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First-trimester utero-placental (vascular) development and embryonic and fetal growth: The Rotterdam periconception cohort

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ABSTRACT

Introduction: Impaired placental development is a major cause of fetal growth restriction (FGR) and early detection will therefore improve antenatal care and birth outcomes. Here we aim to investigate serial first-trimester ultrasound markers of utero-placental (vascular) development in association with embryonic and fetal growth.

Methods: In a prospective cohort, we periconceptionally included 214 pregnant women. Three-dimensional power Doppler ultrasonography at 7, 9 and 11 weeks gestational age (GA) was used to measure placental volumes (PV) and basal plate surface area by Virtual Organ Computer-aided AnaLysis™, and utero-placental vascular volume (uPVV), crown-rump length (CRL) and embryonic volume (EV) by a V-scope volume rendering application. Estimated fetal weight (EFW) was measured by ultrasound at 22 and 32 weeks GA and birth weight percentile (BW) was recorded. Linear mixed models and regression analyses were applied and appropriately adjusted. All analyses were stratified for fetal sex.

Results: PV trajectories were positively associated with CRL ($\beta_{adj} = 0.416$, 95%CI:0.255; 0.576, $p < 0.001$), EV ($\beta_{adj} = 0.220$, 95%CI:0.058; 0.381, $p = 0.008$) and EFW ($\beta_{adj} = 0.182$, 95%CI:0.012; 0.352, $p = 0.037$). uPVV trajectories were positively associated with CRL ($\beta_{adj} = 0.203$, 95%CI 0.021; 0.384, $p = 0.029$). In girls, PV trajectories were positively associated with CRL ($p < 0.001$), EV ($p = 0.018$), EFW ($p = 0.026$), and uPVV trajectories were positively associated with BW ($p = 0.040$). In boys, positive associations were shown between PV trajectories and CRL ($p = 0.002$), and between uPVV trajectories and CRL ($p = 0.046$).

Discussion: First-trimester utero-placental (vascular) development is associated with embryonic and fetal growth, with fetal sex specific modifications. This underlines the opportunity to monitor first-trimester placental development and supports the associations with embryonic and fetal growth.

1. Introduction

Worldwide, fetal growth restriction (FGR) is a main problem in perinatal care, because of the high neonatal morbidity and mortality as well as the health sequelae for these children later in life [1–3]. Impaired placental functioning is a major determinant of FGR and is mainly diagnosed in the second half of pregnancy [4]. The most prevalent cause of FGR is malperfusion of the utero-placental circulation resulting from impaired spiral artery remodeling. To meet the crucial maternal vascular adaptation to pregnancy, this process of remodeling already starts in the first trimester of pregnancy [5–7].

The relationship between embryonic and fetal growth is illustrated by the observed associations between first-trimester embryonic growth, mid-pregnancy fetal size, and birth weight [8]. Since FGR can be caused by reduced placental functioning, our hypothesis is that utero-placental (vascular) development in the first trimester of pregnancy impacts embryonic and fetal growth parameters. Moreover, fetal sex dependency is an increasing issue in perinatal medicine, which we assume to be a

Abbreviations: PV, placental volume; uPVV, utero-placental vascular volume; EV, embryonic volume.

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modifier of these associations [9–11].

To investigate our hypothesis, reliable and non-invasive markers of utero-placental (vascular) development are needed. Ultrasound imaging is mainly used to assess uterine artery blood flow and to quantify placental volume (PV), basal plate surface area and placental vascularization indices using Virtual Organ Computer-aided AnaLysis (VOCAL) in the second half of pregnancy [12–18]. VOCAL uses two-dimensional (2D) planes and the third dimension is not used entirely. Herein lies the advantage of virtual reality (VR) using V-Scope software, enabling actual depth perception to be used for reliable semi-automated offline measurements of first-trimester embryonic growth parameters, i.e., serial crown-rump length (CRL) and embryonic volume (EV) and utero-placental vascular volume (uPVV) [19–22].

In order to contribute to the identification of pregnancies at risk of FGR at the earliest possible moment in pregnancy, we aim to investigate first-trimester serial PV and uPVV measurements, as markers of utero-placental (vascular) development, in association with embryonic and fetal growth in a fetal sex dependent manner.

2. Methods

2.1. Study population

The Virtual Placenta study (registration number Dutch Trial Register: NTR6854) is performed as a nested cohort in the Rotterdam Periconception Cohort, an ongoing prospective study conducted at the Department of Obstetrics and Gynecology of the Erasmus MC, University Medical Centre in Rotterdam, the Netherlands [21]. From January 2017 until March 2018, women pregnant less than 10 weeks of gestation were invited to participate. Excluded from analysis were miscarriages, oocyte donations, twins and drop outs. The study protocol was approved by the Erasmus MC Institutional Review Board (MEC 2015-494) on January 20th, 2016. Participating women and partners signed written informed consent at enrolment, also on behalf of their unborn child.

Eligible for inclusion were pregnancies naturally conceived, including intra-uterine insemination (IUI), and after in vitro fertilization (IVF) with or without intracytoplasmic sperm injection (ICSI). Natural pregnancies were dated based on the first day of the last menstrual period (LMP) in regular cycles between >25 and < 32 days. Gestational age (GA) was estimated using crown-rump length (CRL) in irregular cycles, unknown LMP, or when GA based on LMP differed more than six days from the GA estimated by CRL. The insemination date was used to calculate GA in IUI pregnancies. In IVF/ICSI pregnancies, GA was calculated from oocyte pick-up day plus 14 days, and, for cryopreserved embryo transfer, from the transfer day plus 19 days.

