 weeks of gestation (mid-gestation), and 27 + 0 to 37 + 6 (third trimester). An informed consent approved by the Ethical Committee was signed by each patient willing to participate to this study.

Eligible for the analysis were patients with sonographic assessment of gestational age in the first trimester, who were longitudinally monitored or treated in our center according to standard clinical protocols and who delivered fetuses without chromosomal abnormality or structural malformations.

Gestational age at birth, mode of delivery, birth weight and neonatal outcome were recorded. Gestational hypertension (GH) and preeclampsia (PE) were also recorded [21]. Early and late GH and PE were defined based on the time of first diagnosis before 34 weeks of gestation.

2.2. Ultrasonic procedures

All examinations were performed between 09.00 a.m. and 01.00 p.m. During each ultrasound examination, routine fetal biometry measurements were performed (head and abdominal circumference, and femur length) and an estimated fetal weight was calculated using the Hadlock formula [22]. Fetal growth restriction was defined as abdominal circumference below the 10th percentile or a reduction of at least 40 percentiles in two consecutive measurements in second and third trimester [23], and with newborn weight below the 10th percentile of reference standards. These pregnancies were delivered between 25 and 37 weeks of gestation.

Standard UtA PI and umbilical artery Doppler measurements were performed at the beginning of the ultrasound examination. An abnormal UtA PI was defined according to the reference ranges reported by Acharya [24]. A single ultrasound machine (Voluson Expert General Electric Healthcare, Zipf, Austria) was used to calculate the vessel diameter (D), and blood flow velocity along the UtA approximately 15 mm upstream to vessel bifurcation or 3 to 5 cm after its origin at the hypogastric artery. Both right and left UtA diameters were measured on a perpendicular B-mode view of the longitudinal vessel section at maximum magnification. The lumen of the vessel was identified by colour power angiography and the diameter was measured on a gray-scale image after reducing the colour box by placing the calipers at the inner edges of the vessel itself at the specular reflection (Fig. 1). The average of three consecutive measurements of vessel diameter was used.

UtA PI and blood flow velocity were measured with a Doppler beam angle $<30^{\circ}$. The time-average maximum velocity along the cardiac cycle TAV-max and the mean PI within 3–5 cycles were recorded. The maternal heart rate was also recorded. The length of the uterine artery was not always accessible. According to our previous study we adopted a fixed value of 4 cm [16]. The flow volume through each UtA was calculated according to the formula Volume Flow = hTAVmax $\pi D^2/4$. Total UtA volume flow was calculated as the sum of the two vessels. The spatial velocity profiles along the UtA and corresponding h coefficients were calculated on the basis of Reynolds number (Re), which expresses the convective-to-viscous forces ratio, and the Womersley number (α numbers), which is related to the inertial-to-viscous forces ratio according to the findings of Pennati [17] and Rigano [16].

2.3. Statistics

Uterine blood flow volumes measured in these pregnancies were compared to reference values recently reported in this journal by our group [16]. Non-parametric statistics (Wilcoxon–Mann–Withney test) were used to describe and compare sets of data not normally distributed in AGA and growth restricted fetuses. Data were expressed as median and interquartile range (i.r.).

Eleven patients had three or more uterine blood flow volume measurements throughout gestation. For the purposes of statistical comparison between groups, only values from the earliest examination performed in the second and in the third trimester cases were counted to obtain balanced mixed cross-sectional data. Complete sets of longitudinal data were than used to plot individual longitudinal findings.

3. Results

3.1. Clinical outcome

A total of 73 patients were enrolled in this study. Forty-three patients showed normal fetal growth in utero and delivered newborns of an appropriate weight for gestational age (AGA-pregnancies). Umbilical P.I. was normal in all these cases [24]. Median gestational age at delivery was 39 + 0 (i.r. 38 + 0 ÷ 39 + 2). Median birth weight was 3025 (i.r. 2905 ÷ 3218). In 3 of 38 cases (9%), late GH was diagnosed. According to local clinical protocols, cesarean delivery in labor was performed in 24% of cases. Thirty pregnant patients developed fetal growth restriction (IUGR-pregnancies). In 15 fetuses the umbilical Doppler velocimetry was