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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,

the lower-Doppler threshold level was set at a value of 100. This means that only voxels with a Doppler value of 100 or higher are colored and counted by semi-automatic calculations. This enabled the most optimal visualization of the utero-placental vasculature [20,21]. To measure the uterine vasculature in preconceptional ultrasound volumes, we used differences in echogenicity of the uterine and surrounding tissues. Preconceptional uterine vascular volumes (UVV) were calculated after removing artifacts, recognizable by their stripe-like appearance, with a virtual eraser, i.e. deselecting voxels that were initially selected by the thresholding step. In pregnancy, differences in grey values between placental and myometrial tissue were used to selectively measure placental vasculature. By removing grey values and vessels up to the placenta, only placental blood spaces were measured using semi-automated calculations. The obtained total vascular volume (TVV) was calculated after removing artifacts. Thereafter, the embryonic vascular volume (EVV) was identified and measured by erasing selected embryonic vascular structures and calculating the difference with previously obtained TVV. Finally, to select the placental vascular volume (PVV) only, grey values in the volume were used to identify surrounding myometrial tissues. The complete myometrium was then erased using the virtual brush to the margin of the placental tissue interface, leaving the (PVV) (Fig. 1) [20]. At this stage, it is not possible with VR technology to make a distinction between the maternal blood space and embryonic vasculature within the placental vascular volume.

In VR, the quality of both acquired 3D PD ultrasound volumes at each time point, was scored based on presence of artifacts due to maternal and/or embryonic movements (yes/no), presence of acoustic shadowing (yes/no), volume completeness (complete/incomplete), placental position in relation to the transducer (far/close) and overall quality (low/average/good). The volume with the highest score or, in cases of equal scores, the first volume was used for further analysis. Supplementary Fig. 1 displays a flowchart of the ultrasound volume acquisition, the VR measurements and the comparisons used to assess agreement between two trained observers (IR and AF) and the two VR systems. For intra- and inter-observer reliability, each observer measured the highest quality 3D PD ultrasound volume twice on different days in the I-Space. The same steps were repeated on the VR desktop. The observers performed their measurements independently, and were blinded to each other's results.

2.4. Statistical analysis

Because of skewed distributions, vascular volumes were log transformed prior to analysis. The I-Space system was considered the reference standard when determining intra-and inter-observer as well as VR intersystem reproducibility. Scatterplots with corresponding Pearson's correlation coefficients (R-values) were used to depict correlations between individual measurements for utero-placental vascular volumes. To quantify intra- and inter-observer reproducibility, intra-class correlation coefficients (ICC) were calculated per time point of ultrasound acquisition. Good agreement was defined as an ICC of 0.80 or higher. Of the measurements, the means of the absolute differences (i.e., the difference between first and second measurement) and the relative differences (i.e., the difference between natural log values of the first and second

