First-trimester maternal haemodynamic adaptation to pregnancy and placental, embryonic and fetal development: the prospective observational Rotterdam Periconception cohort

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Objective To investigate whether first-trimester maternal haemodynamic adaptation impacts placental, embryonic and fetal development as well as birth outcomes in pregnancies with and without placenta-related complications.

Design Prospective observational cohort.

Setting A Dutch tertiary hospital.

Population Two hundred and fourteen ongoing pregnancies.

Methods At 7, 9 and 11 weeks of gestation, we assessed maternal haemodynamic adaptation (mean arterial blood pressure [MAP], uterine artery [UtA] blood flow) and placental development (placental volume [PV], uteroplacental vascular volume [uPVV]) using three-dimensional power Doppler ultrasound volumes, and embryonic development (crown–rump length, embryonic volume). At 22 and 32 weeks of gestation, fetal development was assessed by estimated fetal weight. Birth outcomes (birthweight, placental weight) were extracted from medical records. Linear mixed modelling and linear regression analyses were applied.

Main outcome measures Birthweight centile and placental weight.

Results In placenta-related complications ($n = 55$, 25.7%), reduced haemodynamic adaptation, i.e. higher UtA pulsatility index (PI) and resistance index (RI) trajectories, was associated with smaller increase in PV ($\beta = -0.559$, 95% CI -0.841 to -0.278, $P < 0.001$; $\beta = -0.579$, 95% CI -0.878 to -0.280, $P < 0.001$) and uPVV trajectories (UtA PI: $\beta = -0.301$, 95% CI -0.578 to -0.023, $P = 0.034$). At birth, reduced haemodynamic adaptation was associated with lower placental weight (UtA PI: $\beta = -0.502$, 95% CI -0.922 to -0.082, $P = 0.022$; UtA RI: $\beta = -0.435$, 95% CI -0.839 to -0.032, $P = 0.036$). In pregnancies without placenta-related complications, higher MAP trajectories were positively associated with birthweight centile ($\beta = 0.398$, 95% CI 0.049–0.748, $P = 0.025$).

Conclusions Reduced first-trimester maternal haemodynamic adaptation impacts both placental size and vascularisation and birthweight centile, in particular in pregnancies with placenta-related complications.

Keywords 3D ultrasound, birth outcomes, placenta-related complications, uterine artery blood flow.

Tweetable abstract Reduced first-trimester maternal haemodynamic adaptation to pregnancy impairs early placental development.

Introduction

Placental development in the first trimester of pregnancy is key to the success of pregnancy and health during the life course.[1] Insufficient spiral artery remodelling and impaired maternal haemodynamic adaptation of the uteroplacental vascular network during this early period in pregnancy can result in hypoperfusion of the uteroplacental circulation, involved in

the causative pathways of placenta-related complications that present from mid-gestation onwards.[2–4] Placenta-related complications include pregnancy-induced hypertension, pre-eclampsia, fetal growth restriction (FGR), preterm birth and babies born small-for-gestational age (SGA).[5–11]

In clinical practice, maternal haemodynamic adaptation is assessed by mean arterial blood pressure (MAP), determined by cardiac output and systemic vascular resistance, and uterine artery (UtA) blood flow.[3] From the first-trimester onwards, a physiological course of haemodynamic adaptation translates into a decrease in MAP (up to mid-gestation) and resistance to UtA blood flow. Using Doppler ultrasound, UtA blood flow can be measured by the pulsatility index (PI) and resistance index (RI).[12] Persistent high resistance to UtA blood flow in the second- and third-trimester is positively associated with placenta-related complications.[12,13] From this background, we postulate that impaired first-trimester maternal haemodynamic adaptation also increases the risk of adverse early and late placental and embryonic and fetal development.

Previously introduced techniques, such as three-dimensional (3D) ultrasonography combined with Virtual Organ Computer-aided AnaLysis (VOCAL)™, enable the assessment of placental volume (PV).[14] A smaller first-trimester PV is associated with higher second-trimester UtA resistance, as well as placenta-related complications.[15,16] When Virtual Reality (VR) is combined with 3D power Doppler ultrasonography, uteroplacental vascularisation volumes (uPVV) can be measured in a reproducible and accurate manner, using depth perception and offering 3D interaction by creating a hologram from the 3D ultrasound data set.[17–19] The uPVV measurements were performed on a 3D VR desktop system, allowing for more precise and detailed evaluation of placental structures because of the option of image enlargement, image rotation and the actual use of all 3D dimensions.[19] As such, uPVV in the first trimester can be considered a marker representing not only maternal haemodynamic adaptation to pregnancy but also placental development. Here we consider PV and uPVV as surrogate outcomes of placental development only.[20]

A longitudinal 2-weekly assessment of maternal haemodynamic adaptation to pregnancy as early as from 7 weeks onwards is unique. Moreover, the assessment of associations with placental, embryonic and fetal development this early using 3D Power Doppler ultrasound combined with VOCAL and VR has not been performed previously. Therefore, the overall aim of this study is to investigate associations between the extent of early first-trimester maternal haemodynamic adaptation and early placental development, i.e. PV, uPVV and embryonic and fetal development, i.e. crown–rump length (CRL), embryonic volume (EV), estimated fetal weight (EFW), and birth outcomes, i.e. birthweight, placental weight.

