Total uterine artery blood volume flow rate in nulliparous women (TVFR) is associated with birthweight and gestation at delivery

Alastair McKelvey[1,2], Katie Pateman[3], Imelda Balchin[4], Donald M Peebles[2], Charles H Rodeck[2] and Anna L David[2]

[1]The East Anglian Centre for Fetal Medicine, Norfolk and Norwich University College Hospitals Foundation Trust, Norwich, UK; [2]Fetal Medicine Unit, Elizabeth Garrett Anderson Wing, University College London Hospitals NHS Foundation Trust, London UK; [3]The Department of Gynaecological Ultrasound, Elizabeth Garrett Anderson Wing, University College London Hospitals NHS Foundation Trust, London, UK; [4]Department of Obstetrics & Gynaecology, Women and Children Health Complex, University Malaya Medical Centre, Kuala Lumpur, Malaysia

Corresponding author:

Mr Alastair McKelvey MRCOG MB BCh BAO, Consultant Obstetrician and Subspecialist in Maternal Fetal Medicine, The East Anglian Centre for Fetal Medicine, Norfolk and Norwich University College Hospitals Foundation Trust, Colney Lane, Norwich NR4 7UY, United Kingdom of Great Britain and Northern Ireland and Honorary Assistant Professor, St George's University, Grenada. (Formerly Subspecialist Fellow and Senior Registrar, Fetal Medicine Unit, Elizabeth Garrett Anderson Wing, University College London Hospitals NHS Foundation Trust, 235 Euston Road, London WC1E 6DH, United Kingdom

Email Alastair.McKelvey@nnuh.mhs.uk

Abstract

Objectives:

To investigate the relationship between total uterine artery blood volume flow rate (TVFR) and birthweight and gestation at delivery and to establish normal ranges of TVFR through pregnancy.

Methods

A prospective cohort study at University College London Hospital, in which 334 nulliparous women booking for antenatal care had measurement of TVFR by transabdominal ultrasound at 12, 20 and 24 weeks.

Results:

551 scans were performed. There was a significant and positive correlation between total uterine blood volume flow at 11-13 weeks (TVFR1) and 22-26 weeks (TVFR2) and birthweight. For every 100 unit increase in TVFR1 and TVFR2, there was a 45g and 27g increase in birthweight respectively. There was also a positive association between TVFR1 and gestation at delivery, with a 1.4 day increase in gestation for every 100 unit increase of TVFR1.

Conclusion: Ultrasound measurement of TVFR in the first trimester is significantly associated with both birth weight and gestation at delivery.

Introduction

During pregnancy total uterine artery volume blood flow (TVFR) increases substantially from early in the first trimester[1], due to increased maternal cardiac output and trophoblast-driven modification of the uterine spiral arteries into low pressure, passively dilated channels conducting blood to the inter-villous space. Normal fetal growth and development is dependent on this process, and its failure is implicated in fetal growth restriction and preeclampsia[2]. Spontaneous preterm birth may also be associated with uteroplacental insufficiency[3]. Nulliparous women lack an obstetric history on which to base their risk assessment in pregnancy. Therefore it is hard to focus care on those primiparous women who will develop serious obstetric complications; rather resources are spread over all women. While there are risk-assessment models using other historical factors and serum markers, these have not thus far been sufficiently predictive.[4] Effective early screening in pregnancy is an important goal of antenatal care. We sought to assess whether TVFR was associated with birth outcomes in primiparous women.

Our objective was to investigate the relationship between total uterine artery volume blood flow rate (TVFR) at approximately 12, 20 and 24 weeks, measured prospectively in unscreened nulliparous women, and pregnancy outcomes in terms of birth weight and gestation at delivery. Ultrasound Doppler measurement of TVFR has been validated by comparisons with direct measurement by invasive vascular probes in a relevant animal model[5][6].

