Maternal Hemodynamics in Normal Pregnancies: Reference ranges and the Role of Maternal Characteristics

Dimuthu Vinayagam *, Baskaran Thilaganathan *, Oliver Stirrup †,

Elena Mantovani *, Asma Khalil *

Fetal Medicine Unit, St. George's University Hospitals NHS Foundation Trust, London and Molecular & Clinical Sciences Research Institute, St George's University of London, UK*;

† MRC Clinical Trials Unit at UCL, University College London, London, UK

Corresponding author:

Dr Asma Khalil

Fetal Medicine Unit

St George's University of London

London SW17 0RE

Telephone: (Work) +442032998256

Mobile: +447917400164

Fax: +442077339534

E-mail: akhalil@sgul.ac.uk; asmakhalil79@googlemail.com

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1002/uog.17504

Keywords: Non-invasive cardiac output monitoring, maternal hemodynamics, USCOM-1A®, pregnancy, reference ranges

ABSTRACT

Objectives: The main aim of this study was to construct reference ranges of the maternal central hemodynamic parameters during pregnancy. The second aim was to determine the maternal and pregnancy characteristics, which influence these hemodynamic parameters.

Methods: This was a prospective cohort study of low-risk pregnant women attending for routine antenatal care at St George's Hospital, London. The exclusion criteria included any medical disorder present at the time of study recruitment, or development of hypertension or intrauterine fetal growth restriction following study recruitment. Stroke volume (SV), cardiac output (CO) and systemic vascular resistance (SVR) were obtained using non-invasive cardiac output monitoring (USCOM-1A®). USCOM-1A® utilises a non-imaging probe in the suprasternal notch to obtain velocity-time integrals of transaortic blood flow at the left ventricular outflow tract. Once the distribution of the data had been determined with respect to the gestational age (GA), maternal characteristics were added to the model to test whether they provided a significant improvement in the prediction of the median value.

Results: The analysis included 627 singleton pregnancies. The estimated median CO was constant for a maternal age above 32 years, but was around 0.5 L/min higher for women aged 25 or younger ($p<0.001$). Maternal weight ($p<0.001$) and height ($p<0.001$) affected CO and there was a significant interaction ($p=0.002$). In women with a height less than 1.60m, there was no association between median CO and weight. In those with a height exceeding 1.60m, an increase in weight was associated with an increase in CO. SV was primarily associated with height ($p<0.001$), although some positive association with weight ($p<0.001$) can also be observed within the normal body mass index range. Greater height ($p<0.001$) was associated with lower median values of SVR with an estimated difference of around

120 dynes·sec·cm^5 between 1.60m and 1.80m. Advancing maternal age was associated with higher median SVR with an estimated difference of around 50 dynes·sec·cm^5 between 25 and 35 years. Smokers had a lower SVR of 73.5 (95% CI, 8.6 – 138.4) dynes·sec·cm^5.

Conclusion: Maternal hemodynamics are significantly influenced by maternal age, height and weight. We provide USCOM-1A®-specific reference ranges and calculator for SV, CO and SVR in uncomplicated pregnancies that correct for maternal age, height and weight. This will enable clinical application and comparison in both uncomplicated and pathological pregnancies.

INTRODUCTION

Non-invasive hemodynamic monitors have been used in critically ill and high-risk surgical patients. However, their use in an obstetric population is scarce (1-3). Given their non-invasive nature and lack of ionising radiation, they have an obvious advantage over their invasive counterparts. The invasive nature of thermodilution techniques utilising a pulmonary artery catheter, as well as the associated risks of vascular injury, infection and cardiac arrhythmias (4), render invasive monitoring in pregnancy an almost obsolete practice, reserved only for critical cases. There is a need for non-invasive hemodynamic monitoring in pregnant women, both for research and clinical purposes.

A number of non-invasive cardiac output (CO) devices are commercially available. The device used in this study was USCOM-1A® (ultrasound cardiac output monitor, USCOM Ltd, NSW, Australia). Several validation studies of USCOM-1A® have been published in the non-obstetric (5-7) and obstetric (8) populations. Our group conducted a cross comparison study and reported good agreement (mean percentage difference <30%) between USCOM-1A® and two-dimensional transthoracic echocardiography in advanced pregnancy (9). In order to enable clinical application and further research using this methodology, it is imperative that we have device-specific reference ranges for an obstetric population. Furthermore, there is a need to investigate whether maternal central hemodynamic variables, such

as the stroke volume (SV), cardiac output (CO) and systemic vascular resistance (SVR), are influenced by the maternal characteristics such as age, height and weight.

The main aim of this study was to construct reference ranges of the maternal central hemodynamic parameters during pregnancy. The second aim was to determine the maternal and pregnancy characteristics, which influence these hemodynamic parameters.