Methods

Study design

This study was part of the Virtual placenta study (registration number Dutch Trial Register: NTR6854), embedded in the ongoing prospective Rotterdam Periconception Cohort (Predict study).[21] Women were eligible with a singleton pregnancy less than 10 weeks of gestation. Between January 2017 and March 2018, a total of 241 participants were enrolled. Women were excluded from further analysis in the event of a miscarriage, conception after oocyte donation or withdrawal. At enrolment, participants filled out a questionnaire on general characteristics, medical (and obstetric) history and lifestyle behaviours. Measurements of height and weight were standardised to calculate body mass index (BMI) at the first study visit. Geographic origin was categorised as Dutch, Western and Non-Western.[22] Educational level was categorised as low, middle or high according to the classification of Statistics Netherlands.[23]

Visits were scheduled at 7, 9, 11, 22 and 32 weeks of gestation. During all visits, blood pressure in mmHg was assessed by a nurse or physician in a sitting position, on the right arm, using a manual blood-pressure cuff and stethoscope to measure systolic and diastolic blood pressure. The MAP in mmHg was calculated from the systolic blood pressure + 2*diastolic blood pressure, divided by 3.

Gestational age (GA) in spontaneous pregnancies was based on the first day of the last menstrual period in regular cycles defined as a cycle duration between 25 and 35 days. For pregnancies conceived after in vitro fertilisation (IVF) with or without intracytoplasmic sperm injection (ICSI), GA was calculated from the oocyte pick-up day plus 14 days. In pregnancies from cryopreserved embryos, GA was defined as the transfer date plus 19 days. GA was based on CRL when a difference of more than 6 days existed between the GA based on last menstrual period and the GA based on CRL, or in the case of an irregular menstrual cycle or unknown last menstrual period.[17]

Ultrasound

At 7, 9 and 11 weeks of gestation, a transvaginal 3D power Doppler ultrasound volume was obtained to visualise the vascularisation of the whole gestational sac including the placenta. At 22 and 32 weeks of gestation transabdominal ultrasound was performed to estimate fetal growth by parameters needed to calculate EFW using the Hadlock formula (encompassing the biparietal diameter, head circumference, abdominal circumference and femur length).[24] At all study visits, pulsed wave Doppler ultrasound was used in a two-dimensional plane to assess UtA blood flow by determination of the bilateral UtA PI and UtA RI.[25]

Ultrasound scans were performed by trained sonographers using a Voluson Expert E8 or E10 ultrasound system

with a transvaginal 6–12 MHz transducer (GE, Zipf, Austria) with standard power Doppler settings as described previously (power Doppler gain '−8.0', pulse repetition frequency '0.6 kHz', wall motion filter 'low1', quality 'high').[17] During 3D scanning, participants were asked to hold their breath for approximately 30 seconds to minimise breathing artefacts. To increase the chances of obtaining a complete and high-quality volume, a minimum of two uterine volumes was recorded at a perpendicular angle (90°) to each other. Total ultrasound scanning time was always limited to 30 minutes per visit according to international safety guidelines.[26,27]

Offline 3D measurements

Image quality was scored on a four-point scale ranging between zero and three, based on the presence of artefacts (due to fetal movements causing blurring of the volume or acoustic shadowing), the ability to distinguish between myometrial and trophoblastic tissue, and completeness of the placenta. For sufficient quality, a score between zero and two was assigned. An incomplete or bad-quality volume received a score of three and was excluded.

Placental volume was measured offline using VOCAL by two trained observers according to the following protocol: to measure PV, the circumference of the placenta and embryonic cavity was traced in two-dimensional planes with a 15-degree rotation step, resulting in a total of 12 placental slices from which a 3D volume was reconstructed. The placental tissue was distinguished from its surroundings by the difference in echogenicity between trophoblast and myometrium. Placental tracing resulted in a total pregnancy volume including the gestational sac. Next, the gestational sac volume was calculated by tracing the gestational sac contours in a similar way to the placenta. The PV in cubic centimetres was then calculated by subtraction of the embryonic cavity volume from the gestational sac volume.[15]

The uPVV was measured using a VR desktop system with the V-Scope volume rendering application. The VR desktop consists of a 3D monitor, a tracking system for a pointing device, a pair of stereoscopic glasses and a six degrees-of-freedom mouse for 3D volume manipulation. The protocol for uPVV measurements has been shown to be reproducible within and between observers.[17] In short, uPVV was measured by removal of the power Doppler signal of the embryonic or fetal structures. Then, the difference in echogenicity between the myometrium and placenta was used to erase the power Doppler signal of blood vessels up to the myometrial–placental tissue interface.[17]

The CRL was measured three times using a length-measuring tool in VR, placing the calipers in a straight line from the crown to caudal rump. By rotating the hologram, a correct position of the line in the midsagittal plane was verified. The average was used for analysis. Embryonic volume (EV) was measured once based on grey values by a semi-automated volume-measuring application. The technique and reliability of CRL and EV measurements have been validated previously.[28,29]

To determine the relative vascularisation degree of the placental bed, the uPVV/PV ratio was calculated.

