Ultrasound in Med. & Biol., Vol. ■■, No. ■■, pp. ■■–■■, 2017

0301-5629/$ - see front matter

https://doi.org/10.1016/j.ultrasmedbio.2017.11.018

● *Original Contribution*

AUTOMATED VISUALIZATION AND QUANTIFICATION OF SPIRAL ARTERY BLOOD FLOW ENTERING THE FIRST-TRIMESTER PLACENTA, USING 3-D POWER DOPPLER ULTRASOUND

Gordon N. Stevenson,* J. Alison Noble,† Alec W. Welsh,*,‡ Lawrence Impey,§ and Sally L. Collins§,¶

* School of Womens' & Childrens' Health, Faculty of Medicine, University of New South Wales, Sydney, Australia; † Institute of Biomedical Engineering, Department of Engineering Science, University of Oxford, Oxford, United Kingdom; ‡ Department of Maternal-Fetal Medicine, Royal Hospital for Women, Randwick, NSW, Australia; § The Fetal Medicine Unit, The Women's Centre, John Radcliffe Hospital, Oxford, United Kingdom; and ¶ Nuffield Department of Obstetrics and Gynaecology, University of Oxford, Oxford, United Kingdom

(*Received* 27 *June* 2017; *revised* 29 *October* 2017; *in final form* 27 *November* 2017)

Abstract—The goal of our research was to quantify the placental vascularity in 3-D at 11–13 + 6 wk of pregnancy at precise distances from the utero-placental interface (UPI) using 3-D power Doppler ultrasound. With this automated image analysis technique, differences in vascularity between normal and pathologic pregnancies may be observed. The algorithm was validated using a computer-generated image phantom and applied retrospectively in 143 patients. The following features from the PD data were recorded: The number of spiral artery jets into the inter-villous space, total geometric and PD area. These were automatically measured at discrete millimeter distances from the UPI. Differences in features were compared with pregnancy outcomes: Pre-eclamptic versus normal, all small-for-gestational age (SGA) to appropriate-for-gestational age (AGA) patients and AGA versus SGA in normotensives (Mann-Whitney). The Benjamini-Hochberg procedure was used (false discovery rate 10%) for multiple comparison testing. Features decreased with increasing distance from the UPI (Kruskal-Wallis test; $p < 0.001$). At 2– 3 mm from the UPI, all features were smaller in pre-eclamptic compared with normal patients and for some in SGA compared with AGA patients ($p < 0.05$). For AGA versus SGA in normotensive patients, no significant differences were found. Number of jets measured at 2–5 mm from the UPI did not vary because of the position of the placenta in the uterus (ANOVA; $p > 0.05$). This method provides a new *in-vivo* imaging tool for examining spiral artery development through pregnancy. Size and number of entrances of blood flow into the UPI could potentially be used to identify high-risk pregnancies and may provide a new imaging biomarker for placental insufficiency. (E-mail: gordon.n.stevenson@gmail.com) **© 2017 World Federation for Ultrasound in Medicine & Biology. All rights reserved.**

Key Words: **Diagnostic ultrasound, Small for gestational age, Doppler ultrasound, Pre-eclampsia, Placenta, Computer-assisted image analysis.**

INTRODUCTION

In pregnancy, trophoblast cells from the developing placenta invade the muscular, tightly coiled walls of the uterine spiral arteries, converting them into wide, flaccid conduits. This facilitates the dramatic increase in blood flow required to accommodate the demands of the feto-placental unit (Pijnenborg et al. 2006). Impaired transformation of these vessels is widely regarded as the pathology responsible, at least in part, for adverse pregnancy outcomes including pre-eclampsia, utero-placental insufficiency and placental abruption (Lyall et al. 2013). Initially, understanding of the pathology was based on histologic examination of rare collections of uteri with the placenta still *in situ* at different gestations (Burton et al. 1999). However, the effect on the blood flow through the spiral arteries when trophoblast invasion is reduced cannot be determined from static histologic slides and therefore remained almost completely unknown. The pathology may result in a reduced number of spiral arteries that have sufficiently transformed to feed the inter-villous space (IVS), changes in the distribution of the spiral artery jets or reduction in the diameter of their openings resulting in altered

