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New imaging markers for preconceptional and first-trimester utero-placental vascularization

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ABSTRACT

Introduction: The availability of imaging makers of early placental circulation development is limited. This study aims to develop a feasible and reliable method to assess preconceptional and early first-trimester utero-placental vascular volumes using three-dimensional power Doppler (3D PD) ultrasound on two different Virtual Reality (VR) systems.

Methods: 3D PD ultrasound images of the uterine and placental vasculature were obtained in 35 women, either preconceptionally ($n = 5$), or during pregnancy at 7 ($n = 10$), 9 ($n = 10$) or 11 ($n = 10$) weeks of gestation. Preconceptional uterine vascular volume (UVV), first-trimester placental vascular volume (PVV) and embryonic vascular volume (EVV) were measured by two observers on two VR systems, i.e., a Barco I-Space and VR desktop. Intra- and inter-observer agreement and intersystem agreement were assessed by intra-class correlation coefficients (ICC) and absolute and relative differences.

Results: Uterine-, embryonic- and placental vascular volume measurements showed good to excellent intra- and inter-observer agreement and inter-system reproducibility with most ICC above 0.80 and relative differences of less than 20% preconceptionally and almost throughout the entire gestational age range. Inter-observer agreement of PVV at 11 weeks gestation was suboptimal (ICC 0.69, relative difference 50.1%).

Discussion: Preconceptional and first-trimester 3D PD ultrasound utero-placental and embryonic vascular volume measurements using VR are feasible and reliable. Longitudinal cohort studies with repeated measurements are needed to further validate this and assess their value as new imaging markers for placental vascular development and ultimately for the prediction of placenta-related pregnancy complications.

1. Introduction

Worldwide, millions of women develop fertility problems or placenta-related pregnancy complications, such as pregnancy-induced hypertension, preeclampsia, fetal growth restriction and preterm birth every year. These complications not only affect the outcome of a pregnancy, but some can also impact the health of the mother and her offspring later in life [1–3].

These problems in reproduction can be due to derangements in the utero-placental vascularization and originate during the periconception period, i.e., 14 weeks prior to conception until 10 weeks thereafter [4]. Preconceptional uterine vascularization is involved in endometrial receptivity, decidual selectivity and subsequent implantation in combination with complex interactions between hormones, nutrients, growth factors and endometrial genes [5,6]. A

Abbreviations: UVV, Uterine vascular volume; PVV, Placental vascular volume; EVV, Embryonic vascular volume; TVV, Total vascular volume.

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decreased (sub)endometrial blood flow has been associated with decreased pregnancy rates [7,8].

Human placentation is characterized by the remodeling of the uterine circulation, in particular of the spiral arteries. Remodeling optimizes maternal blood distribution through a low-resistance uterine vascular network and ultimately into the placental intervillous chamber [9]. Up to around 9 weeks of gestation, extravillous trophoblast plugs limit maternal blood entry into these intervillous chambers. These plugs disintegrate thereafter, resulting in the onset of the utero-placental circulation [10]. An imbalance in this delicate phenomenon is hypothesized to be the principal mechanism leading to early pregnancy failure. Similarly, if the uterine portion of the utero-placental circulation fails to develop, adequate placental and fetal growth will fail [9].

Doppler ultrasound imaging and maternal serum biomarkers of placental function such as placental growth factor (PlGF) or pregnancy-associated plasma protein-A (PAPP-A) have been used to investigate abnormal placentation [11]. Availability of real-time imaging markers for assessment of *in vivo,* early uterine and placental vascularization and function remains limited. The current state-of-the-art technology for evaluation of *in utero* placental vasculature morphology is three-dimensional power Doppler (3D PD) ultrasound [12]. So far, 3D vascular volumes can be assessed using the Virtual Organ Computer-aided AnaLysis (VOCAL) tool to quantify placental vascularization through calculation of vascularization indices (VI), flow indices (FI) and vascularization-flow indices (VFI). However, results regarding reproducibility are conflicting [12–14]. Variations in ultrasound machine settings and also distance between the range of interest and ultrasound transducer influence VOCAL vascularization indices, by affecting power Doppler calculations. Furthermore, despite availability of 3D volumetric data, measurements are still performed in a two-dimensional (2D) plane, and consequently the third dimension that allows for more precise volume measurements is not used. At the Erasmus MC, we have developed a novel, innovative application, called V-Scope, that displays volumetric ultrasound datasets as holograms, using the Barco I-Space CAVE™-like virtual reality (VR) system (Barco NV, Belgium) [15,16]. Recently, a VR desktop system, based on technical principles of the I-Space, was developed to enable clinical implementation of VR [17]. So far, studies using VR showed accurate and reproducible embryonic and brain development measurements in early pregnancy and utero-placental measurements in the late first trimester of pregnancy [18–21].