Definitions of maternal and fetal placenta-related complications

The occurrence of maternal and fetal placenta-related complications was retrieved from medical records. Pregnancy-induced hypertension was defined as a systolic blood pressure above 140 mmHg or diastolic blood pressure above 90 mmHg after 20 weeks of gestation without signs of hypertension before pregnancy or presence of proteinuria.[30] Pre-eclampsia was defined as hypertension with systolic blood pressure above 140 mmHg or diastolic blood pressure above 90 mmHg after 20 weeks of gestation and presence of more than 300 mg proteinuria in a 24-hour period.[30,31] A fetal abdominal circumference and/or EFW below the tenth centile according to Hadlock curves or a more than twenty-centile decrease on the growth curve, compared with previous measurements with at least a time span of 2 weeks, was defined as FGR.[32,33] A GA at birth below 37 weeks was defined as preterm birth and SGA was defined as birthweight below the tenth centile on growth curves specific for GA at birth, parity and fetal gender.[30,34]

Statistical analysis

Inherent to the explorative nature of our study we did not perform a power calculation. Moreover, no reference values for the placental measurements in VR are available, making it impossible to determine the estimates of expected mean differences needed for power calculation.

Baseline characteristics of the study population were presented as medians with interquartile range or number with percentage. First, to establish normal distributions, data were transformed using a natural log transformation or square root for non-volumetric parameters (MAP, UtA PI, UtA RI and CRL) and cubic root for volumetric parameters (i.e. PV, uPVV, uPVV/PV ratio and EV).

This was followed by a two-step approach to analyse the associations between the haemodynamic and placental parameters. We applied linear mixed models using the individual trajectories of longitudinal measurements (i.e. trajectories of MAP, UtA PI, UtA RI, PV, uPVV, uPVV/PV ratio, CRL, EV and EFW as response variable), with GA as independent variable. In these models we allowed for subject-specific intercepts and slopes (the random effects). Where possible, both the standardised random intercepts and slopes were extracted and used as summaries representing first-trimester haemodynamic adaptation (i.e. MAP, UtA PI and UtA RI). In the next analysis the estimates of

first-trimester haemodynamic adaptation were used as covariates in linear regression analyses. Here we used the random effects of the mixed effects models for the trajectories of first-trimester placental development and the trajectories of first-trimester embryonic growth, trajectories of second- and third-trimester EFW, GA at birth, birthweight centile and placental weight as outcomes. Analyses were stratified for pregnancies with and without placenta-related complications. The associations were assessed in a crude model (data not shown). Thereafter, a second model was adjusted for maternal age, parity, conception mode, smoking, fetal gender, BMI and preconception initiation of folic acid supplement use based on the characteristics of the study population and literature. As a last step, sensitivity analyses were performed in strictly dated pregnancies only.

All analyses were performed using SPSS software (version 25.0; IBM, Armonk, NY, USA) and RStudio Statistics (version 3.5.0, 2018). Values of P less than 0.05 were considered statistically significant.

Results

A total of 214 ongoing pregnancies out of 241 pregnancies were included in the analysis. Twenty-two women were excluded as the result of miscarriage, four women were excluded because of oocyte donation and one woman withdrew from the study (Figure S1). A total of 466 3D ultrasound data sets were available for further analysis (respectively 101 data sets were available at 7 weeks of gestation, 182 data sets at 9 weeks of gestation and 183 data sets at 11 weeks of gestation), of which 328 (70.4%) were usable for VOCAL measurements (respectively 88 data sets were available at 7 weeks of gestation, 138 data sets at 9 weeks of gestation and 102 data sets at 11 weeks of gestation) and 346 (74.2%) for VR measurements (respectively 82 data sets were available at 7 weeks of gestation, 151 data sets at 9 weeks of gestation and 113 data sets at 11 weeks of gestation).[33]

Table 1 shows the study population's baseline characteristics, stratified for pregnancies with and without placenta-related complications. Placenta-related complicated pregnancies ($n = 55$, 25.7%) showed a shorter GA at birth (median 38^{+0} weeks versus 39^{+2} weeks, $P < 0.001$), lower birthweight (median 2735 g versus 3415 g, $P < 0.001$) and lower placental weight at birth (median 353 g versus 459 g, $P < 0.001$) compared with the uncomplicated pregnancies ($n = 159$, 74.3%).

In placenta-related complicated pregnancies, UtA PI and UtA RI values at 11 weeks of gestation were higher compared with uncomplicated pregnancies (median PI: 2.03 versus 1.74, $P = 0.047$; median RI: 0.79 versus 0.75, $P = 0.021$). In addition, in placenta-related complicated pregnancies PV (cm^3) and uPVV (cm^3) values were lower at 9 weeks of gestation (median PV: 39.51 versus 45.50, $P = 0.028$; median uPVV: 5.49 versus 9.27, $P = 0.018$). Furthermore, in these pregnancies PV was lower at 11 weeks of gestation (median: 79.13 versus 95.46, $P = 0.002$) (Figure 1; Table S1).

