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Influence of parity on fetal hemodynamics and amniotic fluid volume at term

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ABSTRACT

Objectives Pregnancy complications, particularly those associated with placental dysfunction, occur more frequently in nulliparous than in parous women. This difference may be a consequence of improved trophoblastic invasion and, as a result, improved placental function following previous pregnancy. Placental dysfunction in cases of fetal growth restriction may be identified by ultrasound assessment of fetoplacental hemodynamics and amniotic fluid volume. In this prospective observational study, we investigated whether differences in these measures of placental function exist between nulliparous and parous women, prior to active labor.

Methods Over a 2-year period, 456 nulliparous and 152 parous women with uncomplicated singleton pregnancies were recruited to this prospective observational study. Each participant underwent an ultrasound assessment prior to active labor, during which fetal biometry, umbilical artery, middle cerebral artery and umbilical venous Dopplers, as well as amniotic fluid volume, were assessed. All cases were followed up within 48 h of delivery. Ultrasound parameters and intrapartum outcomes were then compared between the nulliparous and parous groups.

Results Compared with nulliparous women, parous women had significantly higher fetal middle cerebral artery pulsatility index, cerebroplacental ratio and amniotic fluid volume. In nulliparous women, middle cerebral artery flow rate was also significantly higher and represented a greater percentage of umbilical venous flow than was observed in parous women.

Conclusion Prior to the active phase of labor, ultrasound parameters indicative of placental function differ significantly between nulliparous and parous pregnancy, even amongst an uncomplicated, low-risk cohort. Copyright © 2014 ISUOG. Published by John Wiley & Sons Ltd.

INTRODUCTION

Many complications of pregnancy are known to be more common in nulliparous than in parous women, including those classically associated with placental dysfunction such as pre-eclampsia¹, fetal growth restriction² and stillbirth³. There is evidence that remodeling of uterine spiral arteries in a first pregnancy leads to persistent changes in their architecture, which in turn influences the trophoblast- and perfusion-mediated changes in subsequent pregnancies⁴. The reduced incidence of pregnancy complications associated with placental dysfunction in parous women, including fetal growth restriction and pre-eclampsia, may therefore be the result of improved trophoblastic invasion in these pregnancies⁵. The influence of parity on placental function does not appear to be limited to complicated pregnancies as it is also well documented to have an independent effect on fetal weight⁶, with subsequent babies generally larger than their first-born sibling. The incidence of intrapartum fetal compromise and associated emergency operative delivery is also higher in nulliparous women⁷.

In pregnancies complicated by fetal growth restriction there is an increased resistance in the umbilical artery (UA) and reduced resistance in the middle cerebral artery (MCA)⁸, indicating increased placental resistance and cerebral redistribution, respectively. A reduction in umbilical venous flow⁹ and oligohydramnios¹⁰ are other features seen in these pregnancies. We have previously shown that changes in UA and MCA resistance¹¹, and umbilical venous flow¹², in early labor are predictors of subsequent intrapartum fetal compromise in appropriately-grown term fetuses. We have also shown that babies who have a low cerebroplacental ratio (CPR) at the start of labor are significantly more likely to subsequently develop signs of intrapartum fetal compromise¹¹.

Despite the apparent link between parity, placental dysfunction and fetal hemodynamics, there has been little

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investigation into the differences of measures of placental function (such as fetal hemodynamics and amniotic fluid volume), between nulliparous and parous women in uncomplicated term pregnancies. In this study we aimed to ascertain whether, prior to the active phase of labor, there were any differences in fetal hemodynamics and amniotic fluid volume between appropriately-grown fetuses of nulliparous and parous women. We hypothesized that, in appropriately-grown fetuses at term, nulliparous women would have higher UA pulsatility index (PI), lower fetal MCA-PI, lower umbilical venous flow rates and lower amniotic fluid volumes than their parous counterparts.