METHODS

This was a prospective cohort study in low-risk pregnant women attending a tertiary referral hospital between September 2012 and May 2016. The inclusion criteria were uncomplicated singleton pregnancies attending antenatal care at St George's Hospital, London. The exclusion criteria included any medical disorder present at the time of study recruitment, or development of hypertension or intrauterine fetal growth restriction following study recruitment. Pregnancies complicated by major fetal anomalies, aneuploidy, intrauterine fetal demise or those undergoing termination of the pregnancy were excluded.

Written consent was obtained from all study participants and local research ethics committee approval (12/LO/0810) was obtained prior to data collection. All women were examined by their midwives or obstetricians and both maternal and fetal wellbeing were confirmed prior to hemodynamic assessment. The gestational age (GA) was calculated from the crown–rump length measurement at 11–13 weeks or the head circumference if the first ultrasound scan was performed after 14 weeks' gestation.

Maternal history and characteristics

Women who agreed to participate were invited to complete a questionnaire stating their age, ethnic origin (Caucasian, Afrocaribbean, South Asian, East Asian,

Mixed/Other), method of conception (spontaneous, assisted), smoking during pregnancy (yes/no), history of chronic hypertension (yes/no), medication history and a medical / obstetric history. The history and questionnaire were then reviewed by the study investigators to verify eligibility, and maternal height and weight were obtained (and examination body mass index (BMI) subsequently calculated). Maternal weight and BMI at pregnancy booking were also recorded.

Haemodynamic Assessment

USCOM-1A® measurements were performed under standardised conditions for the entire cohort. The study subjects had one single hemodynamic assessment performed during study recruitment. Measurements were obtained with the patient in a semi-recumbent position. USCOM-1A® employs continuous wave Doppler, with a non-imaging probe in the suprasternal notch to obtain velocity time integrals (VTI) of transaortic blood flow at the left ventricular outflow tract. Using an anthropometric algorithm, which correlates the outflow tract diameter with the patient's given height (10), USCOM-1A® uses the VTIs to compute the hemodynamic parameters. The three variables of interest in this study are SV, CO and SVR.

Statistical Analysis

Models were fitted using the *gamlss* package (11) for R (R Foundation, Vienna, Austria). Improvements in model fit were evaluated using the generalised likelihood ratio test, with statistical significance at $P<0.05$. For each hemodynamic variable, a normal distribution with mean conditional on GA was considered first. The relationship of the mean with GA was flexibly modelled using a natural cubic spline (NCS) basis with boundary knots at the 10^{th} and 90^{th} centiles (87.6 and 266 days, respectively), and internal knots at the 30^{th}, 50^{th} and 70^{th} centiles (152, 210 and 252 days, respectively). The standard deviation was then also allowed to vary with GA, with the same boundary knots but with an internal knot at only the 50^{th} centile. The model was then extended in each case to allow for a skewed distribution using the Box–Cox, Cole and Green (BCCG) distribution, and then to also adjust for the kurtosis (or 'tailedness') of the data using the Box–Cox power exponential distribution (BCPE) (12). For the BCCG and BCPE distributions, the median and scale parameter were modelled as smooth functions of GA using NCS as were the mean and standard deviation for the normal distribution, respectively, and the

skewness and kurtosis parameters were estimated as constants. Plots of standardized residuals were checked.

Once the distribution of the data had been determined with respect to the GA, patient characteristics that might plausibly be associated with the hemodynamic variables were added to the model to test whether they provided a significant improvement in the prediction of the mean/median value. Maternal booking weight and height were added to the models first, each using a cubic spline basis with boundary knots at the 10th and 90th centiles and internal knots at the 50th centiles (59.18, 74 and 96.58 kg, and 1.56, 1.64 and 1.73 m, respectively), and an interaction term (centred at the medians) was then added for weight and height. A constant effect of smoking during pregnancy was then tested, followed by the addition of maternal age using a NCS basis with boundary knots at the 10th and 90th centiles and an internal knot at the 50th centile (24, 32 and 38 years, respectively). Finally, the effects of having conceived using assisted reproduction, being nulliparous and ethnicity (groupings: Caucasian, Afrocaribbean, South Asian, East Asian, Mixed/Other) were tested.

RESULTS

Maternal hemodynamic measurements were performed in 758 pregnancies. A total of 131 cases were excluded (maternal or fetal complications or recruited to the study either before 10 weeks or after 40 weeks of gestation). Final analysis included 627 single measurements. Maternal baseline characteristics and pregnancy outcome data are summarised in Table 1.

