Placenta 38 (2016) 41–48

Contents lists available at ScienceDirect

Placenta

journal homepage: www.elsevier.com/locate/placenta

The relationship between human placental morphometry and ultrasonic measurements of utero-placental blood flow and fetal growth

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ARTICLE INFO

Article history:
Received 19 July 2015
Received in revised form
28 October 2015
Accepted 4 December 2015

Keywords:
Placenta
Morphometry
Doppler flow velocimetry
Fetal growth
Human

ABSTRACT

Introduction: Ultrasonic fetal biometry and arterial Doppler flow velocimetry are widely used to assess the risk of pregnancy complications. There is an extensive literature on the relationship between pregnancy outcomes and the size and shape of the placenta. However, ultrasonic fetal biometry and arterial Doppler flow velocimetry have not previously been studied in relation to postnatal placental morphometry in detail.
Methods: We conducted a prospective cohort study of nulliparous women in The Rosie Hospital, Cambridge (UK). We studied a group of 2120 women who had complete data on uterine and umbilical Doppler velocimetry and fetal biometry at 20, 28 and 36 weeks' gestational age, digital images of the placenta available, and delivered a liveborn infant at term. Associations were expressed as the difference in the standard deviation (SD) score of the gestational age adjusted ultrasound measurement (z-score) comparing the lowest and highest decile of the given placental morphometric measurement.
Results: The lowest decile of placental surface area was associated with 0.87 SD higher uterine artery Doppler mean pulsatility index (PI) at 20 weeks (95% CI: 0.68 to 1.07, P < 0.001). The lowest decile of placental weight was associated with 0.73 SD higher umbilical artery Doppler PI at 36 weeks (95% CI: 0.54 to 0.93, P < 0.001). The lowest decile of both placental weight and placental area were associated with reduced growth velocity of the fetal abdominal circumference between 20 and 36 weeks (both P < 0.001).
Conclusion: Placental area and weight are associated with uterine and umbilical blood flow, respectively, and both are associated with fetal growth rate.

1. Introduction

Placental blood flow and gas and nutrient transport are major determinants of fetal growth [1]. The size, weight and shape of the placenta are all subject to wide variations [2] and placental size is related to its ability to transfer nutrients [2,3]. Several studies have described the relationship between placental morphometry and adverse pregnancy outcome, including fetal growth restriction (FGR) [3]. Small placental size [4], decreased placental surface area [5] and small placental volume [6] have been associated with increased risk of FGR. Smaller surface area and a more oval shape are more common in pregnancies complicated by preeclampsia [6,7]. Moreover, variations in size and placental thickness at birth are associated with increased rates of coronary disease and related disorders such as stroke, hypertension and type-2 diabetes in later life [8].

Placental function can be assessed *in vivo* by utero-placental Doppler flow velocimetry and fetal growth can be assessed by

Abbreviations: AC, abdominal circumference; CCC, concordance correlation coefficient; CI, confidence interval; CV, coefficient of variation; FGR, fetal growth restriction; GV, growth velocity; LA, limits of agreement; PI, pulsatility index; POP, Pregnancy Outcome Prediction; SD, standard deviation; UmA, umbilical artery; UtA, uterine artery.

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http://dx.doi.org/10.1016/j.placenta.2015.12.003

serial ultrasonic biometry. Prior to pregnancy, flow velocity waveforms in the uterine artery (UtA) tend to be high resistance, and the development of a low resistance pattern of flow in the first half of pregnancy is thought to be due to invasion of the maternal resistance vessels by the trophoblast [9,10]. Persistence of high resistance patterns of flow in the UtA in mid-gestation has been associated with an increased risk of obstetric complications [11,12]. The flow velocity waveform in the umbilical artery (UmA) is normally low resistance in the last trimester of pregnancy, and this is thought to reflect the development of the villous vascular tree [2]. A high resistance pattern of flow in the umbilical artery is widely used as an indicator of placental dysfunction, where the structural correlate of high resistance flow is maldevelopment of the tertiary villi [1].

Most studies on the inter-relationships between antenatal utero-placental Doppler blood flow velocimetry and the post-natal findings have focused on the microscopic and ultrastructural characteristics of the placenta and placental bed. However, utero-placental blood flow could also be related to the gross morphology of the placenta. We are unaware of any study employing an appropriate design, methodology and a sufficient sample size that aims to determine these relationships. In the present study, we analysed data from 2120 unselected women having first singleton pregnancies who were recruited to a prospective cohort study. All women delivered at term and there were data from both serial blinded ultrasound scans, and a standardised series of digital images of each placenta obtained after the delivery. The aim of the study was to determine the inter-relationships between the size and shape of the placenta (assessed following birth), utero-placental Doppler flow velocimetry and the rate of growth of the fetal abdomen between 20 and 36 weeks' gestational age (GA).