METHODS

Over a 2-year period, 608 women were recruited to this prospective observational study at Queen Charlotte's and Chelsea Hospital, London, UK. All participants gave informed written consent for inclusion in the research study. Only women at term, with uncomplicated, singleton, low-risk pregnancies, were eligible for inclusion. Exclusion criteria included multiple pregnancy, gestation of < 37 or > 42 weeks, known fetal anomaly, a history of maternal hypertensive disease (in either the current or previous pregnancies) or concerns regarding fetal growth (e.g. estimated fetal weight < 10th centile/ultrasound-detected reduced growth velocity/UA-PI > 95th centile) and cervical dilatation > 4 cm. Women were recruited from the delivery suite, day-assessment unit and antenatal clinic over a 30-month period. Maternal details, including age, body mass index, gestation, ethnicity and parity, were documented. All participants then underwent an ultrasound scan in early labor (< 3 cm dilated) using a Voluson e portable ultrasound machine with an AB2-7R-S curvilinear abdominal transducer (GE Healthcare Ultrasound, Milwaukee, WI, USA). All ultrasound scans were performed by a single operator. During this assessment, UA, MCA and umbilical vein (UV) flow velocity waveforms were recorded, as well as fetal biometry and amniotic fluid index. Women were in a supine position with the head of the bed elevated at 45° and a left lateral tilt to prevent caval compression. Fetal vessels were identified using color Doppler and PIs were captured using automated tracing of at least three consecutive waveforms. All measurements were taken in the absence of fetal breathing movements and contractions and were repeated in triplicate, with the mean of these used for subsequent data analysis. All Doppler waveforms were recorded with an angle of insonation as close to 0° as possible, and always less than 30°. The angle correction function was used to compensate for any waveforms acquired with an angle of insonation other than 0°. For measurements of vessel diameter, the vessel was insonated at a 90° angle, or as close to this as possible. The MCA was identified using power Doppler, and measurements of internal diameter were taken at the junction of the proximal third and distal two-thirds segments. The umbilical vein was imaged in gray scale and its internal diameter recorded. In each case the image was magnified to occupy at least 50% of the

field. The assessment of flow rate in fetal vessels using this measurement technique has been demonstrated to be accurate when compared with gold standard methods of *in-vivo* flow calculation^{13,14}. The CPR was calculated by dividing MCA-PI by UA-PI. The volume of blood flow was calculated using the following formula, the derivation of which is documented in the Appendix:

Flow rate (mL/min) = time-averaged velocity (cm/s) × 0.3 × cross-sectional area (mm²).

Cases were managed according to local protocols and guidelines, with staff who managed the labor being blinded to the ultrasound findings to prevent bias.

Following delivery, cases were categorized, according to parity, as nulliparous (no previous deliveries at > 24 weeks' gestation) and parous (one or more previous deliveries at > 24 weeks' gestation), and ultrasound parameters and intrapartum outcomes were compared between the two groups. Student's *t*-test and the Mann-Whitney *U*-test were used to compare continuous variables between the two groups, and relative risks with 95% CI were calculated for other intrapartum outcomes. The diagnosis of intrapartum fetal compromise was based on pathological fetal heart-rate patterns, abnormal fetal blood sampling or both. Fetal heart-rate patterns were interpreted according to National Institute for Health and Clinical Excellence (NICE) guidelines¹⁵.

RESULTS

Six-hundred and eight women were recruited over a 2-year period. Cases were divided into two groups based on parity (nulliparous/parous). Maternal demographics and Doppler PIs were compared between the two groups (Table 1). Significant differences in both maternal age and gestation at delivery were observed, with the nulliparous group having a lower mean maternal age (31.9 years *vs* 33.9 years, *P* < 0.001), and a later mean gestational age (40.7 weeks *vs* 40.0 weeks, *P* < 0.001). The proportion of women of Afro-Caribbean ethnicity was also higher in the parous group (15.1% *vs* 8.6%, *P* = 0.03).

Whilst no significant difference was observed in UA-PI, both the MCA-PI and the CPR were found to be significantly lower in nulliparous women (MCA-PI: 1.34 in nulliparous women *vs* 1.44 in parous women, *P* < 0.001; CPR: 1.72 in nulliparous women *vs* 1.88 in parous women, *P* < 0.001). Within the study population, the proportion of women with an MCA-PI or CPR < 5th centile did not differ significantly between nulliparous and parous women (MCA-PI < 5th centile: 3.1% in nulliparous women *vs* 2.6% in parous women, *P* = 0.77; CPR < 5th centile: 2% in nulliparous women *vs* 0.7% in parous women, *P* = 0.27).