2.2. Study parameters

Maternal characteristics were obtained from self-reported questionnaires filled out upon enrolment and verified in a personal interview at study entry by a research nurse. Height and weight measurements were standardized to calculate first-trimester body-mass index (BMI). Geographic origin was categorized as Dutch, Western and Non-Western [23]. Educational level was categorized as low, middle or high according to the classification of Statistics Netherlands [24]. To follow up on birth outcomes, mothers filled out a postpartum questionnaire, which were cross-checked with the medical records.

Placenta-related complications were defined as pregnancy-induced hypertension (PIH), preeclampsia (PE), FGR, preterm birth (PTB) and/or small-for-gestational age (SGA). PIH was defined as systolic blood pressure above 140 mmHg or diastolic blood pressure above 90 mmHg after 20 weeks of gestation without signs of hypertension prior to pregnancy or presence of proteinuria [25]. PE was defined as hypertension after 20 weeks of gestation and presence of more than 300 mg proteinuria in a 24 h period [25,26]. FGR was defined as fetal abdominal circumference and/or estimated fetal weight (EFW) below the 10th percentile according to Hadlock curves or a more than twenty percentile decrease on the growth curve with a measurement interval of at least two weeks [27,28]. PTB was defined as GA at birth below 37 weeks. Standardized birth weight percentiles were calculated from the Perinatal Registration of Newborns in the Netherlands (PRN), established in 2008 [29] and SGA was defined as a birth weight below the 10th percentile [25,30].

2.3. Ultrasound

The participating women underwent 3D transvaginal ultrasound examinations at 7, 9 and 11 weeks GA to obtain volumes encompassing the whole pregnancy, including the embryo, gestational sac and placenta. At 22 and 32 weeks GA transabdominal ultrasonography was performed to estimate fetal growth by assessment of parameters to calculate estimated fetal weight (EFW) using the Hadlock formula, including biparietal diameter, head circumference, abdominal circumference and femur length [31]. Ultrasound examinations were performed by trained sonographers using Voluson E8 or E10 ultrasound systems (GE Medical Systems, Zipf, Austria), using a transvaginal 6–12 MHz transducer in the first trimester and an abdominal rm6c transducer in the second and third trimester. The utero-placental vasculature was visualized using power Doppler ultrasound with standardized settings (power Doppler gain '-8.0', pulse repetition frequency '0.6 kHz', wall motion filter 'low 1', quality 'high'). To minimize artifacts and measurement errors caused by movement, participants were asked to hold their breath for approximately 30 s during image acquisition. All (3D) 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 [32,33].

2.4. Offline measurements

Using VOCAL™ (4D View, GE Medical System), the trophoblast was traced to measure PV offline [13]. The basal plate surface area (mm^2) was determined by measuring the longest diameter of the placental base plate in a sagittal plane at the level of the utero-placental interface. The length was then traced using electronic calipers. Then the longest diameter was measured in the transverse plane, 90° perpendicular to the sagittal plane. The surface area of the placenta was estimated using the following formula: sagittal length x transverse length x π/4. The placental thickness (mm) was measured underneath the cord insertion. Placental ellipsivity was assessed from the ratio between the largest and the smallest diameter [17,18].

The in-house developed V-scope volume rendering application was used to measure CRL, embryonic volume (EV) and uPVV offline in VR [19,34]. The method for uPVV measurement was applied as previously described with good to excellent intra-observer and inter-observer agreement [20]. Each recording was scored by a self-developed quality score 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) [20]. The volume with the best score or, in cases of equal scores, the first volume was used for further analysis. Ultrasound datasets with insufficient quality were excluded from measurement and thus analysis.

Using a threshold of the 8-bit (range 0–255) Doppler magnitude data, semi-automatic volume measurements of the utero-placental vasculature were obtained. To enable the most optimal visualization of the utero-placental vasculature the lower-Doppler threshold level was set at a value of 100, meaning that only voxels with a Doppler value of 100 or higher are colored and counted. After removal of embryonic structures, the uPVV was generated by erasing all vascular voxels using a virtual

brush up to the utero-placental border which was identified by differences in grey values. The uPVV, as a representation of the maternal utero-placental vascular bed, was then measured using threshold-based segmentation [20]. A ratio was calculated between uPVV and PV to estimate a vascular index of the placenta.

2.5. Statistics

Data are presented as median [interquartile range (IQR)] or n (%). Differences in baseline characteristics for conception mode were assessed by chi-square test or Mann-Whitney *U* test as appropriate. Because of skewed distributions, all volumetric measurements (i.e. PV, uPVV and EV) were transformed using a square root for non-volumetric parameters and a cubic root for volumetric parameters.

Reference values for placental measurements were modelled in a curve (trajectory) using the R Gamlss package (RStudio statistics). To investigate associations between the placental trajectories and embryonic and fetal growth, a two-step process was followed, taking into account correlations between serial measurements in each pregnancy. First, linear mixed models were used to calculate the subject-specific estimated random effects to extract standardized random intercepts and slopes, summarizing individual trajectories of longitudinal measurements (i.e. PV, uPVV, uPVV/PV ratio, CRL, EV, EFW and birth weight percentile), with GA as independent variable. Z-scores were calculated for all continuous data, to compare values for different normal distributions.