Methods:

Study participants:

Between August 2008 and September 2009 all nulliparous women booking for antenatal care at UCLH were invited to participate in the study before their booking visit at the hospital. Multiparity, miscarriage, fetal anomaly, multiple pregnancy and maternal age <18 years were the exclusion criteria. We did not exclude women on the basis of medical history or raised BMI, but did record ethnicity and smoking status. Pregnant women are offered a screening ultrasound examination at approximately 12 (booking scan, including the option of screening for Down syndrome by the Combined Test) and 20 weeks (fetal anomaly scan) in accordance with the National Health Service (NHS) Fetal Anomaly Screening Programme in England and Wales[7]. In practice these are performed at 11-13 weeks and 19-21 weeks in our institution. Participation in the study involved a transabdominal ultrasound examination of the uterine arteries at either or both of the two routine scans and the option of an additional examination at approximately 24 weeks gestation (23-25 weeks). Demographic details were recorded of study participants; including maternal age, ethnicity (as defined by the hospital booking system of 'White', 'Afro-Caribbean',' South Asian', 'Other') and maternal smoking. The study was approved by the Joint UCL/ University College London Hospital Committees on the Ethics of Human Research (Ref 08/H0715/59). Informed written consent was obtained from all participants.

Sample Size Calculation

Statistical advice was obtained from the University College London Biostatistics Unit before the study to determine appropriate study design, recruitment and powering.

To predict birth weight from blood flow at 12 weeks, blood flow at 20 weeks, and blood flow at 24 weeks, we calculated the sample size for a longitudinal study design. Assuming birth weight to be normally distributed, forward selection linear regression would be used to analyse the data. Eleven coefficients were to be estimated in the regression model and using Harrell's rule, 10 subjects were required for each coefficient estimated giving 110 subjects with complete data, and allowing for 10% drop out, 121 patients would be required for this analysis.

A cohort study design was used to determine the normal ranges (reference intervals) through pregnancy of uterine artery blood volume flow rate at 12, 20 and 24 weeks gestation. Based on the number of women attending hospital and the single observer, we estimated that 185 scans would become available for each of three cohorts of scans at 12, 20 or 24 weeks within the study period of a year. Finally a sample size calculation[8] for reference interval studies was performed, which confirmed a sample size of 176 patients for a normal distribution.

Measurement of uterine artery blood volume flow

During the scan, women lay supine with the head of the couch at an angle of 30^0. Women rested during the routine clinical part of the ultrasound examination at least 20 minutes prior to sonography of the uterine arteries. The uterine arteries were identified using colour Doppler ultrasound by moving a 5 MHz curvilinear transabdominal probe laterally from the midline in the suprapubic position to the point

where the uterine artery crosses the external iliac artery. The vessel was insonated keeping the angle of insonation as close to zero as possible and always below 30^0. Power Doppler at a specific constant preset mode (Digital **Appendix 1**) was then used at lowest output power setting to delineate the uterine artery borders accurately. Over 1 minute duplicate measurements of the diameters were taken and averaged. The images of both uterine arteries and the vessel diameters were captured and recorded. In the same position the pulsed wave Doppler mode was turned on and measurements were taken, keeping the angle of insonation as close to zero as possible and always below 30^0, and with calliper adjustment to include the full vessel diameter previously described[9]. The Pulsatility Index (PI), Resistivity Index (RI), and Time-Averaged mean velocity (TAMEAN) were automatically calculated by software in the machine and recorded at each examination. The presence of pre-diastolic notching in one or both arteries was subjectively recorded. At least four wave cycles were used for each calculation. All images were stored both electronically and as hard copies and all measurements were performed by a single operator (AM) on a specific ultrasound device GE 780 Expert (GE Healthcare UK Ltd, Amersham Place, Little Chalfont, Buckinghamshire HP7 9NA England). TVFR was calculated as the product of the TAMEAN and the cross sectional area of the vessel, assessed by power Doppler, a technique that has been validated against the gold standard invasive method using flow probes in sheep[5] The right uterine artery volume flow rate was calculated by the formula:

Right TVFR (mL/min) =

TAMEAN (cm/sec) x Π (right Uterine Artery Diameter/2)^2 X 60.