Flow rates in the MCA and UV were calculated using vessel diameters and time-averaged velocity measurements. To establish whether the lower MCA-PI values observed in babies of nulliparous women were representative of greater cerebral perfusion, the MCA flow was calculated as a percentage of umbilical venous flow (MCA/UV flow). Higher MCA flow rates were observed

Table 1 Comparison of maternal demographics, Doppler pulsatility indices and outcome between nulliparous and parous women with uncomplicated singleton pregnancies

| Variable | Nulliparous | Parous | P |
|--|--------------------|--------------------|---------|
| Number of women | 456 | 152 | |
| Age (years) | 31.9 (16–46) | 33.9 (21–47) | < 0.001 |
| Body mass index (kg/m ²) | 24.6 (16–42) | 24.9 (17–37) | 0.44 |
| Gestational age at delivery (weeks) | 40.7 (37.0–42.0) | 40.0 (37.0–42.0) | < 0.001 |
| Ethnicity | | | |
| Caucasian | 318 (69.7) | 93 (61.2) | 0.27 |
| Asian | 82 (18.0) | 25 (16.4) | 0.70 |
| Afro-Caribbean | 39 (8.6) | 23 (15.1) | 0.03 |
| Other | 17 (3.7) | 11 (7.2) | 0.08 |
| Doppler indices | | | |
| UA-PI | 0.80 (0.51–1.53) | 0.79 (0.46–1.53) | 0.18 |
| MCA-PI | 1.34 (0.68–2.32) | 1.44 (0.73–2.29) | < 0.001 |
| CPR | 1.72 (0.59–2.99) | 1.88 (0.94–3.15) | < 0.001 |
| UV flow (mL/min) | 211.1 (34.6–577.0) | 220.5 (17.9–371.0) | 0.11 |
| MCA flow (mL/min) | 83.2 (17.2–188.9) | 74.2 (21.8–166.1) | 0.005 |
| MCA/UV flow (%) | 42.3 (8.1–94.0) | 36.5 (3.0–87.2) | 0.006 |
| Amniotic fluid index (cm) | 8.9 (0.1–24.0) | 10.0 (1.0–32.0) | 0.004 |
| Birth weight (g) | 3509 (2144–5026) | 3569 (1780–4940) | 0.17 |
| Birth-weight centile | 51.2 (1–100) | 58.6 (1–100) | 0.006 |
| Emergency LSCS for fetal distress | 66 (14.5) | 7 (4.6) | 0.002 |
| Instrumental delivery for fetal distress | 97 (21.3) | 9 (5.9) | < 0.001 |

Values are given as mean (range) or *n* (%). CPR, cerebroplacental ratio; LSCS, lower segment Cesarean section; MCA, middle cerebral artery; PI, pulsatility index; UA, umbilical artery; UV, umbilical vein.

in the babies of nulliparous women (83.2 mL/min *vs* 74.2 mL/min, $P=0.005$). MCA flow was also found to represent a higher proportion of umbilical venous flow in these babies (42.3% *vs* 36.5%, $P=0.006$). No difference in umbilical venous flow rates were observed (211.1 mL/min *vs* 220.5 mL/min, $P=0.11$).

Other markers of placental function were also investigated. Amniotic fluid volume was assessed using the amniotic fluid index (AFI). Nulliparous women were observed to have significantly lower AFI than were parous women (8.9 cm in nulliparous women *vs* 10 cm in parous women, $P=0.004$). Whilst babies of nulliparous women were not found to have a significantly lower birth weight than those of parous women (3509 g *vs* 3569 g, respectively, $P=0.17$), when gestation was controlled for by the calculation of gestation-matched birth-weight centiles, babies of nulliparous women were found to be significantly smaller than those of parous women (51.2 *vs* 58.6, $P=0.006$).