In the second stage, z-scores of the estimated random effects from the mixed effects models were used as covariate in linear regression analyses for the trajectories of the first-trimester indices of placental development and the association with embryonic growth and fetal growth. Potential confounders were selected based on the characteristics of the study population and from literature. Associations between placental trajectories and embryonic and fetal growth were assessed in a model adjusted for GA (model 1). The second model (model 2) was additionally adjusted for maternal age, parity, conception mode, BMI and preconception initiation of folic acid supplement use. Next, we performed a stratified analysis for fetal sex (model 1 and 2). All models were constructed based on a combination of both an available placental and embryonic/fetal measurement of sufficient quality, resulting in a varying number of measurements per patient to be used for the analyses. As a final step, all prior analyses were repeated in a subgroup of pregnancies without complications to estimate the impact of placenta-related pregnancy complications on the associations. The required cubic transformation of the data and the calculation of trajectories makes the interpretation of data more complex. Therefore, in order to present the results in the simplest form possible, correction for multiple testing was not applied.

The single measurements of the basal plate surface area, placental thickness and placental ellipsivity were also analysed in the associations with embryonic and fetal growth using linear regression analyses.

All analyses were performed using SPSS software (version 25.0; SPSS Inc., Chicago, IL, USA) and RStudio Statistics (version 3.5.0, 2018) and R (version 3.5.0, R Core team 2018). *P*-values ≤ 0.05 were considered statistically significant.

3. Results

In Fig. 1 the flow chart of the study population is depicted. From a total of 241 pregnancies, 27 pregnancies were excluded for analysis: 22 non-vital pregnancies, 1 withdrawal, and 4 oocyte donations. From the ongoing 214 pregnancies, 466 3D ultrasound datasets were available, of which 328 (70.4%) were useable for measurements of PV and 346 (74.2%) for uPVV. The quality of the datasets was good in 60 (12.9%), average in 215 (46.1%) and low in 80 (17.2%).

Because of the high percentage of IVF pregnancies in our cohort, Table 1 represents the baseline characteristics of the total study population with stratification for mode of conception. The average maternal age was 32 years and most women were of Dutch geographic origin and intermediate or high educated, folic acid supplement use was up to 98%, 26% used alcoholic drinks and 13% smoked. In contrast to the IVF/ICSI group, women in the naturally conceived pregnancy group were slightly younger with a higher BMI and reported a lower frequency of preconception initiation of folic acid supplement use.

In the total study population of 214 pregnancies, 55 women developed placenta-related pregnancy complications (25.7%) comprising of

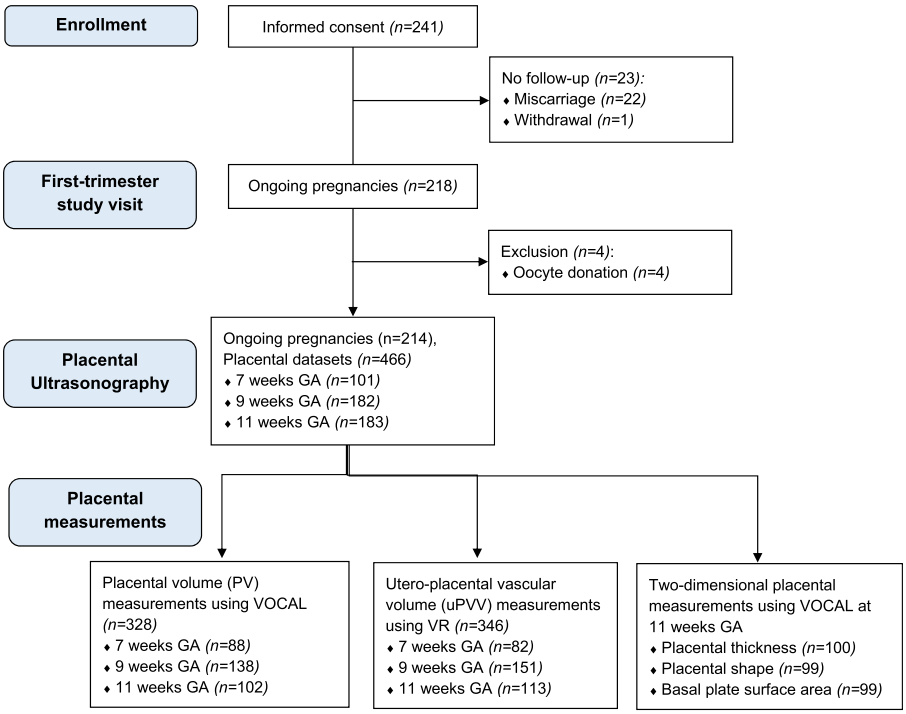

Fig. 1. Flow chart of the study population.

Table 1
Characteristics of the study population.