The left TVFR was similarly calculated. Both measurements were combined to give the TVFR. The intraobserver co-efficient of variation was 5 - 8% for the vessel diameter and 3-5% for the volumetric measurements, which is similar to that quoted in similar published work[10],[11]. Pregnancy outcomes of birth weight, gender, gestation at delivery, placental abruption and stillbirth were recorded. When women delivered outside our unit, we contacted them by telephone and email. Placental abruption was diagnosed as premature separation of a normally implanted placenta, presenting with vaginal bleeding and abdominal pain. Stillbirth was defined as spontaneous fetal demise before labour after 24 weeks completed gestation. Pregnancies affected by fetal growth restriction were not excluded.

Statistical Analysis

Analyses were performed using Stata 12.1 software (StataCorp LP, College Station, Texas, USA). When examined, the distribution of the TVFR was found to be positively skewed. Because TVFR was collected at specific weeks rather than throughout pregnancy, to produce normal ranges for TVFR values throughout gestation, three regression methods were investigated to fit the relationships. Firstly linear regression was used, considering TVFR on its original scale of measurement. A second approach used linear regression, but treated TVFR on the log scale due to the positively skewed distribution. The best relationship between gestation and TVFR was examined, and where necessary, a squared term was added to allow a curved relationship between the variables, rather than a straight line. The fitted regression lines were used to produce different normal ranges by using properties of the normal distribution to calculate the appropriate multiple of the standard error of the prediction.

A third approach used quantile regression models specifically to model each normal range of interest. A separate model was used to calculate each of the normal ranges. A squared term for gestation was used to allow a curved relationship between gestation and TVFR. The fitted lines were used to calculate different normal ranges at varying gestation. Using all approaches, calculations were made for the 1st, 5th, 10th, 25th, 50th, 75th, 90th, 95th and 99th centiles.

Continuous outcomes such as gestation at delivery and birthweight were examined for normal distribution. To study the relationship between TVFR and these continuous outcomes, linear regression was used. Separate analyses were performed to examine the effects of each of the three sets of TVFR values upon gestation or birthweight. The relationship between TVFR and gestation or birthweight was examined without factoring in any other variables, after which the analysis was repeated adjusting for patient age. Placental abruption and stillbirth were grouped due to their small number and the association with TVFR was examined using logistic regression. The analysis was performed with and without an adjustment for age. The relationships between maternal factors (age, ethnicity, and smoking) and TVFR between uterine notching and TVFR were also interrogated.

Results:

A total of 551 ultrasound scans were performed on 334 women. 185 women had only a single scan and 149 women participated in more than one examination (Table 1).

TVFR was determined in 185 women at approximately 12 weeks (range 11+0 – 13+0 weeks, median 12+2, interquartile range (IQR) 12+0 – 12+5, TVFR1), 194 women at approximately 20 weeks (range 18+4 - 21+5 weeks, median 20+2, IQR 20+0 - 20+5, TVFR2) and in 172 women at approximately 24 weeks (range 22+5 –

26+0 weeks, median 24+1, IQR 24+0 – 24+4, TVFR3). Thus TVFR values were available for 334 participants giving 551 values. We were unable to obtain a TVFR value in 8 women who volunteered to participate. Non-visualization of the uterine artery in these women was because of severe maternal obesity, anatomical variation or discomfort. These 8 women (2.3% of all those who volunteered) were not included in the study.

Associations Between TVFR and Pregnancy Outcomes.

TVFR1 and TVFR3 were both significantly associated with birthweight (Table 2) but no such relationship was observed for TVFR2. Where a significant relationship was observed, this was found to be linear in nature, suggesting that birthweight continued to increase with increasing TVFR. For TVFR1 a 100-unit increase was associated with a 45g increase in birthweight, whilst a 100-unit increase in TVFR3 was associated with a 27g increase in birthweight. The age-adjusted relationships between TVFR and birthweight were similar to those observed with no adjustments.

<u>Gestation at delivery</u>

The association between TVFR and gestation at delivery is shown in Table 3. The size of the change in gestation at delivery (in weeks) for a 100unit increase in TVFR is shown with P values indicating the significance. The regression coefficients and their corresponding confidence intervals are also given.

TVFR1 was significantly associated with gestation at delivery. The association was significant both when adjusted and unadjusted for age. Higher TVFR1 values were associated with later deliveries. A 100-unit increase in TVFR1 was associated with an increase in gestation of 0.20 weeks (1.4 days).