Multiple linear regression analysis was used to establish if the variation in MCA-PI, CPR, AFI, birth-weight centile and MCA/UV flow, between babies of nulliparous and parous women, remained statistically significant when the differences in maternal age and gestation between the two groups were controlled for. The variation in the MCA-PI, CPR, AFI, birth-weight centile and MCA/UV flow rates remained statistically significant ($P < 0.001$, $P < 0.001$, $P < 0.004$, $P < 0.006$ and $P < 0.006$, respectively).

As some babies included in the study were small-for-gestational age at delivery (birth weight < 10th centile for gestation) and therefore could have been growth restricted, the analysis was repeated with these cases removed. The differences in MCA-PI (1.34 *vs* 1.44, $P < 0.001$), CPR (1.72 *vs* 1.89, $P < 0.001$), AFI (9.0 *vs*

10.1, $P=0.01$), gestation-matched birth-weight centile (54.8 *vs* 62.0, $P=0.005$) and MCA/UV flow (42.0% *vs* 32.9%, $P=0.002$) between nulliparous and parous cases remained statistically significant.

Intrapartum outcomes were compared between nulliparous and parous women. Nulliparous women were at significantly increased risk of requiring an emergency Cesarean delivery (14.5% *vs* 4.6%, $P=0.002$; relative risk = 3.14; 95% CI, 1.47–6.70), as well as requiring an instrumental delivery (21.3% *vs* 5.9%, $P < 0.001$, relative risk = 3.43; 95% CI, 1.78–6.61) for presumed fetal compromise.

DISCUSSION

The results of this study demonstrate that prior to the active phase of labor, fetal MCA-PI, CPR, AFI, birth-weight centile and MCA/UV flow show significant difference between babies of nulliparous and parous women. Many disorders of pregnancy associated with placental dysfunction have been observed to occur more frequently in nulliparous women but, to our knowledge, this is the first study to identify differences in fetal Doppler parameters and AFI, measured in early labor, between nulliparous and parous women in uncomplicated, low-risk pregnancies.

Cerebral redistribution as an adaptive response of the fetus to placental dysfunction is well reported¹⁶ and is evidenced by a reduction in the MCA-PI¹⁷. However, it is the CPR that has been suggested as the most accurate method of identifying cerebral redistribution¹⁸. The results of this study suggest that fetuses of nulliparous women have significantly greater cerebral perfusion than do those of parous women, as evidenced by their

lower mean CPR as well as greater absolute flow rates. Furthermore, this increased volume represented a greater proportion of umbilical venous flow compared with fetuses of parous women. As other surrogate markers of placental function, including AFI and gestation-matched birth-weight centile, were also comparably reduced in fetuses of nulliparous women, these results suggest that even amongst appropriately-grown babies in uncomplicated pregnancies, differing levels of placental function exist between nulliparous and parous women. This would suggest that in nulliparous women fetuses are more likely to demonstrate a 'growth-restricted' hemodynamic phenotype, in contrast to parous women in whom the uterus has been 'primed' by a previous pregnancy.

The values of the Doppler parameters reported in this study are similar to those of published reference ranges¹⁹. Nomograms for MCA flow volumes are yet to be established; however, Konje *et al.* reported a mean MCA flow volume of 140 mL/min at 38 weeks' gestation¹⁴. This flow rate is higher than that observed in our data and is the result of a larger mean diameter for the MCA reported in the study of Konje *et al.*¹⁴. This difference highlights the requirement for strict measurement criteria when assessing flow in fetal vessels and leads to difficulty in comparing absolute MCA flow rates between studies. However, it is not considered to impact the validity of intrastudy comparisons, in which all ultrasound scans were performed using the same technique and by the same practitioner. Reference ranges for umbilical venous flow have been published²⁰. Acharya *et al.* reported a 50th centile value for umbilical venous flow at term of 262.7 mL/min. This value is slightly higher than that reported in our data, and is possibly a result of the use of a different measurement technique. Whilst Acharya *et al.* measured UV diameter at the intra-abdominal portion of the UV, we chose to measure UV diameter at a free loop of cord. UV diameter has been reported to decrease from the fetus to the placenta, but it is most easily assessed with accuracy at a free loop¹³, hence the use of this site in our study.