Characteristic	Total group (n = 214)	Natural conception (n = 127)	IVF/ICSI (n = 87)	*p*-value
Maternal				
Age, years	32.1 [29.0; 35.5]†	31.5 [28.9; 34.6]†	33.1 [29.3; 36.4]†	0.010*
Nulliparous	115 (53.7%)	68 (53.5%)	47 (54.0%)	0.945
GA at first visit, days	55 [51; 65]†	61 [52; 65]†	54 [51; 64]†	0.095
Geographic origin				0.578
Dutch	165 (77.1%)	95 (74.8%)	71 (81.6%)	
Western other	6 (2.8%)	4 (3.1%)	2 (2.3%)	
Non-western	38 (17.8%)	24 (18.9%)	14 (16.1%)	
Educational level				0.702
Low	18 (8.4%)	10 (7.9%)	8 (9.2%)	
Intermediate	69 (32.2%)	38 (29.9%)	31 (35.6%)	
High	123 (57.5%)	75 (59.1%)	48 (55.2%)	
BMI first trimester, measured (kg/m^2)	24.9 [22.2; 28.4]†	25.3 [22.5; 29.6]†	24.1 [21.0; 26.7]†	0.038*
Folic acid supplement use	210 (98.1%)	123 (96.9%)	87 (100%)	0.095
Preconception initiation	175 (81.8%)	90 (70.9%)	85 (97.7%)	<0.001*
Periconceptional alcohol consumption	57 (26.6%)	34 (26.8%)	23 (26.4%)	0.799
Periconceptional smoking	28 (13.1%)	16 (12.6%)	12 (13.8%)	0.816
Maternal pregnancy complications				
Any placenta-related pregnancy complication**	55 (25.7%)	38 (29.9%)	17 (19.5%)	0.088
PIH	9 (4.2%)	6 (4.7%)	3 (3.4%)	0.648
PE	7 (3.3%)	4 (3.1%)	3 (3.4%)	0.904
Fetal outcomes				
Fetal sex, boys	106 (49.5%)	68 (53.5%)	38 (43.7%)	0.282
GA at birth, days	274 [266; 280]†	273 [264; 279]†	274 [267; 282]†	0.060
Birth weight, grams	3305 [2930; 3565]†	3290 [2880; 3562]†	3338 [3029; 3583]†	0.357
FGR	15 (7.0%)	11 (8.7%)	4 (4.6%)	0.253
SGA	18 (8.4%)	14 (11.0%)	4 (4.6%)	0.096
PTB	23 (10.7%)	16 (12.6%)	7 (8.0%)	0.291
Congenital anomalies	8 (3.7%)	5 (3.9%)	3 (3.4%)	0.853

*Significance at p ≤ 0.05 assessed by chi-square test or Mann Whitney *U* test as appropriate. **Specified as PIH or PE and/or FGR, PTB and SGA; diagnoses may be overlapping.† Expressed as median [interquartile range, p25-p75]. BMI = body-mass index; FGR = fetal growth restriction; ICSI = intracytoplasmic sperm injection; IVF = in vitro fertilization; PE = preeclampsia; PIH = pregnancy-induced hypertension; PTB = preterm birth; SGA = small-for-gestational age.

maternal pregnancy complications: 4.2% PIH and 3.3% PE, and of adverse birth outcomes: 7.0% FGR, 8.4% SGA and 10.7% PTB. There were no significant differences in the prevalence of maternal pregnancy complications or adverse fetal outcomes between the naturally conceived and IVF/ICSI pregnancies.

In Supplementary Figure 1 the first-trimester increase of the trajectories of PV, uPVV, and constant uPVV/PV ratio is depicted for both uncomplicated pregnancies and pregnancies with any placenta-related complication. The estimates of these measurements at 7, 9 and 11 weeks are presented in Supplementary Table 1.

3.1. Embryonic and growth trajectories

In Table 2 positive associations are shown between PV trajectories and CRL (model 2: β = 0.416, 95% CI 0.255; 0.576, $p < 0.001$) and EV (model 2: β = 0.220, 95% CI 0.058; 0.381, $p = 0.008$). uPVV trajectories were positively associated with CRL (model 2: β = 0.203, 95% CI 0.021; 0.384, $p = 0.029$). No significant associations were observed for uPVV/PV ratio trajectories.

A positive association is shown between PV trajectories and EFW (model 2: β = 0.182, 95% CI 0.012; 0.352, $p = 0.037$).

3.2. Stratified analyses for fetal sex

In Table 3, in boys positive associations are shown between PV trajectories and CRL (model 2: β = 0.409, 95% CI 0.156; 0.661, $p = 0.002$) and between uPVV and CRL (model 2: β = 0.252, 95% CI 0.005; 0.500, $p = 0.046$). In boys, no associations were shown with fetal growth trajectories.

In girls, PV trajectories were positively associated with CRL trajectories (model 2: β = 0.442, 95% CI 0.226; 0.658, $p < 0.001$) and EV trajectories (model 2: 0.286, 95% CI 0.050; 0.522, $p = 0.018$) (Table 3). In addition, PV trajectories were positively associated with trajectories of EFW (model 2: β = 0.259, 95% CI 0.032; 0.486, $p = 0.026$). A positive association was established between uPVV trajectories and birth weight percentile (model 2: β = 0.269, 95% CI 0.013; 0.525, $p = 0.040$).

3.3. Sensitivity analysis of uncomplicated pregnancies

All prior analyses were repeated in a subgroup of uncomplicated pregnancies ($n = 159$) to estimate the impact of placenta-related complications on the associations.

In Table 4 positive associations are shown between PV trajectories and CRL (model 2: β = 0.473, 95% CI 0.276; 0.670, $p < 0.001$) and EV (model 2: β = 0.330, 95% CI 0.117; 0.543, $p = 0.003$). A negative association was observed between uPVV/PV ratio trajectories and fetal growth estimated by EFW trajectories (model 2: β = −0.338, 95% CI -0.675;-0.001, $p = 0.049$).

When stratified for fetal sex, uncomplicated pregnancies demonstrated positive associations in boys between PV trajectories and CRL (model 2: β = 0.346, 95% CI 0.023; 0.669, $p = 0.037$) (Table 5). In girls, uncomplicated pregnancies demonstrated positive associations of PV trajectories with CRL trajectories (model 2: β = 0.662, 95% CI 0.407; 0.916, $p < 0.001$) and EV trajectories (model 2: β = 0.562, 95% CI 0.245; 0.879, $p = 0.001$). Also in girls, a positive association was established between uPVV trajectories and birth weight percentile (model 2: β = 0.156, 95% CI 0.003; 0.309, $p = 0.046$).

Additional analysis of placental thickness, placental ellipsivity and basal plate surface area.