2. Methods

2.1. Ethical approval

Ethical approval for the study was given by the Cambridgeshire 2 Research Ethics Committee (reference number 07/H0308/163). All participants gave informed written consent.

2.2. Overview and recruitment

The Pregnancy Outcome Prediction (POP) study was conducted at the Rosie Hospital, Cambridge (UK) and has been previously described in detail [13,14]. In brief, the study design was a prospective cohort study. Nulliparous women with a viable singleton pregnancy who attended for their dating ultrasound scan at the hospital's ultrasound department between 14/08/2008 and 31/07/2012 were eligible. Women recruited to the study had follow-up research ultrasound scans at 20, 28 and 36 weeks of gestation. Following delivery, the fetal and maternal sides of the placenta were photographed and the placenta cut to 1 cm thick strips which were also photographed. Subsequently, the results of the research ultrasound scans were un-blinded, and their associations with placental measurements assessed.

2.3. Study group

Among the participants of the POP study, the inclusion criteria for the present analysis were delivery of a liveborn baby at term ($\geq$37 weeks' GA) and the availability of digital images of the placenta taken after delivery. Photographs of placentas were available for this study only from 01/10/2010. We excluded women who withdrew or were lost to follow up and women who had ultrasonic measurements missing from the 20 or 36 week scans.

2.4. Research ultrasonography

Methods of ultrasonic measurements have previously been described in detail [13,14]. In brief, all study participants had UtA Doppler measurements at 20 weeks, UmA Doppler measurement at 36 weeks, and measurement of abdominal circumference (AC) at 20 weeks and 36 weeks for the purposes of research. The outcome of the research scans was not revealed to the women or the clinician, unless there was a clinically important finding at 36 weeks [14]. This occurred in 108 [5%] women in the study group, 94 [87%] of them being previously undiagnosed breech presentation. GA was defined on the basis of early ultrasonographic examination, as recommended [15].

2.5. Ultrasonic measurements

Quantification of the UtA and UmA Doppler flow velocity waveforms was by the pulsatility index (PI). UtA PI was quantified as the mean PI of the left and right uterine arteries. Measurements were converted into GA-adjusted z-scores defined within the POP study [13], to adjust for minor variation in the exact GA at the scan. Abdominal circumference growth velocity (ACGV) was obtained by calculating the difference in AC z-score between the 20 week and 36 week scans [13].

2.6. Maternal and fetal characteristics

Several maternal characteristics were examined in relation to both placental and ultrasonic measurements to assess potential confounding. Maternal age was defined as age at recruitment. Body mass index (BMI) at the 12 week scan was used as a proxy measurement for pre-pregnancy BMI. Maternal ethnicity, age at leaving full-time education (FTE), smoking and alcohol consumption were defined by self-report at the 20 week questionnaire. Birth weight was measured directly after delivery.

2.7. Collection of placentas

After delivery, the placenta was given as soon as possible to the research technicians when there was no reason to send the placenta to pathology for further investigation. The median collection time in the study cohort was 4 h (interquartile range was 20 min to 10 h). Placental biopsies were obtained as soon after birth as possible [14]. The placentas were then stored for 24 h before dissection. After the membranes and cord were removed, both sides of the placenta were photographed with a ruler and patient identification number (ID) on a clean surface (Canon Powershot A480 camera, Supplementary Fig. 1). The placenta was then cut along the longest diameter in 1 cm thick strips using a disposable brain knife. The placental strips were tipped to the left so that the right hand face of each strip was uppermost, after which a picture was taken with the ruler and patient ID besides the placenta.

2.8. Image analysis in Matlab

Placental measurements (the first seven parameters in Supplementary Table 1) were calculated using Matlab (version r2014a, The Mathworks, Natick, MA, USA). Custom code (available on request from the authors) was written to analyse all the pictures in an objective and reproducible manner. The pixel size in each image was calculated by determining the number of pixels within 20 mm on the ruler in the photograph (Supplementary Fig. 1). To correct for the wedge biopsy taken at the placental edge (Supplementary Fig. 1, red arrow) the outer boundary of the placenta was manually adjusted. Afterwards the umbilical cord