First-trimester maternal haemodynamic adaptation and first-trimester trajectories of placental development

No significant associations were established between first-trimester maternal haemodynamic adaptation, assessed by MAP trajectories, and placental development (Table 2).

In placenta-related complicated pregnancies, reduced first-trimester maternal haemodynamic adaptation, assessed by an increase in the UtA PI trajectory, was negatively associated with PV trajectories (random intercept adjusted $\beta = -0.559$, 95% CI -0.841 to -0.278, $P < 0.001$) and uPVV trajectories (random intercept adjusted $\beta = -0.301$, 95% CI -0.578 to -0.023, $P = 0.034$). Reduced first-trimester maternal haemodynamic adaptation, assessed by an increase in the UtA RI trajectory, was negatively associated with PV trajectories (random intercept adjusted $\beta = -0.579$, 95% CI -0.878 to -0.280, $P < 0.001$) (Table 2).

In pregnancies without placenta-related complications, reduced first-trimester maternal haemodynamic adaptation, assessed by an increase in the UtA PI and UtA RI trajectories was negatively associated with uPVV trajectories (PI: random intercept adjusted $\beta = -0.303$, 95% CI -0.470 to -0.136, $P < 0.001$, RI: random intercept adjusted $\beta = -0.316$, 95% CI -0.483 to -0.150, $P < 0.001$). Moreover, negative associations were observed for trajectories of the uPVV/PV ratio (random intercept adjusted $\beta = -0.244$, 95% CI -0.428 to -0.059, $P = 0.010$; random slope adjusted $\beta = 0.239$, 95% CI 0.053–0.425, $P = 0.012$) (Table 2).

First-trimester maternal haemodynamic adaptation and trajectories of embryonic and fetal development

No significant associations were identified between maternal haemodynamic adaptation and embryonic and fetal development (Table S2 and S3) in pregnancies with or without placenta-related complications.

First-trimester maternal haemodynamic adaptation and birth outcomes

In placenta-related complicated pregnancies, reduced first-trimester maternal haemodynamic adaptation, assessed by an increase in the UtA PI and UtA RI trajectories, was only associated with a lower placental weight (UtA PI random intercept adjusted $\beta = -0.502$, 95% CI -0.922 to -0.082, $P = 0.022$; UtA RI random intercept adjusted $\beta = -0.435$, 95% CI -0.839 to -0.032, $P = 0.036$) (Table 3). No significant associations were revealed between maternal

Table 1. Baseline characteristics of the Virtual Placenta study population

Characteristic	All pregnancies (n = 214)	Placenta-related complications (n = 55)	No placenta-related complications (n = 159)	P value*
Maternal				
Age, years	32.1 [29.0; 35.5]**	30.6 [29.0; 34.3]**	32.5 [29.1; 35.8]**	0.101
Nulliparous	115 (53.7%)	28 (50.9%)	87 (54.7%)	0.625
Mode of conception, IVF/ICSI	87 (40.7%)	17 (30.9%)	70 (44.0%)	0.088
GA at first visit, days	55 [51; 65]**	59 [51; 65]**	55 [51; 65]**	0.917
Geographic origin				
Dutch	165 (78.9%)	38 (73.1%)	127 (80.9%)	0.453
Western other	6 (2.9%)	1 (1.9%)	5 (3.2%)	
Non-Western	38 (18.2%)	13 (25.0%)	25 (15.9%)	
Educational level				
Low	18 (8.6%)	7 (13.5%)	11 (6.9%)	0.262
Intermediate	69 (32.9%)	14 (26.9%)	55 (34.6%)	
High	123 (58.6%)	31 (59.6%)	92 (57.9%)	
BMI measured at first visit in first trimester (kg/m^2)	24.9 [22.2; 28.4]**	24.8 [22.2; 27.5]**	24.0 [21.4; 27.0]**	0.235
Folic acid supplement use, yes	210 (98.1%)	54 (98.2%)	156 (98.1%)	0.974
Preconception initiation	175 (81.8%)	40 (72.7%)	135 (84.9%)	0.131
Alcohol consumption, yes	57 (26.6%)	10 (18.2%)	47 (29.6%)	0.100
Smoking, yes	28 (13.1%)	10 (18.2%)	18 (11.3%)	0.193
Birth outcomes				
Major congenital anomalies	8 (3.7%)	0 (0%)	8 (5.0%)	0.090
GA at birth, weeks	39^{+1} [38^{+2}; 40^{+0}]**	38^{+0} [36^{+1}; 39^{+1}]**	39^{+2} [38^{+4}; 40^{+2}]**	<0.001*
Birthweight, grams	3305 [2930; 3565]**	2735 [2329; 2931]**	3415 [3175; 3685]**	<0.001*
Placental weight, grams	435 [350; 517]**	353 [301; 444]**	459 [407; 567]**	<0.001*
Fetal gender, boys	106 (49.5%)	30 (54.5%)	76 (49.7%)	0.535
Placenta-related complications***	55 (25.7%)	55 (100%)	NA	NA
PIH	9 (4.2%)	9 (16.4%)	NA	NA
Pre-eclampsia	7 (3.3%)	7 (12.7%)	NA	NA
FGR	15 (7.0%)	15 (27.3%)	NA	NA
Preterm birth****	23 (10.7%)	23 (41.8%)	NA	NA
SGA	18 (8.4%)	18 (32.7%)	NA	NA