In Supplementary Table 2 a positive association is shown between placental thickness and PV at 11 weeks GA (model 2: β = 0.351, 95% CI 0.165; 0.537, p < 0.001) and the basal plate surface area (model 2: β = 0.329, 95% CI 0.131; 0.526, p < 0.001). A negative association was demonstrated between placental ellipsivity and EFW trajectories in girls only (model 2: β = −0.278, 95% CI -0.554;-0.001, p = 0.049) (Supplementary Table 4). No significant associations were observed for basal plate surface area.

4. Discussion

This study shows that first-trimester PV and uPVV trajectories are associated with embryonic and fetal growth, with some modification by fetal sex. PV trajectories were positively associated with embryonic growth, which was most pronounced in girls. In the same way, uPVV trajectories were positively associated with embryonic growth, in particular in boys and with birth weight percentile only in girls.

The positive associations between first-trimester utero-placental

Table 2
Associations between first-trimester trajectories of utero-placental (vascular) development and embryonic and fetal growth.

	CRL trajectory (N = 154†)				EV trajectory (N = 154†)				EFW trajectory (N = 136†)				Birth weight percentile (p) (N = 151†)			
	Model 1		Model 2		Model 1		Model 2		Model 1		Model 2		Model 1		Model 2	
	Estimate (β), (95% CI)	*p*-value	Estimate (β), (95% CI)	*p*-value	Estimate (β), (95% CI)	*p*-value	Estimate (β), (95% CI)	*p*-value	Estimate (β), (95% CI)	*p*-value	Estimate (β), (95% CI)	*p*-value	Estimate (β), (95% CI)	*p*-value	Estimate (β), (95% CI)	*p*-value
PV	0.412 (0.253; 0.570)	<0.001**	0.416 (0.255; 0.576)	<0.001**	0.211 (0.051; 0.371)	0.010**	0.220 (0.058; 0.381)	0.008**	0.167 (−0.003; 0.337)	0.054	0.182 (0.012; 0.352)	0.037*	0.079 (−0.017; 0.331)	0.311	0.087 (−0.067; 0.240)	0.265
uPVV	0.218 (0.048; 0.388)	0.012*	0.203 (0.021; 0.384)	0.029*	0.022 (−0.143; 0.187)	0.794	0.008 (−0.167; 0.183)	0.930	−0.012 (−0.194; 0.170)	0.895	−0.056 (−0.244; 0.132)	0.559	0.100 (−0.053; 0.253)	0.200	0.144 (−0.015; 0.303)	0.076
uPVV/PV ratio	−0.142 (−0.417; 0.133)	0.995	−0.165 (−0.447; 0.118)	0.251	−0.185 (−0.446; 0.075)	0.162	−0.186 (−0.453; 0.081)	0.170	−0.193 (−0.472; 0.087)	0.176	−0.226 (−0.508; 0.056)	0.115	0.114 (−0.131; 0.360)	0.359	0.112 (−0.138; 0.362)	0.379

Model 1: Adjusted analysis for gestational age.
Model 2: Model 1 + adjusted for maternal age, parity, conception mode, body-mass index and preconception initiation of folic acid supplement use.
† Number of available measurements for analysis of the placenta and embryo/fetus combined. *Significance at $p \leq 0.05$; **Significance at $p \leq 0.01$.
CRL = crown-rump length (mm); EFW = estimated fetal weight (gram); EV = embryonic volume (cm^3); PV = placental volume (cm^3); uPVV = utero-placental vascular volume (cm^3).

(vascular) development and embryonic and fetal growth suggest that serial PV and uPVV can be used as ultrasound markers for the monitoring of early placental development. The stronger effect estimates observed in the subgroup of pregnancies without a placenta-related complication further support that the markers estimate the physiology of placenta-dependent antenatal growth. Placental functioning is also determined by maternal cardiovascular adaptation to pregnancy, trophoblast tissue metabolism, endocrine and immunological pathways, and epigenetics [35]. However, an increase in first-trimester utero-placental (vascular) development does not guarantee better placental functioning and fetal and birth outcome, because a gold standard of optimal utero-placental (vascular) development is lacking. Therefore, further studies should also include personalized characteristics of first trimester placental growth curves in normal and high risk pregnancies.

Our results, however, are in line with known associations between first-trimester placental volume measurements and both placental weight and birth weight [36,37]. In line with previous publications, we demonstrated an association between placental thickness and basal plate surface area at 11 weeks GA and PV at 11 weeks GA [17,18]. Less clear were the associations between placental thickness and basal plate surface area and trajectories of embryonic and fetal growth. A possible explanation is the relatively small number of available measurements at 11 weeks GA and that a 2D ultrasound approach is compared with 3D ultrasound trajectories. The 2D ultrasound parameters might reflect placental development less reliably since this is based on limited ultrasound data (i.e. information provided by 2 planes only). Moreover, we demonstrated that pregnancies complicated by FGR and PE are associated with decreased placental vascularization indices, higher impedance to uterine blood flow and lower serum placental growth factor levels in the second half of pregnancy [14,15]. This could be due to impaired placental vascular development, i.e. deficient spiral artery remodeling. Because these (patho)physiological processes start already in the first trimester of pregnancy, it is very likely that women with a small placenta in early pregnancy are at risk for developing FGR, PE or other placenta-related pregnancy complications [38–40]. Although our study was not aimed and powered to investigate associations between trajectories of PV and uPVV and placenta-related pregnancy complications, the sensitivity analysis showed that the observed associations were not primarily due to these adverse outcomes.