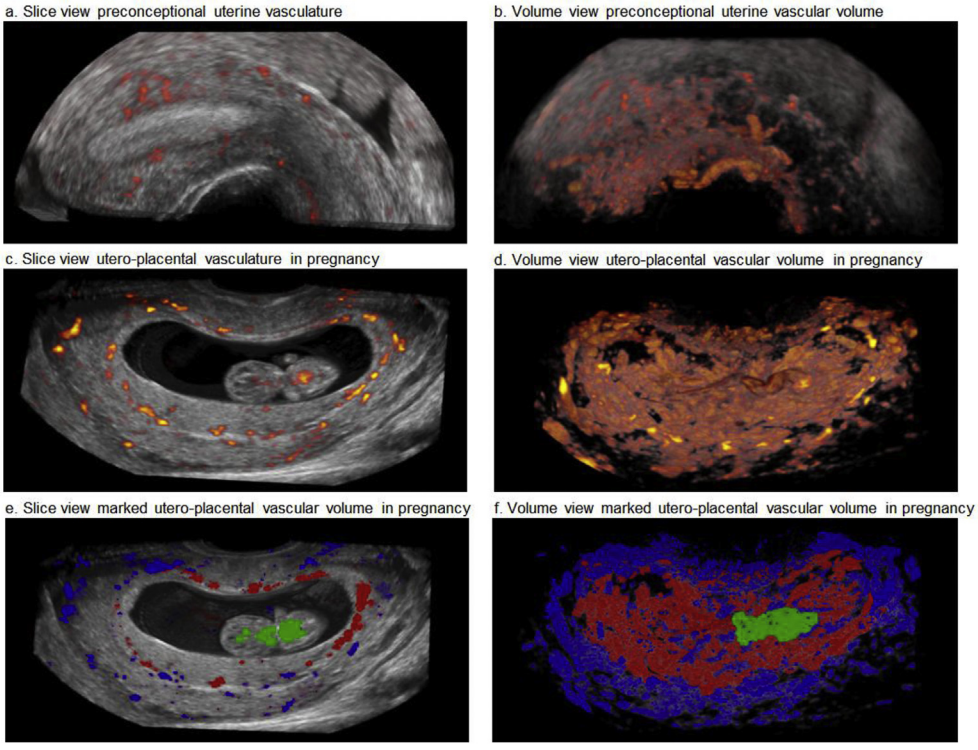

Fig. 1. Three-dimensional power Doppler ultrasound images of utero-placental vascular volumes preconceptional and in pregnancy at 9 weeks GA visualized by Virtual Reality (VR).
a: Slice view of a midsagittal uterine section showing the preconceptional uterine vascular volume (UVV, orange), with surrounding grey values representing the uterine tissue.
b: Volume view of figure 1a showing only the preconceptional uterine vascular volume (UVV, orange), after setting a threshold for grey values.
c: Slice view of a total obtained utero-placental vascular volume in pregnancy, with surrounding grey values representing the uterine tissue.
d: Volume view of figure 1c showing the total obtained utero-placental vascular volume in pregnancy, after setting a threshold for grey values.
e: Slice view of a total obtained utero-placental vascular volume in pregnancy, with surrounding grey values representing the uterine tissue and marked vessel subtypes (uterine vessels (blue); placental vessels (PVV, red); embryonic vessels (EVV, green).
f: Volume view of figure 1e, showing marked vessel subtypes (UVV (blue); placental vascular volume (PVV, red); embryonic vascular volume (EVV, green)).

measurement divided by the mean natural log values of the two measurements) were calculated with corresponding 95% confidence intervals. Bland-Altman plots were composed to assess agreement between the two VR systems, displaying mean differences between utero-placental vascular measurements with corresponding 95% limits of agreement. All analyses were performed using SPSS software (version 21.0; SPSS Inc., Chicago, IL, USA) and *p*-values <0.05 were considered statistically significant.

3. Results

The median age of all women (n = 35) was 33 years (range: 26–41) and median body mass index (BMI) was 23.0 kg/cm^2 (range: 19–35). Seventeen women (49%) were nulliparous. All preconceptional women (n=5) were undergoing IVF/ICSI treatment. Of the 30 pregnant women, 14 (47%) conceived after IVF/ICSI. In pregnancy, we observed higher median utero-placental vascular volumes with advancing GA.

In total, 70 vascular volume measurements were acquired. Quality was good in 31 volumes, average in 35 volumes and low in 4 volumes. All volumes were eligible for further vascular volume measurements.

Table 1 provides an overview of median vascular volumes in cm^3 and intra- and inter-observer agreement of utero-placental vascular measurements using the I-space. Preconceptional, intra- and inter-observer agreement for UVV was excellent with ICC ≥0.93. In pregnancy, ICC for intra- and inter-observer agreement for utero-placental vascular volumes ranged from 0.69 to 0.99 for the entire GA range. Mean relative differences for all utero-placental vascular volumes were below 20%, except for inter-observer agreement of PVV at 7 and 11 weeks GA with a relative mean difference of 20.5% and 50.1%, respectively.

Supplementary table 1 provides an overview of median vascular volumes and the intra- and inter-observer agreement of utero-placental vascular measurements using the VR desktop. Intra- and inter-observer agreement for preconceptional UVV was excellent with ICC ≥0.92. In pregnancy, ICC for intra- and inter-observer agreement for utero-placental vascular volumes ranged from 0.63 to 0.99 for the entire GA range. Mean relative differences for all utero-placental vascular volumes were below 20%, except for inter-observer agreement of EVV at 7 weeks GA of −36.7% and PVV at 7 and 11 weeks GA with a relative mean difference of 21.5% and 21.4% respectively.

Table 2 shows the agreement of utero-placental vascular measurements between the two VR systems preconceptionally and in pregnancy. With ICC >0.85, all utero-placental vascular volume measurements show good to excellent intersystem agreement. Mean relative differences for all utero-placental vascular volumes were below 20%.