Reference ranges

The USCOM-1A®- specific reference ranges, displaying the 5th, 50th and 95th centiles for the SV, CO and SVR are shown in Figures 1-3. The normal distribution was adequate to model SV, but the BCPE distribution provided an improvement in model fit for CO and SVR. Increasing median values of CO and SV were observed from 10 weeks until around 31 and 21 weeks respectively, with a subsequent decrease until

term for each variable. These changes were mirrored by a reduction in the median value of SVR from 10 weeks until around 32 weeks, followed by an increase towards term.

Associations with maternal characteristics

Cardiac Output

Maternal weight ($p<0.001$) and height ($p<0.001$) influenced the CO values and there was a significant interaction ($p=0.002$) (Figure 4). In women with a maternal height less than 1.60m, there was no association between median CO and maternal weight, but in those with a maternal height exceeding 1.60m, an increase in weight was associated with an increase in CO. Maternal age was also significantly associated with the median CO ($p<0.001$). The estimated median CO was constant above the age of 32 years, but was around 0.5 L/min higher for women aged 25 or younger (Figure 5). Smoking was not a statistically significant predictor once age was added to the model, and so this was dropped from the model for analysis ($p=0.07$). No further significant improvements in model fit were gained by the addition of mode of conception ($p=0.11$), parity ($p=0.14$) or ethnicity ($p=0.13$).

Stroke Volume

Significant improvements in model fit were achieved by the addition of maternal weight ($p<0.001$), height ($p<0.001$) and their interaction ($p=0.035$). However, no further improvement to model fit was provided by smoking ($p=0.12$), maternal age ($p=0.999$), mode of conception ($p=0.25$), parity ($p=0.43$) or ethnicity ($p=0.19$). SV was primarily associated with maternal height, although some positive association with weight could also be observed within the normal BMI range (Figure 6).

Systemic Vascular Resistance

Improvements in model fit were achieved by the addition of maternal height ($p<0.001$), but not maternal weight ($p=0.63$). In addition to height, smoking ($p=0.011$) and maternal age ($p=0.018$) led to further improvements in the model fit, but mode of

conception (p=0.75), parity (p=0.07) and ethnicity (p=0.14) did not. Greater maternal height was associated with lower median values of SVR with an estimated difference of around 120 dynes·sec·cm^5 between 1.60m and 1.80m (Figure 7). Advancing maternal age was associated with higher median SVR with an estimated difference of around 50 dynes·sec·cm^5 between 25 and 35 years (Figure 8). Smokers had a lower SVR of 73.5 dynes·sec·cm^5 (95% CI; 8.6 dynes·sec·cm^5-138.4 dynes·sec·cm^5).

A spreadsheet has been provided (Supplementary file S1; supplementary online material) to calculate centile positions of USCOM-1A® measurements dependant on either GA alone or on all significant predictors for each variable.

DISCUSSION

Summary of study findings

This study provides reference ranges for SV, CO and SVR obtained using USCOM-1A® in uncomplicated, singleton pregnancies. We report a significant effect of maternal age, weight and height on CO, of maternal weight and height on SV, and of maternal age, height and smoking status on SVR.

Comparison with the existing literature

This is the largest study of maternal hemodynamics in a low-risk obstetric population using USCOM-1A®. Kager et al (13) reported on the CO estimates of 172 patients across all trimesters of pregnancy, obtained using USCOM-1A®. There are currently no published device-specific reference ranges for USCOM-1A® in a large cohort consisting of uncomplicated pregnancies. There are no reported studies of this scale which investigate the effects of various maternal characteristics on central hemodynamic variables in an obstetric cohort.

Clinical and research implications

Prior to the introduction of non-invasive maternal hemodynamic monitoring in clinical practice, it is imperative that methodology-specific reference ranges are established. Previous work investigating hemodynamics have been performed using thermodilution (14-16) and echocardiography (17-19). These methods have significant drawbacks, including the invasive nature and the requirement of specialist training and expertise, respectively.

In the published literature, assessment of the performance of novel CO monitors against a reference method has been carried out using Bland–Altman analysis, which is the recommended method of statistical analysis when assessing two cardiac output devices (20). A mean percentage difference of <30% between two devices has been proposed as the level of clinical acceptability (21). Previous investigations focused on assessing the adequacy of interchangeable use of the two methods, or on the potential replacement of one method by another. However, these aims can be questioned in the present setting. USCOM-1A®, or any other similar device, will not replace thermodilution as the 'gold standard' method of CO estimation, and achieving a mean percentage difference of less than 30% remains difficult to attain. Indeed many comparison studies (5-8) evaluating USCOM against thermodilution have reported poor agreement (MPD >30%) when assessed against thermodilution or echocardiography. However, the limitations of the reference methods used in the studies should be taken into account, as these do not provide an error-free measurement of CO. Instead, we propose that USCOM-1A® will provide an alternative, non-invasive methodology enabling simple, bedside assessment of maternal hemodynamics. The benefits include excellent intra-observer repeatability and inter-observer reproducibility (9, 13), and the potential for the measurements to be obtained by all levels of healthcare professional (22).