We observed that first-trimester placental development was most strongly associated with first-trimester embryonic development. The association with second- and third-trimester fetal development as well as birth outcomes was weaker. Explanations are that there is indeed a stronger developmental correlation in the first trimester. Moreover, the time frame between 7 and 11 weeks GA covers a period of exceptionally rapid placental and embryonic development. The onset of the feto-maternal circulation after spiral artery unplugging lies in this period, although the exact timing is known to be variable. As such, placental vascular development may not be as strongly associated as overall placental development, reflected by the association between PV and embryonic growth that was demonstrated from our data. In addition, the first-trimester parameters are temporally remote from the parameters that were assessed from the second trimester onwards. This provides an opportunity for other impacting factors to interact with the later stages of fetal growth. Finally, it needs to be considered that EFW may not be the most robust marker, as the inherent measurement error of EFW by ultrasound could have contributed to the lack of association.

PV trajectories were associated with both increased embryonic and fetal growth, most pronounced in girls. While the association between uPVV trajectories and increased embryonic growth was only present in boys, these trajectories in girls were also associated with a higher birth weight percentile. These observed gender modifications in early placental development are in line with previous findings describing that early fetal growth is modified in a fetal sex dependent manner and persists up until birth [9,41]. In addition, it has been shown that girls use more energy for placenta development compared to boys, while boys

Table 3
Stratified analysis for fetal sex: associations between first-trimester trajectories of utero-placental (vascular) development and embryonic and fetal growth.

	CRL trajectory (N = 154†)				EV trajectory (N = 154†)				EFW trajectory (N = 136†)				Birth weight percentile (p) (N = 151†)			
	Model 1		Model 2		Model 1		Model 2		Model 1		Model 2		Model 1		Model 2	
	Estimate (β), (95% CI)	*p*-value	Estimate (β), (95% CI)	*p*-value	Estimate (β), (95% CI)	*p*-value	Estimate (β), (95% CI)	*p*-value	Estimate (β), (95% CI)	*p*-value	Estimate (β), (95% CI)	*p*-value	Estimate (β), (95% CI)	*p*-value	Estimate (β), (95% CI)	*p*-value
Boys (n=72†)																
PV	0.384 (0.136; 0.632)	0.003**	0.409 (0.156; 0.661)	0.002**	0.122 (−0.099; 0.343)	0.273	0.147 (−0.073; 0.367)	0.187	0.012 (−0.266; 0.291)	0.930	0.002 (−0.267; 0.272)	0.985	0.190 (−0.042; 0.422)	0.106	0.193 (−0.040; 0.425)	0.103
uPVV	0.214 (−0.008; 0.437)	0.059	0.252 (0.005; 0.500)	0.046*	−0.005 (−0.198; 0.187)	0.956	0.047 (−0.162; 0.255)	0.657	0.055 (−0.194; 0.303)	0.662	0.040 (−0.217; 0.297)	0.758	0.065 (−0.150; 0.280)	0.549	0.063 (−0.156; 0.281)	0.568
uPVV/PV ratio	−0.074 (−0.484; 0.337)	0.772	−0.076 (−0.504; 0.351)	0.723	−0.193 (−0.537; 0.150)	0.265	−0.160 (−0.508; 0.188)	0.265	−0.072 (−0.487 ;0.344)	0.731	−0.053 (−0.464; 0.359)	0.799	0.067 (−0.273; 0.407)	0.695	0.121 (−0.227; 0.469)	0.491
Girls (n=80†)																
PV	0.430 (0.216; 0.644)	<0.001**	0.442 (0.226; 0.658)	<0.001**	0.260 (0.026; 0.494)	0.030*	0.286 (0.050; 0.522)	0.018*	0.254 (0.035; 0.472)	0.024*	0.259 (0.032; 0.486)	0.026*	0.011 (−0.199; 0.220)	0.920	−0.010 (−0.222; 0.202)	0.927
uPVV	0.211 (−0.066; 0.487)	0.133	0.163 (−0.127; 0.452)	0.266	−0.024 (−0.274; 0.227)	0.824	−0.014 (−0.313; 0.285)	0.924	−0.051 (−0.329 ;0.226)	0.713	−0.107 (−0.394; 0.181)	0.460	0.259 (0.011; 0.507)	0.041*	0.269 (0.013; 0.525)	0.040*
uPVV/PV ratio	−0.239 (−0.627; 0.150)	0.323	−0.245 (−0.644; 0.154)	0.225	−0.224 (−0.622; 0.174)	0.266	−0.222 (−0.631; 0.187)	0.283	−0.272 (−0.668; 0.123)	0.174	−0.290 (−0.700; 0.120)	0.163	0.213 (−0.144; 0.571)	0.239	0.167 (−0.203; 0.536)	0.371

Model 1: Adjusted analysis for gestational age.
Model 2: Model 1 + adjusted for maternal age, parity, conception mode, body-mass index and preconception initiation of folic acid supplement use.
† Number of available measurements for analysis of the placenta and embryo/fetus combined. *Significance at $p \leq 0.05$; **Significance at $p \leq 0.01$.
CRL = crown-rump length (mm); EFW = estimated fetal weight (gram); EV = embryonic volume (cm^3); PV = placental volume (cm^3); uPVV = utero-placental vascular volume (cm^3).

Table 4
Associations between first-trimester trajectories of utero-placental (vascular) development and embryonic and fetal growth in uncomplicated pregnancies.