Supplementary Fig. 2 shows strong correlations (R = 0.89–1.00) of utero-placental vascular measurements between the two VR systems. Fig. 2 shows the Bland-Altman plots for relative differences of utero-placental vascular measurements between the VR systems, with mean relative differences below 20%.

4. Discussion

The data of our pilot study indicate that the utero-placental and embryonic circulations can be evaluated reliably and accurately with 3D PD ultrasound and VR techniques. Overall, utero-placental vascular measurements were feasible and reliable with good to excellent intra- and inter-observer agreement. Furthermore, there was excellent VR intersystem agreement with most ICC >0.85 and relative differences <20% both preconceptionally and throughout the entire GA range. Only the PVV at 11 weeks GA measured in the I-Space had a suboptimal inter-observer agreement (ICC 0.69, relative difference 50.1%). This is probably due to a less clear visualization of the boundary between the placenta and underlying uterine tissue at that gestational age. It highlights the potential use of these utero-placental circulation assessment at an early stage of development.

Previous studies have mainly focused on quantification of placental vascularization by using VOCAL to measure VI, FI and VFI, with average to good reproducibility [12–14,20,21]. Differences in machine settings, circumstances for image acquisition (i.e. distance of utero-placental vessels from the transducer either due to patient characteristics or mode of image acquisition (transvaginally or transabdominally)), or relatively small sample sizes could be related to variations in reproducibility. VOCAL also uses 3D PD ultrasound to acquire volumes, but offline assessment takes place in a 2D setting, instead of a 3D setting, let alone a VR environment. Some studies have used VOCAL preconceptionally to assess associations of (sub)endometrial vascularization with pregnancy rates after assisted reproduction [7,8]. In pregnancy, this technique has mainly been used in the late first trimester or thereafter [26,27]. Only Ballering *et al.* have investigated such measurements in the early first trimester in 48 women between 8 and 12 weeks GA and found that early placental vascular development is different in nulliparous women from multiparous women [28].

The addition of VR when assessing the uterine, placental and embryonic vascularization is unique, because it enables evaluation following ultrasound acquisition and fully benefits the third dimension resulting in more reliable and detailed quantification of vascular volumes. We already have wide experience in using VR for

Table 1
Measurements and intra- and inter-observer reliability parameters of utero-placental vascular volumes using the I-space Virtual Reality system.

		Median [range] (cm^3)		Intra-observer variability					Inter-observer variability				
				ICC	Mean difference (cm^3) [+ 95% CI]		Relative mean difference (%) [+ 95% CI]		ICC	Mean difference (cm^3) [+ 95% CI]		Relative mean difference (%) [+ 95% CI]	
Preconception *(n=5)*	**UVV**	1.80	[0.97; 5.52]	0.97	0.41	[−0.01; 0.84]	14.2	[8.0; 14.2]	0.93	−0.27	[−0.55; 0.01]	−0.27	[−0.55; 0.01]
Pregnancy													
7 weeks GA	**PVV**	0.37	[0.10; 1.04]	0.97	0.03	[−0.01; 0.07]	4.0	[−7.3; 15.4]	0.88	0.00	[−0.16; 0.16]	0.00	[−0.16; 0.16]
(n=10)	**EVV**	0.04	[0.01; 0.18]	0.97	0.00	[0.00; 0.01]	11.6	[−2.0; 25.2]	0.95	−0.01	[−0.02; 0.00]	−0.01	[−0.02; 0.00]
9 weeks GA	**PVV**	4.48	[1.57; 9.16]	0.95	−0.23	[−0.76; 0.31]	−3.6	[−15.6; 8.5]	0.90	0.62	[−0.16; 1.40]	0.62	[−0.16; 1.40]
(n=10)	**EVV**	0.44	[0.23; 0.78]	0.98	0.00	[−0.02; 0.03]	0.8	[−5.0; 6.7]	1.00	0.01	[0.00; 0.01]	0.01	[0.00; 0.01]
11 weeks GA	**PVV**	6.99	[1.90; 16.21]	0.94	1.05	[−0.17; 2.26]	8.0	[−1.3; 18.8]	0.69	2.56	[0.90; 4.21]	2.56	[0.90; 4.21]
(n=10)	**EVV**	1.34	[0.57; 2.20]	0.90	0.16	[−0.05; 0.36]	8.8	[−6.6; 22.6]	0.99	0.00	[−0.05; 0.06]	0.00	−0.05; 0.06]

ICC = intraclass correlation coefficients; CI = confidence interval; GA = gestational age; UVV = uterine vascular volume; PVV = placental vascular volume; EVV = embryonic vascular volume.