There was no association between TVFR2 and gestation at delivery. TVFR3 showed only very slight evidence of an association with gestation at delivery.

There were three potentially outlying points for patients with gestations before 30 weeks. As a sensitivity analysis, the previous analyses were repeated omitting these 3 patients from the analysis. The results again showed that TVFR1 was significantly associated with gestation at delivery. Similar results were observed both adjusted and unadjusted for age. Higher TVFR values were associated with later deliveries. A 100-unit increase in TVFR1 was still associated with an increase in gestation of 0.14 weeks (0.98 day, Table 4). There was no significant difference in TVFR values between male and female sex infants.

Complications

The final analyses examined the associations between TVFR and placental abruption and stillbirth. The results suggested that none of the three sets of TVFR values were associated with these complications. There was one stillbirth in the cohort (diagnosed at 24 weeks) where the TVFR1 had been 74.6mL/min (around the 1st centile).

Normal ranges for TVFR

Analyses were performed to produce normal ranges for different gestational ages. Three different approaches were used to produce the normal ranges - linear regression with TVFR on original scale; linear regression with TVFR analyzed on the log scale and quantile regression, modelling each centile separately. The final approach generated a better fit to the data and is shown in Graph 1, with calculated normal

ranges plotted together with the original data. A version without the raw data can be found in digital Appendix 2). Calculated centiles for TVFR (mL/min) at gestations from 11 to 26 weeks can be found in digital Appendix 3.

TVFR and Maternal Age and Uterine Artery Notching

The relationship between TVFR and the absence of uterine artery notching, unilateral or bilateral nothing is summarised in Table 5. The figures reported are the median and inter-quartile range TVFR in each group at each gestation.

The results found that TVFR2 values fell as the amount of notching increased from unilateral to bilateral, which just reached statistical significance. There was a tendency of decreasing TVFR1 values with increased amount of notching, but there was no difference in TVFR3 between notching groups. There was no association between maternal age and TVFR at any of the three gestations.

Missing Outcome Data

We were unable to make contact with 32 women (9.6% of participants) who delivered outside our facility to obtain their pregnancy outcomes, despite phone, email and family doctor contact. Their characteristics (Table 6) are similar to women for whom we did have ascertainment. There were no significant differences in TVFR values between women for whom we did have outcomes and women for whom we did not.

Data Summary

Key variables for TVFR values with outcomes are summarized in table 7. Separate summaries are produced for each of the three time periods. In each period the analysis was restricted only to those women whose TVFR value was measured during that period. Continuous outcomes found to be normally distributed were summarised with the mean, standard deviation and data range, whilst continuous outcomes not found to be normally distributed were summarised with the median, inter-quartile range and data range. It is worth noting that the number values are slightly smaller than the original number of scans, because in this table TVFR values from subjects with missing outcome data are not included.

<u>Discussion</u>

Effective screening of nulliparous women for pregnancy complications could target resources to those most likely to benefit. We found that TVFR1 in nulliparous women is significantly and independently associated with birthweight. Birthweight increased by 45g for every 100 unit increase in TVFR1 and by 27g for every 100 unit increase in TVFR3. TVFR1 was also associated with gestation at delivery, with a 1.4 day increase in gestation at birth for every 100 unit increase in TVFR1. We were able to establish normal ranges for TVFR through pregnancy.

Direct measurement[12], [13] of TVFR is not ethically acceptable and ultrasound is now the standard method. The technique we used has been validated in ovine models using surgically-placed probes[5].

Abnormal patterns of vascular resistance are believed to be caused by failure of the normal trophoblastic invasive process, leading to 'backpressure' changes in the proximal arterial supply[14]. The association between certain Doppler flow patterns in

later pregnancy and adverse outcomes is an established tool for the assessment of high-risk pregnancies[15][16].