The aim of this study is to assess feasibility and reliability of 3D PD ultrasound in combination with two VR systems (I-Space and VR desktop) to measure preconceptional and first-trimester vascular volumes of the uterus, placenta and embryo.

2. Methods

2.1. Study design

Preconceptional, 5 women undergoing *in vitro* fertilization (IVF) or intra-cytoplasmic sperm injection (ICSI) treatment were recruited from the Department of Reproductive Medicine. Two 3D PD ultrasound images of the utero-placental vasculature were obtained before ovum pick-up. Further, this study was embedded in the prospective, tertiary hospital-based Rotterdam periconception cohort (Predict study) with a focus on the influence of periconceptional lifestyle and environmental factors on human embryonic and fetal growth and development [22]. In 30 pregnant Predict study participants, two 3D PD ultrasound utero-placental vascularization images were obtained in the first trimester of pregnancy, i.e., either at 7 ($n = 10$), 9 (n=10) or 11 (n=10) weeks gestational age (GA). Women at least 18 years of age and prior to pregnancy or with a singleton pregnancy were eligible for inclusion. GA was calculated from the first day of the last menstrual period (LMP) in spontaneous pregnancies, or from oocyte pick-up day plus 14 days in IVF/ICSI pregnancies. In pregnancies originating from cryopreserved embryo transfer it was calculated from the transfer day plus 17 or 18 days, depending on the number of days between oocyte pick-up and embryonic cryopreservation. In regular menstrual cycles, but more than 3 days different from 28 days, we adjusted GA for cycle duration. If the LMP was unknown or GA determined by crown-rump length (CRL) differed more than 7 days from the LMP, GA was based on CRL [22]. Study protocols were approved by the Erasmus MC medical ethics review board and written informed consent was obtained from all participants (MEC 2004-227 and METC 2015-494).

2.2. Ultrasound scans

Ultrasound scans were performed by one experienced sonographer (IR) using a Voluson Expert E8 or E10 system (GE, Zipf, Austria) ultrasound machine with standard settings (pulse repetition frequency 0.6 kHz, wall motion filter ‘low1’, quality ‘high’, gain adjusted to individual image characteristics), using a 6–12 MHz transvaginal probe. To minimize artifacts and measurement errors by movement, participants were asked to hold their breath for approximately 30 s during image acquisition. As variations in uterine position require individual adaptions to optimize image acquisition, two ultrasound volumes were obtained per participant. The first volume was acquired visualizing the uterus in the midsagittal plane. The second volume was obtained after turning the ultrasound transducer 90° perpendicular to the first position. All ultrasound examinations were performed according to international guidelines on safe use of Doppler ultrasound in the first trimester of pregnancy and as such, total scanning time was kept as low as possible (ALARA-principle) and always <30 min to avoid unnecessary exposure [23–25]. The settings during 3D PD ultrasound use resulted in average power levels (i.e. thermal index <0.7) theoretically allowing for unlimited scanning time. However, 3D PD ultrasound use was limited to averagely 1 minute (two times a volume acquisition of 30 seconds).

2.3. Virtual reality technique

In the Barco I-Space, a CAVE™-like VR environment, using the V-Scope volume rendering application, 3D ultrasound volumes can be visualized as true 3D “holograms” [16]. Additional depth perception of VR enables better visualization and thus assessment of the utero-placental vascularization. Also, 3D interaction makes accurate volumetric measurements feasible. To enable future clinical implementation of VR, a VR desktop system, using the same V-Scope software, was developed and validated by using the I-Space as reference standard [17]. The VR desktop consists of a personal computer with V-Scope software, a 2D monitor displaying the user interface for selecting the measurement tools, a 3D monitor to display the 3D volume, a tracking system for observer interaction with the 3D volume, a pair of stereoscopic glasses to obtain depth perception and a six degrees-of-freedom mouse for 3D volume manipulation as demonstrated in Supplementary Video 1 [17].

Supplementary video related to this article can be found at https://doi.org/10.1016/j.placenta.2017.11.013.

Detailed measurements in the I-Space and on the VR desktop were performed by two researchers according to a standard protocol. Semi-automatic volume measurements of the utero-placental vasculature were obtained by thresholding the 8-bit (range 0–255) Doppler magnitude data. As previously published,