FGR, fetal growth restriction, defined as abdominal circumference and/or estimated fetal weight (EFW) below the tenth centile; GA, gestational age or a more than twenty-centile decrease on the growth curve, compared with previous measurements with a time span of at least 2 weeks; NA, not applicable; PIH, pregnancy-induced hypertension; SGA, small-for-gestational age, defined as birth weight below the tenth percentile.
*P value tested between pregnancies with and without placenta-related complications, significance at P < 0.05.
**Expressed as median [interquartile range, p25; p75].
***Overlapping diagnoses.
****Iatrogenic and spontaneous preterm births.

haemodynamic adaptation reflected by MAP and birth outcomes (GA at birth, birthweight centile and placental weight).
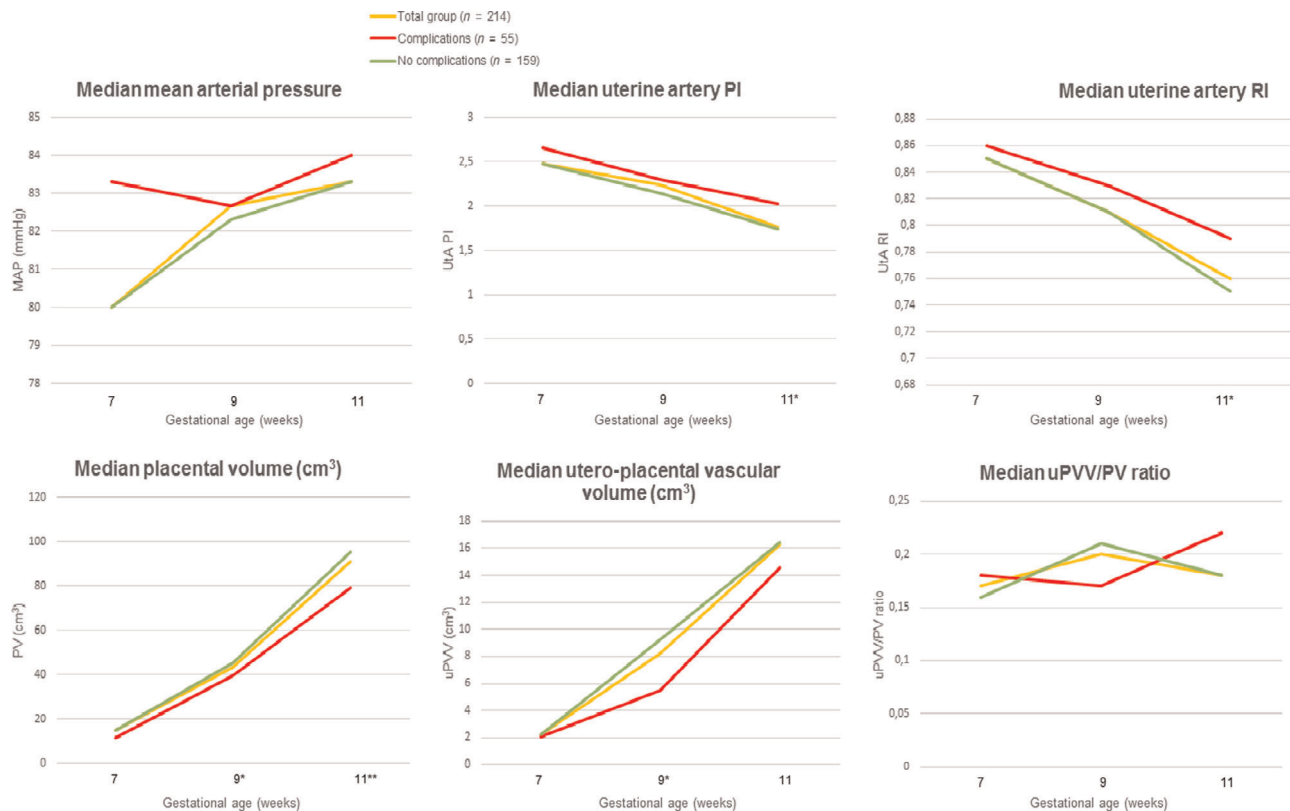
In pregnancies without placenta-related complications, reduced first-trimester maternal haemodynamic adaptation, assessed by an increase in the MAP trajectories, was associated with a higher birthweight centile (adjusted β = 0.398, 95% CI 0.049–0.748, P = 0.026). Furthermore, reduced first-trimester maternal haemodynamic adaptation, assessed by an increase in the UtA PI and UtA RI trajectories, was associated with a lower GA at birth (PI: random intercept adjusted β = −0.092, 95% CI −0.171 to −0.012, P = 0.024;

RI random intercept adjusted β = −0.110, 95% CI −0.187 to −0.033, P = 0.005) (Table 3).