The relationship between maternal hemodynamic variables and patient characteristics reported in this study are novel. CO decreases with advancing maternal age up until the age of 32, and SVR increases over a similar period. These findings are consistent with the inverse relationship observed between cardiac function and age, supporting the notion of increasing cardiovascular risk with advancing maternal age. Furthermore, the physiological consequence of a decrease in SVR in taller individuals will result in an increase in SV, as we report in this study.

Hypertensive disorders of pregnancy are associated with aberrations in maternal hemodynamics prior to the onset of clinical disease (23-26). Advancing maternal age is a recognised risk factor for hypertension in pregnancy (27). The findings of increased SVR and decreased CO observed in our cohort lend further support to the observed association between advancing age and risk of developing hypertension in pregnancy. Smoking is a known risk factor for cardiovascular disease, and is hazardous to fetal, child and maternal wellbeing (28-30). However, maternal smoking does have a protective effect on the development of pre-eclampsia, which has been demonstrated in epidemiological and molecular studies (31-33). Our reported finding of reduced SVR in smokers, provides further central hemodynamic evidence for the protective role of smoking with respect to hypertension in pregnancy.

An unexpected finding was the lack of effect of maternal weight on SVR. Increasing maternal weight is also a known risk factor for hypertension in pregnancy. We postulate that the most likely explanation for the lack of effect of maternal weight on SVR, is that SVR is derived from mean arterial pressure and CO. Even though CO increases with weight, and should result in a decrease in SVR, mean arterial pressure also increases with weight. It would appear that these two cancel out, thereby explaining the lack of effect of maternal weight on SVR. Furthermore, the increase in BP seen with increasing maternal weight is due to an increase in CO, this is independent of SVR. Previous work from our group has shown no difference in SVR between morbidly obese pregnant women and normal BMI controls (submitted manuscript). Future studies to assess the structural and functional myocardial changes (using echocardiography) associated with increased maternal weight, and more specifically, weight gain in pregnancy are required to explore this.

Study strengths and limitations

This study includes a large cohort of uncomplicated low-risk singleton pregnancies. All patients who developed hypertension in pregnancy after being recruited to the study were excluded from the analysis, and therefore women who have altered haemodynamic function prior to the onset of clinical disease were not included in the study. Furthermore, the statistical modelling has enabled the construction of reference ranges and the assessment of the potential relationship between maternal

characteristics and hemodynamics. Using a solitary hemodynamic assessment instead of multiple readings is a study limitation; one way to address this is o perform multiple, serial measurements in a subject over a defined time period – this is the aim of an ongoing research study. We have previously reported excellent repeatability (ICC 0.969, 95% CI 0.953-0.980) and reproducibility (ICC 0.896, 95% CI 0.812-944) of USCOM® (9). One recognised limitation of the methodology used in this study is the use of an inherent normogram that estimates the left ventricular outflow tract (LVOT) diameter from the patients given height. The difference between the estimated and measured LVOT could be a source of potential bias. The bias resulting from this is a possible explanation for the difference in relationship observed between CO and maternal height below and above 1.6m. The authors recognise that a significant limitation of the methodology employed in this study is the poor agreement when assessed against invasive, reference methods in previously conducted comparison studies. A final study limitation is the lack of pre-pregnancy and early pregnancy data, however this is the focus of ongoing research studies.

Conclusion

This study reports the SV, CO and SVR reference ranges, obtained using USCOM-1A®, in uncomplicated singleton pregnancies. We also demonstrate the interrelationships between these hemodynamic parameters and maternal characteristics. The implications of the latter findings extend beyond pregnancy and are likely to influence the design and interpretation of future studies.

ACKNOWLEDGEMENTS

We would like to thank all of the women who took the time to participate in this study, as well as all the staff (sonographers, midwives and administrative staff) who helped us to recruit patients.

REFERENCES

1. Valtier B, Cholley BP, Belot J-P, de la Coussaye JE, Mateo J, Payen DM. Noninvasive monitoring of cardiac output in critically ill patients using transesophageal Doppler. Am J Respir Crit Care Med. 1998;158(1):77-83.

2. Funk DJ, Moretti EW, Gan TJ. Minimally invasive cardiac output monitoring in the perioperative setting. Anesth Analg. 2009;108(3):887-97.

