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Exploring sexual dimorphism in placental circulation at 22–24 weeks of gestation: A cross-sectional observational study

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ABSTRACT

Introduction: Placental blood flow is closely associated with fetal growth and wellbeing. Recent studies suggest that there are differences in blood flow between male and female fetuses. We hypothesized that sexual dimorphism exists in fetal and placental blood flow at 22–24 weeks of gestation.
Methods: This was a prospective cross-sectional study of 520 healthy pregnant women. Blood flow velocities of the middle cerebral artery (MCA), umbilical artery (UA), umbilical vein (UV) and the uterine arteries (UtA) were measured using Doppler ultrasonography. UV and UtA diameters were measured using two-dimensional ultrasonography and power Doppler angiography. Volume blood flows (Q) of the UV and UtA were calculated. Maternal haemodynamics was assessed with impedance cardiography. UtA resistance (R_{uta}) was computed as MAP/Q_{uta}.
Results: UA PI was significantly ($p = 0.008$) higher in female fetuses (1.19 ± 0.15) compared with male fetuses (1.15 ± 0.14). MCA PI, cerebro-placental ratio (MCA PI/UA PI), Q_{uv}, UtA PI, Q_{uta} and R_{uta} were not significantly different between groups. At delivery, the mean birth weight and placental weight of female infants (3504 g and 610 g) were significantly ($p = 0.0005$ and $p = 0.039$) lower than that of the male infants (3642 g and 634 g).
Discussion: We have demonstrated sexual dimorphism in UA PI, a surrogate for placental vascular resistance, at 22–24 weeks of gestation. Therefore, it would be useful to know when this difference emerges and whether it translates into blood flow differences that may impact upon the fetal growth trajectory.

1. Introduction

There is growing evidence for sex-specific differences in fetal growth and adaption to the intrauterine environment [1]. It has been shown that males are more at risk for various adverse outcomes such as premature birth [2,3], fetal distress during labour [4], poor neonatal outcome [5] and early neonatal death than females [1]. It is often referred to as "the male disadvantage" [6]. In pregnancies complicated by preeclampsia and intrauterine growth retardation (IUGR), perinatal mortality and morbidity are worse for males than for females [7]. Fetal sex also influences placental gene expression and inflammatory response [8,9] resulting in differences in placental function, with the potential of a sex-bias for certain diseases later in life [10,11].

Placental circulation is closely associated with fetal growth and wellbeing [12]. Doppler ultrasonographic measurements of feto-placental and utero-placental blood flow have been used extensively to identify and monitor pregnancies at risk for adverse outcomes, such as preeclampsia and IUGR. One recent study demonstrated differences in middle cerebral artery (MCA) blood flow velocity waveforms and umbilical vein (UV) volume blood flow between male and female fetuses at term [13]. However, the measured differences were not related to fetal outcomes. Studies on ductus venosus Doppler in the first trimester have shown conflicting results regarding sex differences [14–16].

Umbilical artery (UA) blood flow velocity waveforms are used to assess fetal wellbeing in clinical practice, and increased pulsatility index (PI) in the UA has been shown to correlate with morphologic alterations in the placenta (reduced vascularity) and impaired

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placental function [17].

Measurements of the UA and MCA blood flow velocities are used to identify redistribution of blood flow in favour of the brain, i.e. "brain-sparing" [18] in IUGR fetuses. Furthermore, the cerebro-placental ratio (CPR) can be useful in the detection of subtle growth restriction [18]. The UV volume blood flow has been reported to be reduced in fetuses subsequently developing IUGR even before the UA PI is changed [19]. On the maternal side the uterine artery (UtA) PI is increased in pregnancies at risk of preeclampsia and IUGR [20]. Although hemodynamic assessment of fetal and placental circulations are routinely used to make clinical decisions, sex differences in the measured Doppler parameters have been scarcely investigated and are not taken into account.

The objective of this study was to explore sexual dimorphism in fetal and placental circulation in uncomplicated pregnancies at 22–24 weeks of gestation. We tested the null hypothesis that no sex differences exist in the Doppler-derived haemodynamic parameters of feto-placental and utero-placental circulation in normal pregnancy when the placentation has fully established.

2. Methods

2.1. Participants

This is a part of an ongoing prospective cross-sectional study on maternal haemodynamics and feto-placental circulation in normal and complicated pregnancies at the Department of Obstetrics and Gynaecology, University Hospital of North Norway, Tromsø, Norway. All pregnant women ≥18 years of age attending the routine antenatal ultrasound screening at 17–20 weeks of gestation were informed about the study and invited to participate. A total of 584 healthy pregnant women with uncomplicated singleton pregnancy who consented to participate in this study were examined once between 22^{+0} and 24^{+0} weeks of gestation. The gestational age was based on pregnancy dating from second trimester ultrasound biometry of fetal head. The following participants were subsequently excluded due to pregnancy complications: 41 with pre-eclampsia, 20 who delivered preterm, one that had placental abruption and two with IUGR. Thus a total of 520 women were included in the final analysis. The research protocol was approved by the Regional Committee for Medical Research Ethics (ref. no. 5.2005.1386) and an informed written consent was obtained from each participant.