Address correspondence to: Gordon N. Stevenson, Perinatal Imaging Research Group, School of Womens' & Childrens' Health, Royal Hospital for Women, University of New South Wales, Barker Street, Sydney, Australia. E-mail: gordon.n.stevenson@gmail.com

hemodynamics within the IVS. With the introduction of the use of ultrasound (US) in pregnancy, it was hoped that these questions would be readily answered *in utero*. Early 2-D US studies, however, yielded conflicting results (Jurkovic et al. 1991; Murakoshi et al. 1996). With improvement in Doppler US technology, blood flow can now be measured in the IVS from 8 wk of gestation (Jauniaux et al. 2003; Valentin et al. 1996). The size and velocity waveform of single-spiral arteries entering into the IVS have been reproducibly measured by color and pulse-wave Doppler US, respectively, and demonstrate variations in pathologic pregnancies compared with normal ones (Collins et al. 2012a). Examining single vessels, however, cannot fully explain the changes occurring throughout the whole placental bed. A natural extension, therefore, is the use of 3-D US to investigate simultaneously the whole vascular supply to the placenta. Power Doppler (PD) US is ideally placed to perform this as it is relatively angle independent, does not alias and is able to measure much slower-moving blood flow compared with color Doppler (Rubin et al. 1994). Using a combination of 3-D and PD US, the vascularity of the whole utero-placental interface (UPI) can be examined.

Studies using 3-D PD US have attempted to measure the vascularity of the whole placenta but provide conflicting results. This is partly because of the incorporation of the cord insertion and chorionic side of the placenta, meaning both circulatory systems were included rather than simply the maternal side, where the pathology is thought to occur (Welsh et al. 2005), but mainly because of a lack of standardization in the tools available (Welsh et al. 2012). These methods also have a degree of operator dependency, leading to low reproducibility (Lai et al. 2010), and require appropriate machine settings that are not always used (Collins et al. 2012b). These issues aside, the available methods only provide a numerical estimate of overall vascularity. They cannot be used to count the number of individual jets entering the IVS or to report their size, pattern or distribution. Study of the characteristics of the jets themselves should increase understanding of the development of the placenta in the first trimester. Identifying where differences occur between normal and pathologic pregnancies will potentially lead to development of an early screening test to predict women at risk of adverse pregnancy outcomes.

We aimed to develop a medical image-analysis–based method that can accurately measure image features: The number, size (expressed as cross-sectional area) and distribution of the spiral artery jets entering the IVS. The technique was then validated using a computer-generated 3-D vascular phantom and applied to previously collected 3-D PD US data. Using this method, we aimed to show whether differences in the jets were observed in pregnancies that developed pre-eclampsia and/or resulted in small-for-gestational-age (SGA) babies.

MATERIALS AND METHODS

Computer-generated phantom

The Insight Toolkit (ITK v. 4.8.2; Kitware Inc, Clifton Park, NY, USA) was used to develop a 3-D synthetic model (computer-generated phantom) of the placenta. A 3-D ellipsoid of radius $128 \times 128 \times 64$ was centered within a $256 \times 256 \times 128$-volume with isotropic spacing of 1 mm. The derivative of the image in the direction of short or z-axis was then computed to generate normals and the values thresholded at 0 in order to split the ellipsoid into upper or lower hemispheres representative of the maternal or fetal sides of the placenta. Figure 1(a) presents the surface colored based on the normal calculated on the surface relative to the z-axis. A cut-away view in Figure 1(b) presents the signed distance transform generated for the whole 3-D ellipsoid, showing the distance from the artificial UPI in millimeter increments into the center of the ellipsoid. The signed distance transform provides a labelling of the volume where each voxel is labelled based on the voxel's geometric distance from the UPI, signed positive for voxels outside the placenta and negative when within the placenta.

We modelled 3-D jets, using a 3-D Gaussian kernel ($11 \times 11 \times 11$-kernel size, $\sigma = 2.0$). The center of the kernel was then placed on the boundary of the maternal side of the ellipsoid (akin to the UPI). Any kernel values set outside the bounds of the ellipsoid were removed to provide a 3-D jet-like pattern within the volume. Phantoms were generated procedurally with various numbers of jets on the UPI surface. We created 10 computer-generated phantoms for each number of jets (10, 20, 30 and 40). Figure 1(c) presents an example of a 40-jet computer-generated phantom visualized at set distances 0–3 mm of depth from the UPI. With these data constructed, the number of artificial jets and their area were then measured at discrete distances at the UPI in 1-mm steps into the model up to 5 mm deep, reflecting how the entrances of blood into the IVS would be investigated *in vivo*.

3-D PD US acquisition

This work was a retrospective study of scans obtained as part of a prospective study investigating placental imaging biomarkers. This human study was approved by a UK National Health Service Research & Ethics Committee (08/H0604/163). All adult participants provided written informed consent to participate in this study. We invited 143 women with singleton pregnancies undergoing first-trimester scans between December 2008 and December 2010 to participate and informed written consent was obtained before enrollment. Patients under the age of 16 y, those with a body mass index >35 or significant maternal chronic illnesses, including diabetes and treatment with medications associated with fetal growth restriction,