Discussion

Main findings

We demonstrated that in particular in placenta-related complicated pregnancies, reduced first-trimester maternal haemodynamic adaptation, assessed by higher MAP and UtA blood flow resistance, is associated with a smaller increase in first-trimester placental development, i.e. PV and uPVV. No significant associations were identified

Figure 1. First-trimester maternal haemodynamic parameters and placental parameters, stratified for pregnancies with and without placenta-related complications.

between maternal haemodynamic adaptation and embryonic and fetal development. At birth, reduced first-trimester maternal haemodynamic adaptation to pregnancy, as assessed by higher UtA blood flow resistance, is associated with lower placental weight in pregnancies with placenta-related complications. In pregnancies without placenta-related complications, reduced first-trimester maternal haemodynamic adaptation, assessed by an increase in MAP trajectories, was associated with a higher birthweight centile, and an increase in UtA PI and UtA RI trajectories was associated with a shorter GA at birth.

Strengths and limitations

The longitudinal early first-trimester measurements of MAP, UtA PI and UtA RI as markers of maternal haemodynamic adaptation to pregnancy are unique. Unfortunately, it was not possible to estimate both the random intercept and slope for all parameters representing haemodynamic adaptation due to the size of the study population.

Moreover, we used 3D Power Doppler ultrasound combined with VOCAL and VR as an innovative technique to measure PV, uPVV, CRL and EV. At our center there is

broad experience in assessment of placental, embryonic and fetal measurements using VR.[17] We observed wide ranges of PV and uPVV values in this population. This is probably a result of (patho)physiological differences in placental development instead of inaccuracies, as these measurements of placental development were proven to be reproducible within and between observers.[17]

Inclusion of participants from as early as 7 weeks gestation is unique in Doppler ultrasound. However, recruitment was performed in a tertiary hospital setting to enable this. The tertiary setting created a high-risk and less generalisable study population, limiting external validity due to a high percentage of IVF/ICSI pregnancies (40.9%), presence of comorbidities and high median age (32 years).

In addition, for reasons of interaction with uteroplacental vascular development and inaccuracy of gestational age determination, miscarriages were excluded from analysis. As a downside this could have introduced selection bias because the data may not reflect all early first-trimester pregnancies in the whole general population.

We corrected for a broad range of confounders. Conception mode is relevant because IVF/ICSI pregnancies are more at risk of developing pregnancy complications like

Table 2. Associations between reduced first-trimester maternal haemodynamic adaptation and trajectories of placental development, stratified for pregnancies with and without placenta-related complications

	First-trimester PV trajectory ($\sqrt[3]{cm^3}$) Random intercept	First-trimester uPVV trajectory ($\sqrt[3]{cm^3}$) Random intercept	First-trimester uPVV/PV ratio trajectory Random intercept	First-trimester uPVV/PV ratio trajectory Random slope
Pregnancies with placenta-related complications (n = 55)				
Higher first-trimester trajectory of MAP				
Random intercept (β), 95% CI	0.154 (−0.772; 1.080)	0.036 (−0.796; 0.868)	−0.191 (−0.923; 0.540)	0.210 (−0.484; 0.903)
Random slope (β), 95% CI	−0.343 (−1.262; 0.577)	−0.189 (−0.992; 0.614)	0.201 (−0.517; 0.920)	−0.236 (−0.917; 0.445)
Higher 1st trimester trajectory of UtA PI				
Random intercept (β), 95% CI	−0.559 (−0.841;−0.278)**	−0.301 (−0.578;−0.023)*	−0.134 (−0.391; 0.122)	−0.034 (−0.282; 0.212)
Random slope (β), 95% CI	NA	NA	NA	NA
Higher first-trimester trajectory of UtA RI				
Random intercept (β), 95% CI	−0.579 (−0.878;−0.280)**	−0.255 (−0.553; 0.043)	−0.086 (−0.361; 0.190)	−0.084 (−0.347; 0.178)
Random slope (β), 95% CI	NA	NA	NA	NA
Pregnancies without placenta-related complications (n = 159)				
Higher first-trimester trajectory of MAP				
Random intercept (β), 95% CI	−0.166 (−0.552; 0.220)	−0.229 (−0.617; 0.180)	−0.198 (−0.615; 0.220)	−0.133 (−0.557; 0.291)
Random slope (β), 95% CI	0.230 (−0.161; 0.620)	0.203 (−0.197; 0.602)	0.112 (−0.313; 0.537)	0.134 (−0.297; 0.566)
Higher first-trimester trajectory of UtA PI				
Random intercept (β), 95% CI	−0.090 (−0.260; 0.080)	−0.303 (−0.470;−0.136)**	−0.214 (−0.397; 0.031)	0.179 (−0.006; 0.365)
Random slope (β), 95% CI	NA	NA	NA	NA
Higher first-trimester trajectory of UtA RI				
Random intercept (β), 95% CI	−0.057 (−0.228; 0.114)	−0.316 (−0.483;−0.150)**	−0.244 (−0.428;−0.059)*	0.239 (0.053; 0.425)*
Random slope (β), 95% CI	NA	NA	NA	NA

Fully adjusted model for maternal age, parity, conception mode, body mass index, smoking, preconception initiation of folic acid supplement use and fetal gender. Random slope not available for first-trimester UtA PI, UtA RI, PV and uPVV.
* Significance at $P < 0.05$.
** Significance at $P < 0.01$.

