Placenta 34, Supplement A, Trophoblast Research, Vol. 27 (2013) S85–S89

Contents lists available at SciVerse ScienceDirect

Placenta

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

Elsevier Trophoblast Research Award Lecture: Searching for an early pregnancy 3-D morphometric ultrasound marker to predict fetal growth restriction

S.L. Collins [a,b,*], G.N. Stevenson [c], J.A. Noble [c], L. Impey [b]

[a] The Nuffield Dept. of Obstetrics & Gynaecology, University of Oxford, Oxford, UK
[b] The Fetal Medicine Unit, John Radcliffe Hospital, Oxford, UK
[c] The Institute of Biomedical Engineering, Dept. Engineering Science, University of Oxford, Oxford, UK

ARTICLE INFO

Article history:
Accepted 29 November 2012

Keywords:
Fetal growth restriction
Placental volume
Placental morphometry
Small for gestational age

ABSTRACT

Fetal growth restriction (FGR) is a major cause of perinatal morbidity and mortality, even in term babies. An effective screening test to identify pregnancies at risk of FGR, leading to increased antenatal surveillance with timely delivery, could decrease perinatal mortality and morbidity. Placental volume, measured with commercially available packages and a novel, semi-automated technique, has been shown to predict small for gestational age babies. Placental morphology measured in 2-D in the second trimester and *ex-vivo* post delivery, correlates with FGR. This has also been investigated using 2-D estimates of diameter and site of cord insertion obtained using the Virtual Organ Computer-aided AnaLysis (VOCAL) software. Data is presented describing a pilot study of a novel 3-D method for defining compactness of placental shape. We prospectively recruited women with a singleton pregnancy and BMI of <35. A 3-D ultrasound scan was performed between 11 and 13 + 6 weeks' gestation. The placental volume, total placental surface area and the area of the utero–placental interface were calculated using our validated technique. From these we generated dimensionless indices including sphericity (ψ), standardised placental volume (sPlaV) and standardised functional area (sFA) using Buckingham π theorem. The marker for FGR used was small for gestational age, defined as <10th customised birth weight centile (cSGA). Regression analysis examined which of the morphometric indices were independent predictors of cSGA. Data were collected for 143 women, 20 had cSGA babies. Only sPlaV and sFA were significantly correlated to birth weight ($p < 0.001$). Regression demonstrated all dimensionless indices were inter-dependent co-factors. ROC curves showed no advantage for using sFA over the simpler sPlaV. The generated placental indices are not independent of placental volume this early in gestation. It is hoped that another placental ultrasound marker based on vascularity can improve the prediction of FGR offered by a model based on placental volume.

1. Introduction

1.1. Fetal growth restriction (FGR): the problem and need for a screening test

Forty-four in every 10,000 babies born in the UK will be stillborn [1]. This statistic has not appreciably changed for the last two decades [2]. FGR is widely recognised as the largest single risk factor for stillbirth [2]. Unfortunately, as many as 75% of growth-restricted fetuses are not diagnosed until delivery [3]. The methods routinely used to stratify the risk of FGR at booking, and therefore guide the level of antenatal surveillance, rely solely on the woman's past history. Those women deemed to be low-risk are mostly monitored by measuring the symphysis-fundal height (SFH), but the detection rate for FGR is as poor as 15% [4]. With increasing maternal obesity, a reliance on SFH can only make matters worse. Growth-restricted babies are also at increased risk of perinatal morbidity following labour [5]. An effective screening test to identify pregnancies at risk of FGR, leading to increased antenatal surveillance with delivery when appropriate, could potentially decrease perinatal mortality and morbidity rates in high income countries.

Recent studies have demonstrated that adenoviral-mediated gene transfer of IGF-1 can alleviate FGR in multiple animal models [6–8]. Once safety and efficacy issues have been addressed, a research group in London is planning to undertake a human trial using gene therapy for the treatment of severe growth restriction.

* Corresponding author. The Nuffield Dept. of Obstetrics & Gynaecology, University of Oxford, Oxford OX3 9DU, UK. Tel.: +44 7958 656 885.
E-mail address: sally.collins@obs-gyn.ox.ac.uk (S.L. Collins).

0143-4004/$ – see front matter © 2012 Published by IFPA and Elsevier Ltd.
http://dx.doi.org/10.1016/j.placenta.2012.11.033

With an effective screening test for FGR in place to target the pregnancies at risk early on, the real possibility of treating the condition in the future cannot be ignored. As the sequelae of FGR include an increased risk of obesity, diabetes and cardiovascular disease in adulthood [9], the long-term health benefits, to both the fetus and society in general, of any such treatment would be considerable.

The major pathology linked with FGR is utero–placental insufficiency [10]. The placenta and much of its vasculature is readily identifiable with ultrasonography at 11–14 weeks' gestation [11]. It is somewhat surprising, therefore, that currently there are few placenta-based ultrasound screening markers. This may be due in part to the technical difficulties associated with many of the newer ultrasound tools including power Doppler and 3-D ultrasonography. Much of the accepted histological evidence regarding the underlying pathology within the placental bed has yet to be fully explored with standard ultrasound techniques, let alone the newer, more controversial ones such as 3-D power Doppler. The uterine artery waveform has consequently been used as a surrogate marker for the actual pathology [12]. The performance of this in predicting FGR in the first trimester is, however, poor [13].