2.2. Measurements

An ultrasound system with a 6-MHz curvilinear transducer (Acuson Sequoia 512, Mountain View, CA, USA) was used for ultrasonography. All participants were examined in the supine semi-recumbent position. Two experienced clinicians (KF and CW) performed all the ultrasonographic examinations and the sex of the fetus was not identified or acknowledged. Only one clinician performed the measurements per patient. Estimated Fetal weight (EFW) was computed based on the fetal biometry using the Hadlock formula [21], and amniotic fluid index (AFI) was measured. Blood flow velocity waveforms were obtained from the UA, UV, MCA and UtA using pulsed-wave Doppler keeping the angle of insonation close to 0°, and always less than 30°. A large sample volume (Doppler gate 5–10 mm) was used to include the entire cross-section of the insonated blood vessels. The blood flow velocities were measured using the maximum velocity envelope recorded over the cardiac cycle. The pulsatility index (PI) was calculated as: (peak systolic velocity − end-diastolic velocity)/time-averaged maximum velocity. Measurements from the UA and UV were obtained from a free-floating loop of the umbilical cord. The UtA measurements were obtained just proximal to the apparent crossing of the external iliac artery seen on color Doppler. The MCA was imaged using color Doppler and measured by placing the Doppler gate at the proximal third of the distance from its origin at the circle of Willis. The average value from three consecutive heart cycles was used. The CPR was calculated as MCA PI/UA PI.

The UV and UtA diameters were measured on the same portion of the vessel from where the blood velocity measurements were obtained, using two-dimensional ultrasonography and power Doppler angiography, respectively. For the latter the scale of Doppler intensity was set at maximum and the gain was optimised to avoid possible overestimation of the UtA diameter. The volume blood flow (Q) of the UV and UtA was calculated as the product of the cross-sectional area (CSA) of the vessel and the time-averaged intensity weighted mean velocity (TAV). The total Q_{uta} was calculated as the sum of volume blood flow in the right and left UtA.

The reproducibility of the Doppler parameters studied has been extensively evaluated and reported previously. We have reported the intra-observer coefficient of variation (CV) for UA PI to be 10.5% (95% CI, 9.9%–11.1%), based on three sets of 513 observations [22], and the mean inter-observer CV between six operator pairs was reported to be 8.4% by Gudmundsson et al. [23]. We have reported the intra-observer CV of 11.6% (95% CI, 4.7–7.3%) for the left Q_{uta} and 13.2% (95% CI, 10.1–15.7%) for the right Q_{uta} [24]. For the Q_{uv}, Barbera et al. evaluated the intra- and inter-observer variations and report to be 10.9% and 12.7%, respectively [25], whereas Figueras et al. have reported the intra-observer intra-class correlation coefficient (ICC) of 0.55 (95% CI, 0.35–0.7) and inter-observer ICC of 0.6 (95% CI, 0.4–0.74), respectively [26].

To measure maternal stroke volume, heart rate and mean arterial blood pressure (MAP) impedance cardiography (ICG) (Phillips Medical Systems, Androver, MA, USA) was used, as described previously [24]. The cardiac output (CO) and the systemic vascular resistance (SVR) were automatically calculated. The body mass index (BMI) was calculated as height/weight^2 using the current weight, and the body surface area (BSA) was computed using the Du Bois formula [27]. UtA resistance (R_{uta}) was computed as MAP/Q_{uta}. The normalized placental volume blood flow was calculated as Q_{UV}/EFW. Following delivery, information on the course and outcome of the pregnancy was recorded from the woman's electronic medical record.

2.3. Statistical analysis

Continuous variables are presented as means ± SDs or median (range) and categorical variables as number (%), as appropriate. Data were checked for normality using Shapiro-Wilk test and parametric tests were used for comparing groups only after verifying normal data distribution. Comparison between the two groups was performed using independent samples t-tests (IBM SPSS Statistics, Version 22) for continuous variables and chi-square tests for categorical variables. Association between parametric variables was tested using Pearson correlation. A two-tailed p-value ≤0.05 was considered significant.

3. Results

The baseline characteristics of the study population, including pregnancy and neonatal outcomes, are listed in Table 1. There were no statistically significant differences between the two groups in maternal characteristics such as age, BMI, parity, previous caesarean section, or previous history of preeclampsia and hypertension. At delivery, the mean birth weight and placental weight of female infants (3504 g and 610 g) were significantly ($p = 0.0005$ and $p = 0.039$) lower than that of the male infants (3642 g and