	CRL trajectory (N = 107†)				EV trajectory (N = 107†)				EFW trajectory (N = 104†)				Birth weight percentile (p) (N = 112†)			
	Model 1		Model 2		Model 1		Model 2		Model 1		Model 2		Model 1		Model 2	
	Estimate (β), (95% CI)	*p*-value	Estimate (β), (95% CI)	*p*-value	Estimate (β), (95% CI)	*p*-value	Estimate (β), (95% CI)	*p*-value	Estimate (β), (95% CI)	*p*-value	Estimate (β), (95% CI)	*p*-value	Estimate (β), (95% CI)	*p*-value	Estimate (β), (95% CI)	*p*-value
PV	0.467 (0.271; 0.663)	<0.001**	0.473 (0.276; 0.670)	<0.001**	0.318 (0.106; 0.529)	0.004**	0.330 (0.117; 0.543)	0.003**	0.147 (−0.066; 0.361)	0.174	0.168 (−0.043; 0.380)	0.117	−0.010 (−0.120; 0.101)	0.865	−0.004 (−0.115; 0.107)	0.943
uPVV	0.192 (−0.020; 0.404)	0.075	0.150 (−0.079; 0.378)	0.198	0.037 (−0.182; 0.256)	0.738	0.001 (−0.235; 0.236)	0.994	−0.084 (−0.289; 0.122)	0.421	−0.145 (−0.360; 0.070)	0.185	0.001 (−0.104; 0.103)	0.996	0.036 (−0.072; 0.145)	0.508
uPVV/PV ratio	−0.215 (−0.569; 0.118)	0.230	−0.254 (−0.617; 0.110)	0.169	−0.279 (−0.638; 0.079)	0.126	−0.288 (−0.658; 0.082)	0.126	−0.303 (−0.635; 0.030)	0.074	−0.338 (−0.675;-0.001)	0.049*	−0.039 (−0.209; 0.130)	0.646	−0.004 (−0.179; 0.171)	0.965

Model 1: Adjusted analysis for gestational age.
Model 2: Model 1 + adjusted for maternal age, parity, conception mode, body-mass index and preconception initiation of folic acid supplement use.
† Number of available measurements for analysis of the placenta and embryo/fetus combined. *Significance at $p \leq 0.05$; **Significance at $p \leq 0.01$.
CRL = crown-rump length (mm); EFW = estimated fetal weight (gram); EV = embryonic volume (cm^3); PV = placental volume (cm^3); uPVV = utero-placental vascular volume (cm^3).

direct more energy towards body growth and development [42]. The proposed mechanism by which this is regulated suggests an intensive interplay between mother, fetus and placenta [43]. A review on fetal sex dependency and placental growth and function in animal models described that utero-placental trophoblast function in female fetuses was most sensitive to disruptions in the periconception period, while placental trophoblast function in male fetuses was more sensitive to disruptions mid to late gestation [44]. The sensitivity analysis of the subgroup of uncomplicated pregnancies showed, after stratification for fetal sex, stronger positive associations between placenta development, in particular serial PV, and embryonic and fetal growth in girls. Our results substantiate that the sex specific differences in early utero-placental (vascular) development with an impact on embryonic and fetal growth can be due to sex-specific epigenetic programming of in particular imprinted genes, such as IGF_2 [45] of which the involved fetal sex specific pathways needs to be unraveled.

The main strengths of our prospective study are its high internal validity due to the recruitment of patients from a single hospital together with the standardized collection of serial 3D ultrasonography and VR measurements from the early first-trimester onwards, precise PV, uPVV, CRL and EV measurements, and the detailed information on baseline characteristics and pregnancy outcome data [21]. We applied advanced statistical models for adjustment of maternal age, parity, conception mode, BMI, and folic acid supplement use, and stratified the analysis for fetal sex. Inherent to the observational study design, we also encountered some limitations. A limitation of our study is the selective participation of high-risk and relatively high-educated Dutch women and a large group of IVF/ICSI pregnancies, which confines external validity. Therefore, we adjusted our analyses for conception mode and recommend validation of our findings in a general population. However, the effects of residual confounding cannot be excluded due to the observational character of this study. Moreover, other factors involved in utero-placental (vascular) development were not evaluated, for example biomarkers derived from placental endocrine and metabolic processes, such as placental growth factor [32].

So far, the availability of the VR technique is not widespread. Because of the accuracy and precision of the measurements possibilities for implementation in clinical practice have emerged [46]. The desktop setting in particular makes VR more easily applicable in a clinical setting. Although this is a one centre study, we have developed broad expertise in our clinic with a broad range of embryonic, fetal and placental measurements in the different trimesters of pregnancy using the VR desktop system [19]. A large number of observers have shown good to excellent intra- and interobserver reproducibility performing VR measurements. Currently, a clinical trial is conducted addressing the detection of congenital anomalies in the first trimester using the VR desktop system. This trial also studies patient and clinician perspectives and satisfaction [47].

It was not our aim to investigate FGR or SGA as a separate group and therefore our study was not powered for this aim. However, in the future it would be most interesting to investigate a large group of strictly defined FGR and SGA based on more robust criteria such as abdominal circumference <3rd percentile or abnormal Dopplers. This would distinguish the true FGR from the constitutionally SGA.

The inclusion of PTB in the group of placenta-related complications could be considered as a limitation of this study, because also the pathophysiology of PTB is multifactorial and cannot be solely attributed to suboptimal placental development. In future studies with a larger sample size it would be interesting to investigate PTB as a separate group and stratify the analysis for a placental or non-placental origin.

Our data further support that first-trimester utero-placental (vascular) development is not uniform in every pregnancy and woman, and in the same manner associated with embryonic and fetal growth. Therefore, the next step should be, after confirmation of our findings in the general population, to investigate the predictive value of FGR using first-trimester PV and uPVV measured by 3D ultrasonography and VR. In

Table 5
Stratified analysis for fetal sex: associations between first-trimester trajectories of utero-placental (vascular) development and embryonic and fetal growth in uncomplicated pregnancies.