1.2. Placental volume

The relationship between the ultimate weight of the placenta and the fetal birth weight has long been recognised [14,15], as has the pathological significance of a small placenta at delivery [16]. However, it was only with the advent of ultrasound that it became possible to investigate if placental size early in pregnancy could predict growth restriction. This was first attempted in 2-D [17–19] but accurately identifying the required planes appeared to limit the usefulness of this technique.

The research expanded again with the introduction of 3-D ultrasound in the mid-1990s [20–22]. A low placental volume (PlaV) calculated with either manual delineation or Virtual Organ Computer-aided AnaLysis (VOCAL™-GE Healthcare, Milwaukee, WI, USA) between 11 and 13 weeks is associated with fetal growth restriction [20,23,24] and pre-eclampsia [25] A recent pilot study suggested that placental volume generated with a simple, automated technique, correlates with fetal growth restriction [26]. It also suggests that combination with other routinely available data may improve this correlation. This combination of multiple risk factors to improve a predictive algorithm for SGA babies has recently been highlighted by Poon et al. [27]. They used a number of risk factors including maternal history, biochemical markers and uterine artery Doppler indices. If placental volume is demonstrated to be an independent risk factor, it has the potential to further improve this algorithm.

1.3. Placental shape

Many factors are thought to influence the shape of the placenta during development, including the site of implantation [28], differential placental growth according to the perfusion of the utero–placental interface (UPI) [29] and developmental changes in the uterus itself (thinning of the lower segment) [29]. It has also been suggested that inadequate spiral artery transformation may lead to an increase in the force of blood entering the intervillous space (IVS), literally 'pushing' the placenta from the UPI and changing its shape [30,31]. Attempts to compare the morphology of the *ex-vivo* placenta with both histological findings and clinical outcome have yielded conflicting results [32–35]. Yampolsky reported that a placenta with an umbilical cord displaced from the central position showed reduced transport efficiency, and hence a smaller birth weight for a given placental weight [35]. Another, similarly sized, study indicated that the cord is commonly 'off centre' and that there was no difference in any of their derived 'cord centrality' indices between normal pregnancies and those with adverse outcomes [33]. It also appears that the macroscopic appearance of the placenta may not always correlate with histological findings [34]. One of the difficulties interpreting these findings is that each research group uses their own different indices to define 'normal' and 'abnormal'. Also, as the placenta is being examined flattened *ex-vivo*, assumptions must be made that it is appropriately representing the curved shape it would have had when perfused *in utero*.

A more clinically useful assessment would be of the placental shape *in vivo*. This has been attempted with simple 2-D ultrasound measurements of length and thickness, mostly at 18–23 weeks' gestation, with promising results for predicting adverse pregnancy outcomes [36–40]. The development of 3-D ultrasound has also facilitated examination of the placental shape early in pregnancy with promising results [41]. However, whilst VOCAL can provide an estimate of placental volume, it cannot provide information on surface areas to enable analysis of overall shape. Using this tool placental shape must be estimated from 2-D measures taken by the operator post hoc, such as the diameter, and the package does not allow the placenta to be flattened out to increase the accuracy of this estimate. This is important, as it is plausible that the larger the proportionate area of the UPI, the better the placenta will function as an organ of nutrition and gaseous exchange. This might not be detected by placental volume measurement alone as a large, thin, 'pancake-like' placenta could potentially have the same placental volume as a short, thick one yet the size of the functional areas would be very different. This might account for the finding that 'globular' appearing placentas have been linked with adverse pregnancy outcome [39], although the difficulty still remains with the subjective definition of 'globular'. A quantitative measure of placental shape based on the relative surface areas and volume is needed to identify the thin 'pancake-like' placenta from the 'globular' one. Until recently such a measure has not been available.

2. Our recent approach

2.1. New semi-automated placental segmentation technique

A rapid segmentation technique producing a 3-D volume which can be saved and further manipulated to generate total surface area (TSA), the area of the UPI and hence an estimate of shape, has been developed at the Institute of Biomedical Engineering (IBME), University of Oxford [42,43]. This uses a random walker segmentation algorithm [44] to generate an estimate of the placental volume. The operator labels the voxels representing the placenta within the 3-D volume and the other voxels as being background (maternal tissue or amniotic fluid). This is 'seeding' the image. The random walker then generates a volume by taking successive 3-D random steps and calculating the probability that each unlabelled voxel encountered is either placenta or background tissue. Based on these probabilities, a threshold and weighting can be applied which generates an image segmentation. This can then be used to provide an estimate of the placental volume and total surface area. By re-seeding the segmentation to indicate the amnio–placental interface the area of the UPI can then be calculated [45]. The segmentations can then be re-seeded to identify the feto–placental surface (the fetal side of the placenta which provides an interface between the placenta and the amniotic fluid). The algorithm then subtracts the feto–placental surface area from the total surface area (A_t) enabling calculation of the area of the UPI, which can be regarded as the 'functional area' of the placenta (A_f), and the amnio–placental interface (Fig. 1).