Abnormal patterns of flow by Doppler ultrasound correlate with abnormal placentation, underlying the pathology of intrauterine growth restriction (IUGR) and preeclampsia[17]. When measured at mid-gestation (24 weeks of pregnancy), a raised Pulsatility Index (PI) with bilateral pre-diastolic notched waveforms can predict the risk of IUGR and preeclampsia (PET)[18]. Raised uterine artery PI in the first trimester is also predictive of later IUGR and PET but has a lower sensitivity and specificity than in the second trimester[19]. In a study comparing TVFR and Fetal weight (in women with normal and abnormal uterine artery PI), at mid-gestation[20] there was a significantly lower uterine artery blood flow volume per unit weight observed between IUGR (142 ml/min/kg) and appropriately-grown fetuses delivered at term (217 ml/min/kg) when compared to control women with normal mid-gestation PI (538 ml/min/kg). The differences in blood flow volume were present at mid-gestation, when estimated weight was still normal.

Work in this field has often used transvaginal measurement in the first trimester, frequently selected high risk populations, or has not distinguished parity. A 1997 study[21] of 652 women between 12 and 16 weeks gestation suggested a multivariate tool of 7 Doppler-derived values could predict the relative risk of developing preeclampsia or delivering a low-birth weight baby. Volume flow and mean velocity were found to be significant predictors. Actual values and ranges were not quoted nor was parity distinguished. As ultrasound technology advances, transabdominal uterine artery measurement in the first trimester has improved and some women may find transvaginal examination less acceptable[22].

Of the studies which have examined TVFR by Doppler ultrasound, ours is relatively large[23]. A 2010 paper[24] measured volume flow in 53 women (of any parity) from 22 weeks. Observations were made under strict conditions – including 8 hours fasting - which would be difficult in clinical practice.

A 2001 study[25] examined 57 women serially after 20 weeks, excluding abnormal uterine waveforms and without distinguishing between parity. TVFR increased from a mean of 513mL/min (SD, 127 mL/min) at 20 weeks to 970 mL/min (SD, 193 mL/min) at 38 weeks. The 20 week TVFR is rather lower than we observed (mean of 513mL/min vs our median of 690.9 mL/min).

A 1995 study of TVFR in 44 women by transvaginal Doppler up to 16 weeks[26] showed an accelerating rate of volume flow with advancing gestation. Their TVFR1 was similar to ours (a mean TVFR1 of approximately 280mL/min vs our median of 282mL/min).

One of the strengths of our study was that it observed nulliparous women. Reliable screening of these women is challenging since they have no obstetric history on which to assess risk. The uterine arteries may be permanently remodelled after parturition[27]. This study establishes normal values of TVFR through pregnancy in this population.

We recognize that our study's limitations. We were unable to achieve total outcome ascertainment because some of the women who delivered outside our unit could not be contacted, probably due to the mobility of inner city populations. Uterine Doppler assessment requires experience and training. Our measurements were taken by one operator, excluding inter-observer variation. We were surprised that we were unable to demonstrate a correlation between TVFR2 and birth weight, having found significant associations for TVFR1 and TVFR3. However, for screening purposes, a

risk assessment early in pregnancy would potentially prove more useful. We did not discriminate in recruitment on the basis of maternal health (including diabetes, hypertension and obesity), nor did we record these data.

Screening for pregnancy complications is a vital and developing part of pregnancy care. This study demonstrates that TVFR in nulliparous women is correlated with obstetric outcomes but the sensitivity and specificity is probably insufficient for it to be used in isolation to predict obstetric outcome. There is significant effort currently to develop effective therapies for uteroplacental insufficiency. These include trial of vasodilator pharmacological agents[28] or modified viral vectors[29]. We would suggest that measurement of TVFR would be an important component of assessing the efficacy of therapies under investigation.

References

[1] Al-Ghazali W, Chapman MG, Allan LD. Doppler assessment of the cardiac and uteroplacental circulations in normal and complicated pregnancies. Br J Obstet Gynaecol. 1988 Jun;95(6):575-80.

[2] Olofsson P, Laurini RN, Marsál K . A high uterine artery pulsatility index reflects a defective development of placental bed spiral arteries in pregnancies complicated by hypertension and fetal growth retardation.Eur J Obstet Gynecol Reprod Biol. 1993 May;49(3):161-8.

[3] Salafia CM, Vogel CA, Bantham KF, Vintzileos AM, Pezzullo J, Silberman L. Preterm delivery: correlations of fetal growth and placental pathology. Am J Perinatol. 1992 May;9(3):190-3.