FGR and pre-eclampsia.[35,36] It is hypothesised that the hormonal treatment in IVF/ICSI pregnancies influences maternal vascular adaptation to pregnancy.[37] We also corrected for parity, because the placentas of nulliparous women are on average smaller at birth and nulliparous women more often develop placenta-related complications.[38] Moreover, parity impacts UtA blood flow.[39] We also adjusted for fetal gender as it was demonstrated previously that this modifies first-trimester placental development. However, residual confounding cannot be excluded being inherent to a prospective observational design.

Not all participants were included in the study as early as 7 weeks of gestation, resulting in missing ultrasound volumes in early pregnancy. Following critical appraisal of the quality of our 3D ultrasound data sets to ensure appropriate evaluation and generalisability, not all obtained data sets were included for assessment. The highest number of ultrasound volumes was available at 9 weeks of gestation. Subsequently, beyond 9 weeks of gestation these numbers were reduced because of increasing quality loss of the acquired ultrasound data or following a large placental size beyond this period. Moreover, obesity and/or uterine position may attenuate image quality. Therefore the included percentage of 3D data sets (70.4% for VOCAL data sets and 74.2% for VR, respectively) matched our expectations.

In general, we observed that directions of non-significant effect estimates matched the directions of statistically significant values. Inherent to the explorative and observational design of our study, the likelihood of any Type 1 or Type 2 errors cannot be eliminated. We therefore propose that our results are considered most suitable for the purpose of hypothesis-generating and hopefully to stimulate future investigations.

Table 3. Associations between reduced first-trimester maternal haemodynamic adaptation and birth outcomes, stratified for pregnancies with and without placenta-related complications

	GA at birth (days)	Birthweight centile (p)	Placental weight (grams)
Pregnancies with placenta-related complications (n = 55)			
Higher first-trimester trajectory of MAP			
Random intercept (β), 95% CI	−0.048 (−1.246; 1.149)	−0.066 (−0.799; 0.668)	−0.900 (−2.302; 0.501)
Random slope (β), 95% CI	0.066 (−1.091; 1.224)	0.193 (−0.517; 0.903)	0.754 (−0.571; 2.079)
Higher first-trimester trajectory of UtA PI			
Random intercept (β), 95% CI	−0.018 (−0.434; 0.398)	−0.166 (−0.442; 0.090)	−0.502 (−0.922;−0.082)*
Random slope (β), 95% CI	NA	NA	NA
Higher first-trimester trajectory of UtA RI			
Random intercept (β), 95% CI	0.035 (−0.408; 0.479)	−0.234 (−0.503; 0.036)	−0.435 (−0.839;−0.032)*
Random slope (β), 95% CI	NA	NA	NA
Pregnancies without placenta-related complications (n = 159)			
Higher first-trimester trajectory of MAP			
Random intercept (β), 95% CI	0.148 (−0.035; 0.330)	0.398 (0.049; 0.748)*	0.095 (−0.585; 0.771)
Random slope (β), 95% CI	−0.174 (−0.362; 0.014)	−0.342 (−0.701; 0.018)	0.072 (−0.655; 0.799)
Higher first-trimester trajectory of UtA PI			
Random intercept (β), 95% CI	−0.092 (−0.171;−0.012)*	−0.126 (−0.280; 0.028)	−0.147 (−0.433; 0.140)
Random slope (β), 95% CI	NA	NA	NA
Higher first-trimester trajectory of UtA RI			
Random intercept (β), 95% CI	−0.110 (−0.187;−0.033)**	−0.107 (−0.258; 0.044)	−0.017 (−0.296; 0.263)
Random slope (β), 95% CI	NA	NA	NA

Fully adjusted model for maternal age, parity, conception mode, body mass index, smoking, preconception initiation of folic acid supplement use and fetal gender. Random slope not available for first-trimester UtA PI and UtA RI.

* Significance at $P < 0.05$.