	CRL trajectory (N = 154†)				EV trajectory (N = 154†)				EFW trajectory (N = 136†)				Birth weight percentile (p) (N = 151†)			
	Model 1		Model 2		Model 1		Model 2		Model 1		Model 2		Model 1		Model 2	
	Estimate (β), (95% CI)	*p*-value	Estimate (β), (95% CI)	*p*-value	Estimate (β), (95% CI)	*p*-value	Estimate (β), (95% CI)	*p*-value	Estimate (β), (95% CI)	*p*-value	Estimate (β), (95% CI)	*p*-value	Estimate (β), (95% CI)	*p*-value	Estimate (β), (95% CI)	*p*-value
Boys (n=72†)																
PV	0.288 (−0.022; 0.598)	0.068	0.346 (0.023; 0.669)	0.037*	0.105 (−0.180; 0.390)	0.462	0.143 (−0.148; 0.435)	0.327	−0.006 (−0.330; 0.318)	0.970	−0.023 (−0.342; 0.295)	0.883	0.076 (−0.099; 0.250)	0.387	0.037 (−0.139; 0.213)	0.673
uPVV	0.172 (−0.117; 0.462)	0.238	0.278 (−0.042; 0.598)	0.087	0.002 (−0.259; 0.264)	0.985	0.109 (−0.175; 0.394)	0.443	0.003 (−0.282; 0.287)	0.986	0.062 (−0.248; 0.373)	0.687	−0.120 (−0.268; 0.027)	0.108	−0.113 (−0.276; 0.050)	0.170
uPVV/ PV ratio	−0.185 (−0.690; 0.320)	0.465	−0.055 (−0.613; 0.504)	0.723	−0.220 (−0.667; 0.227)	0.326	−0.059 (−0.541; 0.423)	0.807	−0.171 (−0.643; 0.301)	0.470	0.013 (−0.498; 0.524)	0.959	−0.226 (−0.468; 0.016)	0.066	−0.203 (−0.450; 0.044)	0.104
Girls (n=80†)																
PV	0.608 (0.348; 0.869)	<0.001**	0.662 (0.407; 0.916)	<0.001**	0.472 (0.157; 0.787)	0.004**	0.562 (0.245; 0.879)	0.001**	0.238 (−0.052; 0.528)	0.106	0.249 (−0.053; 0.551)	0.104	−0.074 (−0.217; 0.068)	0.303	−0.092 (−0.237; 0.053)	0.209
uPVV	0.216 (−0.119; 0.550)	0.202	0.099 (−0.255; 0.453)	0.576	0.047 (−0.327; 0.422)	0.801	−0.061 (−0.458; 0.337)	0.761	−0.130 (−0.440; 0.181)	0.405	−0.228 (−0.549; 0.093)	0.160	0.128 (−0.020; 0.275)	0.089	0.156 (0.003; 0.309)	0.046*
uPVV/ PV ratio	−0.281 (−0.808; 0.245)	0.289	−0.325 (−0.862; 0.211)	0.229	−0.393 (−0.971; 0.186)	0.179	−0.437 (−1.041; 0.167)	0.152	−0.386 (−0.873;0.101)	0.226	−0.429 (−0.937; 0.080)	0.096	0.151 (−0.076; 0.378)	0.188	0.154 (−0.084; 0.391)	0.199

Model 1: Adjusted analysis for gestational age.
Model 2: Model 1 + adjusted for maternal age, parity, conception mode, body-mass index and preconception initiation of folic acid supplement use.
† Number of available measurements for analysis of the placenta and embryo/fetus combined. *Significance at $p \leq 0.05$; **Significance at $p \leq 0.01$.
CRL = crown-rump length (mm); EFW = estimated fetal weight (gram); EV = embryonic volume (cm^3); PV = placental volume (cm^3); uPVV = utero-placental vascular volume (cm^3).

the meantime, the following topics should be addressed in future research settings. First, calculating PV in VR by semi-automated utero-placental border detection is impossible so far and manual delineation is too time-consuming. Furthermore, despite the used preset, power Doppler ultrasound remains sensitive to artifacts during image acquisition and the selected gain may not be appropriate for all patients in the cohort. For example, obesity may attenuate image quality. Some studies recommend using individualized sub-noise gain to guarantee acquisition with minimum noise artifact [48]. Future exchange of protocols for 3D power Doppler ultrasound settings to measure the utero-placental vasculature could ensure more general recommendations.

Finally, the volume and quality of the uterine vasculature prior to pregnancy and its postconceptional increase could be a determinant of placental development and subsequent fetal growth. Endometrial receptivity enables embryonic implantation, initiating subsequent physiological vascular transformation of spiral arteries into low resistance vessels [49,50]. Endometrial pregnancy preparation and the possible impact of maternal lifestyle exposure on periconceptional endometrial quality, ideally studied in low-risk settings is therefore another interesting topic for future research.

To conclude, first-trimester PV and uPVV trajectories are associated with embryonic and fetal growth, in a fetal sex dependent manner. These findings underline the opportunity to monitor placental development as early as in the first trimester and therefore support the associations with embryonic and fetal growth.

Declaration of competing interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Author's contributions

I.R. was involved in the study design, data-acquisition, performance of measurements, data-analysis and wrote the first drafts of the manuscript together with A.M. and R.S.T.

E.V. was involved in the performance of measurements.

A.M., M.K., A.K., E.S. and R.S.T. were involved in the study design, and inference of the data. S.W., I.R. and R.S.T. are responsible for statistical data analysis. All authors contributed to the writing of the manuscript and have read and approved the final version of the manuscript. R.S.T. is the guarantor of this work.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.placenta.2021.03.017.

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