Table 2
Inter-system reliability parameters of utero-placental vascular volume measurements using the I-Space and Virtual Reality desktop systems.

		ICC	Mean difference (cm^3) [+ 95% CI]		Relative mean difference (%) [+ 95% CI]	
Preconception *(n=5)*	**UVV**	1.00	−0.13	[-0.20; 0.06]	−5.5	[−6.8; −4.2]
Pregnancy						
7 weeks GA	**PVV**	0.99	−0.01	[−0.05; 0.02]	−0.7	[−7.2; 5.8]
(n=10)	**EVV**	0.98	0.00	[−0.01; 0.00]	−10.9	[−20.1;−1.8]
9 weeks GA	**PVV**	0.87	0.00	[−0.41; 0.75]	8.5	[−9.1; 26.0]
(n=10)	**EVV**	0.98	0.17	[−0.02; 0.02]	−0.9	[−6.7; 4.9]
11 weeks GA	**PVV**	0.93	1.50	[0.14; 2.87]	16.5	[1.9; 31.1]
(n=10)	**EVV**	0.97	0.06	[−0.02; 0.13]	4.9	[−0.4; 10.2]

ICC = intraclass correlation coefficients; CI = confidence interval; GA = gestational age; UVV = uterine vascular volume; PVV = placental vascular volume; EVV = embryonic vascular volume.