3. Lorne E, Mahjoub Y, Diouf M, Sleghem J, Buchalet C, Guinot PG, Petiot S, Kessavani A, Dehedin B, Dupont H. Accuracy of impedance cardiography for evaluating trends in cardiac output: a comparison with oesophageal Doppler. Br J Anaesth. 2014;113(4):596-602.

4. Marik PE. Noninvasive cardiac output monitors: a state-of the-art review. J Cardiothorac Vasc Anesth. 2013;27(1):121-34.

5. Knirsch W, Kretschmar O, Tomaske M, Stutz K, Nagdyman N, Balmer C, Schmitz A, Bettex D, Berger F, Bauersfeld U, Weiss M. Cardiac output measurement in children: comparison of the Ultrasound Cardiac Output Monitor with thermodilution cardiac output measurement. Intensive Care Med. 2008;34(6):1060-4.

6. Tan H, Pinder M, Parsons R, Roberts B, Van Heerden P. Clinical evaluation of USCOM ultrasonic cardiac output monitor in cardiac surgical patients in intensive care unit. Br J Anaesth. 2005;94(3):287-91.

7. Thom O, Taylor DM, Wolfe RE, Cade J, Myles P, Krum H, Wolfe A. Comparison of a supra-sternal cardiac output monitor (USCOM) with the pulmonary artery catheter. Br J Anaesth. 2009;103(6):800-4.

8. McNamara H, Barclay P, Sharma V. Accuracy and precision of the ultrasound cardiac output monitor (USCOM 1A) in pregnancy: comparison with three-dimensional transthoracic echocardiography. Br J Anaesth. 2014;113(4):669-76.

9. Vinayagam D, Patey O, Thilaganathan B, Khalil A. Non-invasive cardiac output monitoring in pregnancy: comparison to echocardiographic assessment. Ultrasound in Obstetrics & Gynecology. 2017;49:32-38.

10. Nidorf SM, Picard MH, Triulzi MO, Thomas JD, Newell J, King ME, Weyman AE. New perspectives in the assessment of cardiac chamber dimensions during development and adulthood. J Am Coll Cardiol. 1992;19(5):983-8.

11. Stasinopoulos DM, Rigby RA. Generalized additive models for location scale and shape (GAMLSS) in R. Journal of Statistical Software. 2007;23(7):1-46.

12. Rigby RA, Stasinopoulos DM. Smooth centile curves for skew and kurtotic data modelled using the Box–Cox power exponential distribution. Statistics in medicine. 2004;23(19):3053-76.

13. Kager CCM, Dekker GA, Stam MC. Measurement of cardiac output in normal pregnancy by a non-invasive two-dimensional independent Doppler device. Australian and New Zealand Journal of Obstetrics and Gynaecology. 2009;49(2):142-4.

14. Ganz W, Donoso R, Marcus HS, Forrester JS, Swan HJ. A new technique for measurement of cardiac output by thermodilution in man. Am J cardiol. 1971;27(4):392-6.

15. Ganz W, Swan H. Measurement of blood flow by thermodilution. The Am J cardiol. 1972;29(2):241-6.

16. Easterling TR, Watts DH, Schmucker BC, Benedetti TJ. Measurement of cardiac output during pregnancy: validation of Doppler technique and clinical observations in preeclampsia. Obstetrics & Gynecology. 1987;69(6):845-50.

17. Dennis AT. Transthoracic echocardiography in obstetric anaesthesia and obstetric critical illness. Int J Obstet Anesth. 2011;20(2):160-8.

18. Robson SC, Hunter S, Boys RJ, Dunlop W. Serial study of factors influencing changes in cardiac output during human pregnancy. Am J Physiol. 1989 256(4)2

19. Robson SC DW, Moore M, Hunter S. Combined Doppler and echocardiographic measurement of cardiac output: theory and application in pregnancy. BJOG. 1987;94:1014–27.

20. Bland JM, Altman D. Statistical methods for assessing agreement between two methods of clinical measurement. The Lancet. 1986;327(8476):307-10.

21. Critchley LH, Critchley JJH. A Meta-Analysis of Studies Using Bias and Precision Statistics to Compare Cardiac Output Measurement Techniques. Journal of Clinical Monitoring and Computing. 1999;15(2):85-91.

22. Boyle M, Steel L, Flynn GM, Murgo M, Nicholson L, O'Brien M, Bihari D. Assessment of the clinical utility of an ultrasonic monitor of cardiac output (the USCOM) and agreement with thermodilution measurement. Crit Care Resusc. 2009;11(3):198-203.

23. Khalil AA, Cooper DJ, Harrington KF. Pulse wave analysis: a preliminary study of a novel technique for the prediction of pre-eclampsia. BJOG. 2009;116(2):268-277.