[4] Van Ravenswaaij R, Tesselaar-Van der Goot M, de Wolf S, Van Leeuwen-Spruijt M, Visser GH, Schielen PC. First-trimester serum PAPP-A and fβ-hCG concentrations and other maternal characteristics to establish logistic regression-based predictive rules for adverse pregnancy outcome. Prenat Diagn. 2011 Jan;31(1):50-7.

[5] Acharya G, Sitras V, Erkinaro T, Mäkikallio K, Kavasmaa T, Päkkilä M, Huhta JC, Räsänen J. Experimental validation of uterine artery volume blood flow measurement by Doppler ultrasonography in pregnant sheep. Ultrasound Obstet Gynecol. 2007 Apr;29(4):401-6.

[6] Abi-Nader KN1, Mehta V, Wigley V, Filippi E, Tezcan B, Boyd M, Peebles DM, David AL. Doppler ultrasonography for the noninvasive measurement of uterine artery volume blood flow through gestation in the pregnant sheep. Reprod Sci. 2010 Jan;17(1):13-9.

[7] http://fetalanomaly.screening.nhs.uk/

[8] Jennen-Steinmetz C, Wellek S. A new approach to sample size calculation for reference interval studies. Stat Med. 2005 Oct 30;24(20):3199-212.

[9] Konje JC, Kaufmann P, Bell SC, Taylor DJ. A longitudinal study of quantitative uterine blood flow with the use of color power angiography in appropriate for gestational age pregnancies. Am J Obstet Gynecol. 2001 Sep;185(3):608-13.

[10] Konje JC, Howarth ES, Kaufmann P, Taylor DJ. Longitudinal quantification of uterine artery blood volume flow changes during gestation in pregnancies complicated by intrauterine growth restriction. BJOG. 2003 Mar;110(3):301-5.

[11] Ferreira AE, Mauad Filho F, Abreu PS, Mauad FM, Martins WP. The reproducibility of first and second trimester uterine artery pulsatility index by transvaginal and transabdominal ultrasound. Ultrasound Obstet Gynecol. 2014 Dec 11. doi: 10.1002/uog.14762. [Epub ahead of print] PubMed PMID: 25504919.

[12] Metcalfe J, Romney SL, Ramsey LH, Reid De, Burwell CS. Estimation of uterine blood flow in normal human pregnancy at term.
J Clin Invest. 1955 Nov;34(11):1632-8.

[13] Barcroft J, Herkel W, Hill S. The rate of blood flow and gaseous metabolism of the uterus during pregnancy.
J Physiol. 1933 Jan 16;77(2):194-206.

[14] Prefumo F, Sebire NJ, Thilaganathan B. Decreased endovascular trophoblast invasion in first trimester pregnancies with high-resistance uterine artery Doppler indices. *Hum Reprod* 2004; 19: 206–209.

[15] Adamson SL, Morrow RJ, Bascom PA, Mo LY, Ritchie JW. Effect of placental resistance, arterial diameter, and blood pressure on the uterine arterial velocity waveform: a computer modeling approach.

Ultrasound Med Biol. 1989;15(5):437-42.

[16] Stampalija T, Gyte GM, Alfirevic Z. Utero-placental Doppler ultrasound for improving pregnancy outcome. Cochrane Database Syst Rev. 2010 Sep 8;(9):CD008363.

[17] Lin S, Shimizu I, Suehara N, Nakayama M, Aono T. Uterine artery Doppler velocimetry in relation to trophoblast migration into the myometrium of the placental bed. Obstet Gynecol. 1995 May;85(5 Pt 1):760-5.

[18] Zimmermann P, Eiriö V, Koskinen J, Kujansuu E, Ranta T. Doppler assessment of the uterine and uteroplacental circulation in the second trimester in pregnancies at high risk for pre-eclampsia and/or intrauterine growth retardation: comparison and correlation between different Doppler parameters. Ultrasound Obstet Gynecol. 1997 May;9(5):330-8

[19] Poon LC, Nicolaides KH. Early prediction of preeclampsia. Obstet Gynecol Int. 2014;2014:297397. doi: 10.1155/2014/297397. Epub 2014 Jul 17.