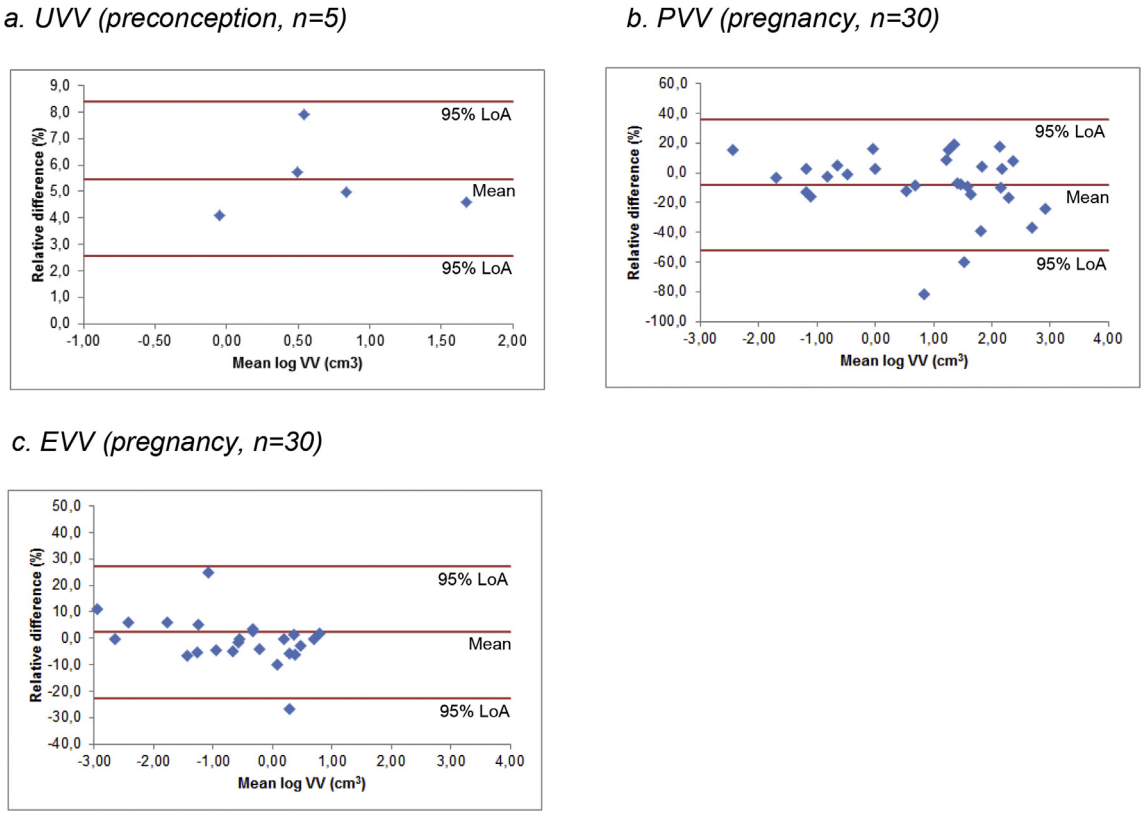

Fig. 2. Bland-Altman plots: relative differences in utero-placental vascular volume measurements between two Virtual Reality systems.
UVV = uterine vascular volume; PVV = placental vascular volume; EVV = embryonic vascular volume; GA = gestational age; Mean = average measurement bias in relative differences; 95% LoA = Upper and lower 95% limit of agreement for relative differences (mean difference ±2SD); Log = natural log transformation of utero-placental vascular volumes to achieve a normal distribution.

measurement and assessment of uterine, placental, embryonic and fetal structures [15,16,26,28,29].

An advantage of the VR desktop is that it could potentially be integrated within existing ultrasound machines for application in any clinical setting. The system is less expensive and has fewer logistical constraints, using only a regular personal computer with V-Scope software, a 3D monitor or television screen and attached tracking system [17]. These factors facilitate research collaborations and clinical use of the VR desktop.

To date, imaging methods to assess periconceptional utero-placental health remain limited. Using 3D PD ultrasound enables minimally invasive and complete visualization of *in vivo* human utero-placental vasculature. Therefore, we hypothesize that utero-placental vascular volumes can be used as potential markers of endometrial and placental health and pregnancy outcome. Describing the vasculature by different parameters preconceptionally (UVV) and in pregnancy (PVV and EVV) allows to relate separate volumes to individual patient characteristics, such as parity, maternal lifestyle and reproductive complications that affect endometrial quality, placentation, embryonic health and (adverse) pregnancy outcome. Ultimately, 3D PD ultrasound measurements could be part of a move towards more accurate prevention and treatment strategies starting as early as the periconception period [12,13].

During the periconception period, ultrasound is a safe method to assess uterine, embryonic and placental structures. International guidelines as set for obstetric scanning throughout pregnancy and the ALARA-principle were followed [23–25]. Further, 3D PD ultrasound volume acquisition time was much lower than exposure time during traditional two-dimensional (2D) scanning and the

embryo only occupied a small segment in the 3D volume, therefore receiving minimal insonation [30,31].

There are limitations for our study. Firstly, the use of 3D PD image quality relies on ultrasound settings and is sensitive to artefacts. To achieve optimal comparability, ultrasound machine settings were standardized for all patients based on several expert opinions. It appears that the pulse repetition frequency (PRF) is the principal factor influencing 3D PD ultrasound image quality by affecting detection sensitivity for vascular blood flow. It is therefore necessary, that the effects of various settings to optimize acquisition of 3D utero-placental vascular images are evaluated in future studies. Secondly, even if the impact of maternal movements was reduced to a minimum during volume acquisition, factors such as maternal adiposity and artefacts due to embryonic movement or uterine position (ante- or retroverted) can still interfere with image quality. In this study, we have not evaluated effects of characteristics such as maternal BMI or parity on image quality, but in none of the volumes quality was so low that measurements could not be performed. Thus, a larger study population with longitudinal data collection is necessary to establish normal distributions for utero-placental vascularization and associations of these measurements with maternal characteristics, embryonic growth trajectories and pregnancy outcome.

In conclusion, preconceptional and first trimester utero-placental vascular volume measurements using 3D PD ultrasound in the I-Space and VR desktop system are feasible and reliable. These results support the need for future larger cohort studies to improve measurement precision. They also support further investigation of the efficacy of utero-placental vascular measurements by VR as potential markers for uterine and placental function and ultimately their use for prediction and prevention of adverse placenta-related outcomes.

Author's contributions

I.R. was involved in the study design, data-acquisition, performance of measurements, data-analysis and wrote the first draft of the manuscript. A.M., M.K., R.S.T., A.K. and S.W. were involved in the study design, data-analysis and co-writing of the manuscript. A.F. performed the offline virtual reality measurements as second observer. G.B. and E.J. co-wrote the manuscript. E.S. is the guarantor of this work and was involved in the rationale and study design and co-wrote the manuscript. All authors have read and approved the final version of the manuscript.

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Appendix A. Supplementary data

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