** Significance at $P < 0.01$.

Interpretation

We hypothesised that the extent of first-trimester maternal haemodynamic adaptation to pregnancy is associated with first-trimester placental development, and also with fetal development and birth outcome. This is substantiated by our results, showing that in placenta-related complicated pregnancies reduced first-trimester maternal haemodynamic adaptation to pregnancy is associated with less optimal first-trimester placental development and lower placental weight at birth. Available evidence of impaired maternal haemodynamic adaptation and a higher risk to develop placenta-related complications supports these findings.[40–43] Moreover, previous research confirms that impaired vascular development in pre-eclampsia or FGR in the presence of higher uterine artery Doppler indices is associated with lower serum placental growth factor and lower placental vascularisation indices.[14,17,44]

Blood pressure and uterine artery blood flow are traditionally considered to be markers of placental development because increased values with advancing gestation are associated with many placenta-related complications.[45] The direction of causality could be both ways; either less increase in uPVV as a result of reduced maternal haemodynamic adaptation, or reduced maternal haemodynamic adaptation as a response to impaired trophoblastic invasion, marked by less development of the uteroplacental vasculature. Accumulating evidence is pointing to the first direction, suggesting that changes in maternal uterine and spiral arteries, as reflected by UtA Doppler indices, are not a direct consequence from trophoblast invasion, but that pre-pregnancy maternal haemodynamics precede placental development.[9,46] In future studies, other periconceptional determinants of maternal haemodynamics can be studied, e.g. cardiac function and small-vessel endothelial function. Together they will likely contribute to improved preconception screening and treatment, thereby preventing placenta-related complicated pregnancies.[47]

Only in placenta-related complicated pregnancies was reduced haemodynamic adaptation associated with a smaller increase in PV trajectories. This suggests that placental tissue and vasculature development are impacted differently and that the impact of first-trimester haemodynamic (mal)adaptation seems more profound in placenta-related complicated pregnancies.[46] Previous studies also describe reduced PV in pregnancies complicated by pre-eclampsia or FGR.[48,49]

Earlier work from our group revealed an inverse association between first-trimester maternal vascular risk factors

and embryonic size in pregnancies conceived after assisted reproduction.[50] In the current study, reduced first-trimester maternal haemodynamic adaptation was not associated with embryonic or fetal development, possibly because we were challenged with a more restricted availability of embryonic/fetal measurements.

We recorded a significant association between reduced first-trimester maternal haemodynamic adaptation and higher birthweight centile in uncomplicated pregnancies. A first explanation is the uncomplicated nature of this group and that median blood pressure levels remained within normal ranges for pregnancy (Figure 1). Second, factors impacting fetal growth during the second and third trimesters may have had a stronger influence the association between first-trimester maternal haemodynamic adaptation and birthweight centile. Alternatively, the direction of this association could be considered a fetal compensatory phenomenon in response to a more unfavourable uteroplacental environment, which is substantiated by the developmental origins of health and disease paradigm.[10] A higher birthweight centile was not observed in placenta-related complicated pregnancies, which advocates a reduced capacity to compensate for an unfavourable periconceptional uteroplacental environment.

The association between reduced first-trimester maternal haemodynamic adaptation and lower placental weight in placenta-related complicated pregnancies corresponds with previously reported findings of lower placental weight and birthweight in pregnancies complicated by pre-eclampsia.[51] Furthermore, first-trimester and postpartum placental size parameters are correlated with each other.[52] We attribute the absence of significance for other birth outcomes to the limited number of placenta-related complications in this cohort and their onset beyond 32 weeks of gestation. For example, preterm birth comprised spontaneous and iatrogenic cases and the different pathophysiology of early-onset versus late-onset placenta-related complications may have diluted the effect estimates.

Conclusion

This study suggests that reduced first-trimester maternal haemodynamic adaptation to pregnancy, assessed by MAP and UtA blood flow, impairs early placental size and vascularisation, as measured by PV and uPVV, and birthweight centile. The impact was different for placenta-related complicated pregnancies. Moreover, median values for MAP and UtA PI and UtA RI were higher in placenta-related complicated pregnancies. Although these values were within normal ranges for the first trimester of pregnancy,[53] future investigation is necessary to study which clinical thresholds are sensitive to classify women with a vascular phenotype predisposed to placenta-related complications. This might improve the accurate identification of those women who can benefit from preventive measures, such as daily acetylsalicylic acid administration, to diminish the risk of developing placenta-related complications. Further, early identification of women at risk allows for implementation of a tailored scheme for antenatal surveillance already from the first trimester onwards. Also the lifestyle intervention www.smarterpregnancy.co.uk and blended lifestyle approach are promising evidence-based interventions.[54]

Assessment of first-trimester maternal haemodynamic adaptation and placental development as performed in this study will also enhance future knowledge on the pathophysiology of placenta-related complications. However, the added value of integrating first-trimester parameters of maternal haemodynamic adaptation and PV and uPVV measurements into prediction models for placenta-related complications has to be investigated in larger cohorts first.

Data availability statement

Data is available on request.

Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Figure S1. Flow chart of the Virtual Placenta Study population.

Table S1. Medians and interquartile ranges of first-trimester maternal haemodynamic adaptation parameters and placental parameters, stratified for pregnancies with and without placenta-related complications.

Table S2. Associations between reduced first-trimester maternal haemodynamic adaptation and trajectories of embryonic development, stratified for pregnancies with and without placenta-related complications.

Table S3. Associations between reduced first-trimester maternal haemodynamic adaptation and fetal development, stratified for pregnancies with and without placenta-related complications.■ ▪

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