Other possible causes for the increased cerebral blood flow observed in babies of nulliparous mothers must be considered. During this study, ultrasound assessments were performed during early labor. This may have the potential to introduce bias, as impedance within the cerebral vasculature is related to the proximity of labor, with lower PIs seen closer to the onset of labor²¹. There is therefore a possibility that the difference we observed in cerebral blood flow between nulliparous and parous women may be evidence of a differing hemodynamic adaptation to labor. However, this would not explain the associated differences in amniotic fluid volume and birth weight between nulliparous and parous women, both of which are consistent with a more prolonged alteration in placental function.

A significant difference in both maternal age and gestation was also observed between groups. However, the absolute difference was small (2 years and 0.7 weeks, respectively). Furthermore, the differences in fetal hemodynamics and amniotic fluid volume remained statistically

significant when multiple linear regression analysis was used to adjust for these confounders.

Differing amounts of pressure on the maternal abdomen have been demonstrated to affect fetal cerebral blood flow²². As a result, variation in the degree of fetal head engagement in the maternal pelvis between nulliparous and parous women may have had an effect on fetal cerebral blood flow measurements. At term, babies of nulliparous women are likely to be deeper in the pelvis than those of parous women. However, a greater degree of head engagement is likely to result in greater pressure on the fetal head, which would, in turn, be expected to result in reduced cerebral perfusion, rather than the increased cerebral perfusion observed in this study. Furthermore, differences in other markers of fetal growth and wellbeing, such as reduced gestational-age-matched birth-weight centile and amniotic fluid volume, support the suggestion that the relatively increased cerebral blood flow observed in babies of nulliparous women is a fetal adaptation secondary to the relatively reduced placental function in nulliparous compared with parous women.

Data from this study did not demonstrate any difference in UA flow between babies of nulliparous and parous women. Doppler assessment of the UA has been suggested as a surrogate marker of placental function¹⁶. However, significant loss of placental function is needed before the upstream effects on umbilical arterial flow become evident. Evaluation of small-for-gestational-age fetuses has demonstrated that increased cerebral perfusion, as evidenced by a reduced MCA-PI, can occur in the presence of normal UA waveforms, and that such changes in fetal hemodynamics can be correlated with an increase in adverse neonatal outcomes²³.

Significant differences in UA Doppler parameters have been observed previously between nulliparous and parous women²⁴. Differences in trophoblastic invasion, as well as in vascular endothelial growth factor (VEGF) expression, have also been reported in animal studies²⁵. The alteration in VEGF expression is particularly interesting given its involvement in degradation of the extracellular matrix required for trophoblastic invasion²⁶. The results of this study demonstrating that prior to active labor the MCA-PI and the CPR, as well as other markers of placental function, are also affected by parity, supports the previous findings of significant differences in uterine, placental and fetal perfusion in late pregnancy and adds to current knowledge. These data suggest that differences in placentation between nulliparous and parous pregnancy, which result in the former having a higher incidence of complications, may also influence fetal hemodynamics (prior to active labor) and growth in normal pregnancy, in a manner not dissimilar to that seen in fetal growth restriction.

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APPENDIX

Cross-sectional area was calculated using the measured diameter of the vessel and the formula for the area of a circle (πr^2)

$$1 \text{ mL/min} = 1 \text{ cm/s/cm}^2 \times 60$$

A multiplication factor of 0.5 is required to correct for laminar flow in a cylindrical vessel (owing to slower flow at the perimeter of the vessel caused by friction with the vessel walls).

$$1 \text{ mL/min} = 1 \text{ cm/s/cm}^2 \times 60 \times 0.5$$

$$1 \text{ mL/min} = 1 \text{ cm/s/cm}^2 \times 30$$

$$\text{As } 1 \text{ cm}^2 = 100 \text{ mm}^2$$

$$1 \text{ mL/min} = 1 \text{ cm/s/mm}^2 \times 30/100$$

$$1 \text{ mL/min} = 1 \text{ cm/s/mm}^2 \times 0.3$$