24. Bosio PM, McKenna PJ, Conroy R, O'Herlihy C. Maternal central hemodynamics in hypertensive disorders of pregnancy. Obstetrics & Gynecology. 1999;94(6):978-84.

25. Valensise H, Vasapollo B, Gagliardi G, Novelli GP. Early and late preeclampsia: two different maternal hemodynamic states in the latent phase of the disease. Hypertension. 2008;52(5):873-80.

26. Easterling TR, Benedetti TJ, Schmucker BC, Millard SP. Maternal hemodynamics in normal and preeclamptic pregnancies: a longitudinal study. Obstetrics & Gynecology. 1990;76(6):1061-9.

27. Poon LC, Syngelaki A, Akolekar R, Lai J, Nicolaides KH. Combined screening for preeclampsia and small for gestational age at 11-13 weeks. Fetal Diagn Ther. 2013;33(1):16-27.

28. Bush JS, Dolen WK. Pre-and Postnatal Exposure to Parental Smoking and Allergic Disease Through Adolescence. Pediatrics. 2015 Dec 1;136 (Supplement 3):S235-S235.

29. Kelso J. Environmental Tobacco Smoke Exposure and Risk of Allergic Sensitisation in Children: A Systematic Review and Meta-analysis. Pediatrics. 2015 Dec 1;136 (Supplement 3):S235-6.

30. Gunnerbeck A, Wikström AK, Bonamy AK, Wickström R, Cnattingius S. Relationship of maternal snuff use and cigarette smoking with neonatal apnea. Pediatrics. 2011 Sep 1;128(3):503-9.

31. Karumanchi SA, Levine RJ. How does smoking reduce the risk of preeclampsia? Hypertension. 2010;55(5):1100-1.

32. Wikström A-K, Stephansson O, Cnattingius S. Tobacco use during pregnancy and preeclampsia risk effects of cigarette smoking and snuff. Hypertension. 2010;55(5):1254-9.

33. Jeyabalan A, Powers RW, Durica AR, Harger GF, Roberts JM, Ness RB. Cigarette smoke exposure and angiogenic factors in pregnancy and preeclampsia. Am J Hyperten. 2008;21(8):943-7.

Table 1 Baseline characteristics and pregnancy outcomes of the study cohort.

Maternal and pregnancy characteristics	**Value**
Maternal age in years, median (IQR)	32 (28-35)
Ethnicity, n (%)	
Caucasian	401 (64)
Afrocarribbean	97 (15)
Asian	103 (16)
Mixed / Other	22 (4)
Not stated	4 (1)
Mode of Conception, n (%)	
Spontaneous	611 (97)
Assisted	16 (3)
Smoking status, n (%)	
Non-smoker	588 (94)
Stopped in the first trimester	5 (1)
Smoker (≤5/day)	19 (3)
Smoker (≥6/day)	15 (2)
Parity, n (%)	
Nulliparous	325 (52)
Multiparous	302 (48)
Maternal weight in kilograms, median (IQR)	74.0 (65.0-84.4)
Maternal height in metres, median (IQR)	1.64 (1.60-1.69)
Maternal BMI in kg/m^2, median (IQR)	27.1 (24.3-31.2)
Maternal mean arterial pressure in mmHg, median (IQR)	85 (79-92)
Mode of delivery, n (%)	
Spontaneous vaginal delivery	330 (53)
Operative vaginal delivery	94 (15)
Caesarean Section	141 (22)
No delivery details	62 (10)
Gestational age at delivery, n (%)	
<37/40 (preterm)	32 (5)
>37/40 (term)	533 (85)
No delivery details	62 (10)
Birthweight in grams, median (IQR)	3350 (3100-3680)

FIGURE LEGENDS

Figure 1. Scatterplot demonstrating reference ranges for maternal cardiac output (L/min) during pregnancy. The red line represents the median (50th centile), blue lines represent the 5th and 95th centiles.