[20] Ferrazzi E, Rigano S, Padoan A, Boito S, Pennati G, Galan HL.Uterine artery blood flow volume in pregnant women with an abnormal pulsatility index of the uterine arteries delivering normal or intrauterine growth restricted newborns.
Placenta. 2011 Jul;32(7):487-92

[21] Harrington K, Carpenter RG, Goldfrad C, Campbell S. Transvaginal Doppler ultrasound of the uteroplacental circulation in the early prediction of pre-eclampsia and intrauterine growth retardation.
Br J Obstet Gynaecol. 1997 Jun;104(6):674-81.

[22] Clement S, Candy B, Heath V, To M, Nicolaides KH. Transvaginal ultrasound in pregnancy: its acceptability to women and maternal psychological morbidity. Ultrasound Obstet Gynecol. 2003 Nov;22(5):508-14.

[23] Urban G, Vergani P, Ghidini A, Tortoli P, Ricci S, Patrizio P, Paidas MJ. State of the art: non-invasive ultrasound assessment of the uteroplacental circulation. Semin Perinatol. 2007 Aug;31(4):232-9.

[24] Flo K, Wilsgaard T, Vårtun A, Acharya G. A longitudinal study of the relationship between maternal cardiac output measured by impedance cardiography and uterine artery blood flow in the second half of pregnancy. BJOG. 2010 Jun;117(7):837-44.

[25] Konje JC, Kaufmann P, Bell SC, Taylor DJ. A longitudinal study of quantitative uterine blood flow with the use of color power angiography in appropriate for gestational age pregnancies.
Am J Obstet Gynecol. 2001 Sep;185(3):608-13.

[26] Dickey RP, Hower JF. Ultrasonographic features of uterine blood flow during the first 16 weeks of pregnancy.
Hum Reprod. 1995 Sep;10(9):2448-52.

[27] Wassel K, Kuhn G, Gassmann M, Vogel J. Permanently increased conductance of the murine uterine arcade after the first pregnancy. Eur J Morphol. 2005 Oct-Dec;42(4-5):225-32

[28] Ganzevoort W, Alfirevic Z, Wessel G, Von Dadelszen P, Kenny L, Papageorghiou A, Van Wassenaer-Leemhuis A, Gluud C, Willem B, Baker PN. STRIDER: Sildenafil therapy in dismal prognosis early-onset intrauterine growth restriction – a protocol for a systematic review with individual participant data and aggregate data meta-analysis and trial sequential analysis. Systematic Reviews 2014 3:23

[29] Mehta V, Abi-Nader KN, Shangaris P, Shaw SW, Filippi E, Benjamin E, Boyd M, Peebles DM, Martin J, Zachary I, David AL. Local over-expression of VEGF-DΔNΔC in the uterine arteries of pregnant sheep results in long-term changes in uterine artery contractility and angiogenesis. PLoS One. 2014 Jun 30;9(6):e100021.

Table 1. Participation in the study

Number of scans	12 week scan	20 week scan	24 week scan	Total number of scans
12 week only	102	-	-	102
20 week only	-	52	-	52
24 week only	-	-	31	31
All three scans	68	68	68	204
12 and 20 week	8	8	-	16
20 and 24 week	-	66	66	132
12 and 24 week	7	-	7	14
Total	185	194	172	551

Table 2. TVFR and Birthweight. Regression Coefficients and confidence intervals showing size of change in Birthweight (g) for 100 unit increase in TVFR (mL/min).

Gestation (weeks and days)	Unadjusted Coefficient (95% CI)	P-value	Age adjusted Coefficient (95% CI)	P-value	Age + Gestation adj. Coefficient (95% CI)	P-value
11+0 – 13+0	45 (7, 84)	**0.02**	47 (9, 85)	**0.02**	47 (8, 87)	**0.02**
18+4 – 21+5	-1 (-22, 19)	0.89	-1 (-22, 19)	0.89	-2 (-23, 18)	0.83
22+5 – 26+0	27 (6, 48)	**0.01**	27 (6, 48)	**0.01**	28 (7, 50)	**0.01**

Table 3. TVFR and Gestation at Delivery.
Regression Coefficients and confidence intervals showing size of change in gestation at delivery (weeks) for 100 unit increase in TVFR (mL/min).

Gestation (weeks and days)	Unadjusted Coefficient (95% CI)	P-value	Age adjusted Coefficient (95% CI)	P-value	Age + Gestation adj. Coefficient (95% CI)	P-value
11+0 – 13+0	0.20 (0.02, 0.37)	**0.03**	0.19 (0.02, 0.37)	**0.03**	0.21 (0.03, 0.39)	**0.02**
18+4 – 21+5	0.01 (-0.07, 0.09)	0.82	0.01 (-0.07, 0.09)	0.81	0.01 (-0.07, 0.09)	0.84
22+5 – 26+0	0.06 (-0.02, 0.14)	0.16	0.06 (-0.02, 0.14)	0.13	0.06 (-0.02, 0.14)	0.12

Table 4. TVFR and Gestation at delivery with 3 low gestation outliers removed. Regression Coefficients and confidence intervals showing size of change in gestation at delivery (weeks) for 100 unit increase in TVFR (mL/min).

Gestation (weeks)	Unadjusted Coefficient (95% CI)	P-value	Age adjusted Coefficient (95% CI)	P-value	Age + Gestation adj. Coefficient (95% CI)	P-value
11+0 – 13+0	0.14 (0.02, 0.27)	**0.03**	0.14 (0.02, 0.27)	**0.03**	0.16 (0.03, 0.29)	**0.02**
18+4 – 21+5	0.01 (-0.05, 0.07)	0.75	0.01 (-0.05, 0.07)	0.74	0.01 (-0.05, 0.08)	0.71
22+5 – 26+0	0.06 (-0.02, 0.14)	0.16	0.06 (-0.02, 0.14)	0.13	0.06 (-0.02, 0.14)	0.12

(*) Coefficients reported for a 100-unit increase in TVFR

Table 5. TVFR and Uterine Artery Notching. Median and interquartile ranges of TVFR (mL/min)

Gestation (wks)	No notch		Unilateral		Bilateral		P-value
	N	Median (IQR)	N	Median (IQR)	N	Median (IQR)	
11+0 – 13+0	40	308 (211, 670)	42	306 (194, 399)	71	256 (170, 371)	0.06
18+4 – 21+5	122	742 (574, 1075)	43	643 (493, 856)	26	637 (476, 803)	**0.05**
22+5 – 26+0	117	877 (701, 1192)	32	989 (724, 1255)	22	907 (756, 1225)	0.77

Table 6: The characteristics of women where data were available compared to those of women for whom data were missing.

	Outcomes available (n = 302)	Outcomes unavailable (n = 32)
Age	Median 31 (range 16 to 44)	Median 30 (range 20 to 35)
Smoker	22 (7.2%)	1 (3.1%)
Ethnicity	White (69.9%, n = 211), Afro-Caribbean (10.6%, n = 32) South Asian (6.3%, n = 19) Other (13.2%, n = 40)	White (68.8%, n = 22), Afro-Caribbean (9.4%, n = 3) South Asian (6.3%, n = 2) Other (15.6%, n = 5)

Table 7. A summary of some of the key variables is given in the subsequently table. Separate summaries are produced for each of the three time periods, restricted only to those women whose TVFR value was measured during that period. Continuous outcomes found to be normally distributed are summarised with the mean, standard deviation and data range. Continuous outcomes not normally distributed are summarised with the median, inter-quartile range and data range. (TVFR values without outcomes excluded)

	Gestation 11+0 – 13+0	Gestation 18+4 – 21+5	Gestation 22+5 – 26+0
Number values	153	193	171
TVFR [**]	282 (182, 407) [43, 1457]	699 (546, 1022) [70, 2670]	894 (725, 1208) [272, 2364]
Gestation at birth (weeks) [*]	39.8 (2.6) [24.1, 49.1]	39.7 (2.1) [27.0, 49.1]	39.8 (1.8) [34.0, 49.1]
Birthweight (g) [*]	3339 (563) [448, 4780]	3356 (548) [944, 4780]	3393 (490) [1950, 4780]

(*) Mean (standard deviation) [data range] reported
(**) Median (inter-quartile range) [data range] reported