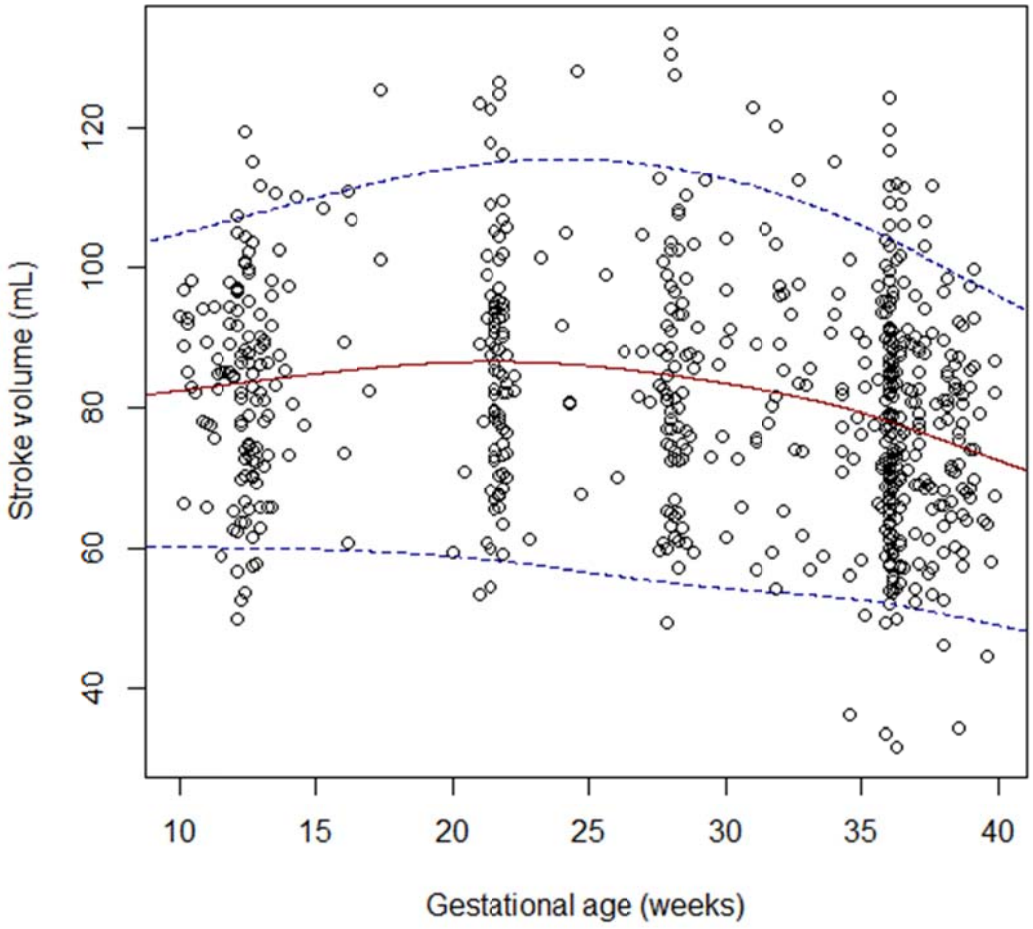


Figure 2. Scatterplot demonstrating reference ranges for maternal stroke volume (ml) during pregnancy. The red line represents the median (50th centile), blue lines represent the 5th and 95th centiles.

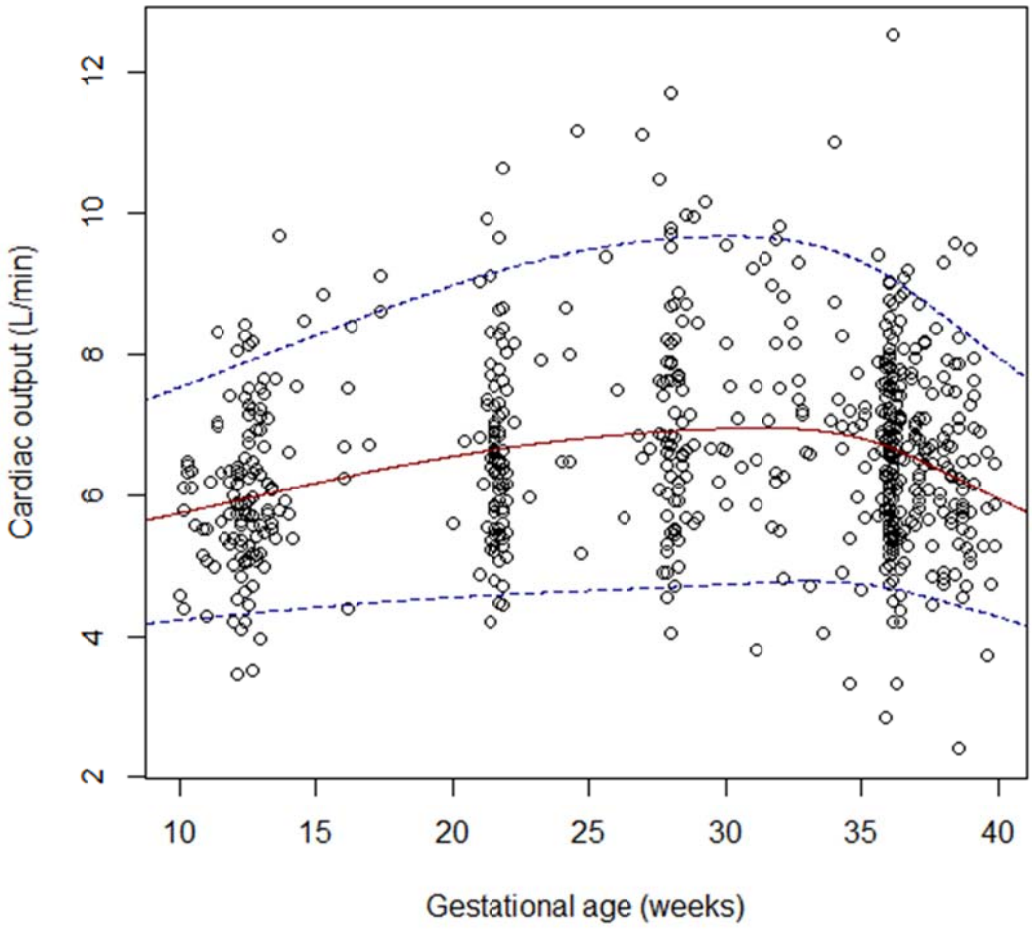


Figure 3. Scatterplot demonstrating reference ranges for maternal systemic vascular resistance (dynes·sec·cm^5) during pregnancy. The red line represents the median (50th centile), blue lines represent the 5th and 95th centiles.

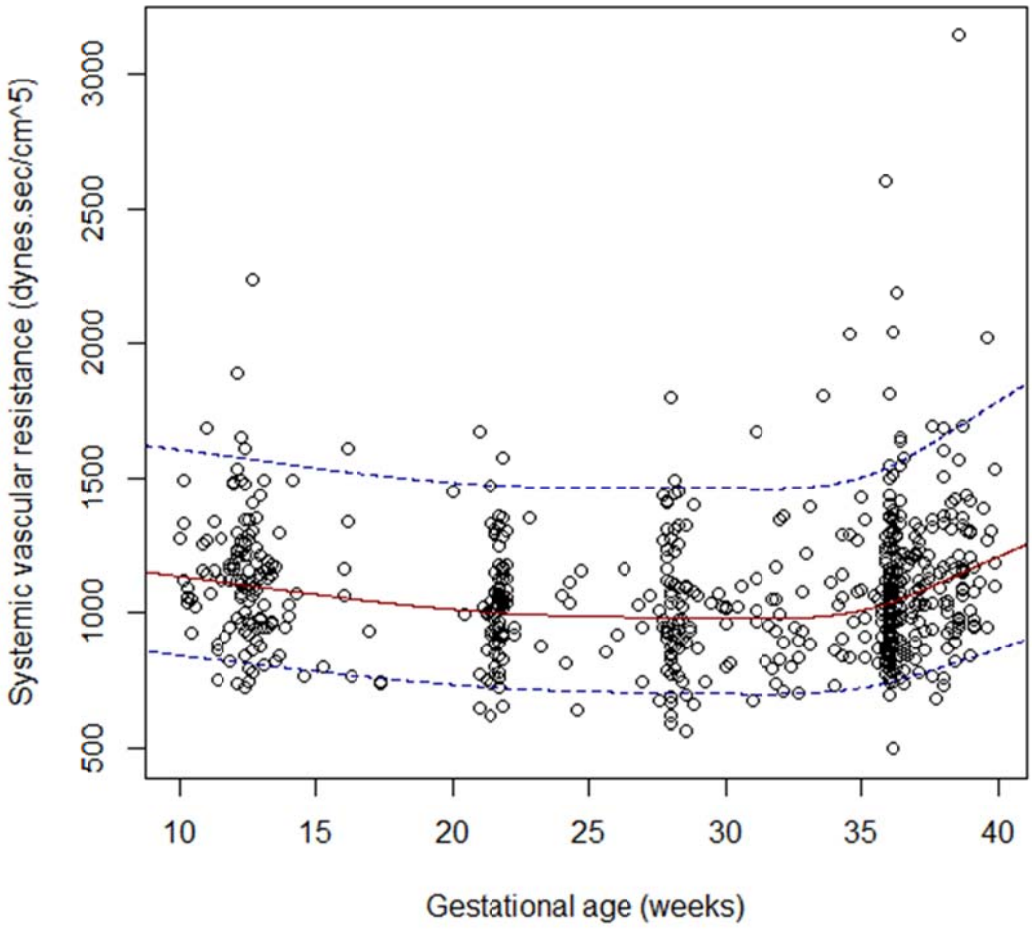


Figure 4. Contour plot of cardiac output (L/min) in a 25-year-old woman at 20 weeks' gestation. The labelled black lines represent median cardiac output values according to maternal height and weight, while the coloured lines represent the body mass index values of 18.5Kg/m^2 (blue), 25Kg/m^2 (orange) and 30Kg/m^2 (red).

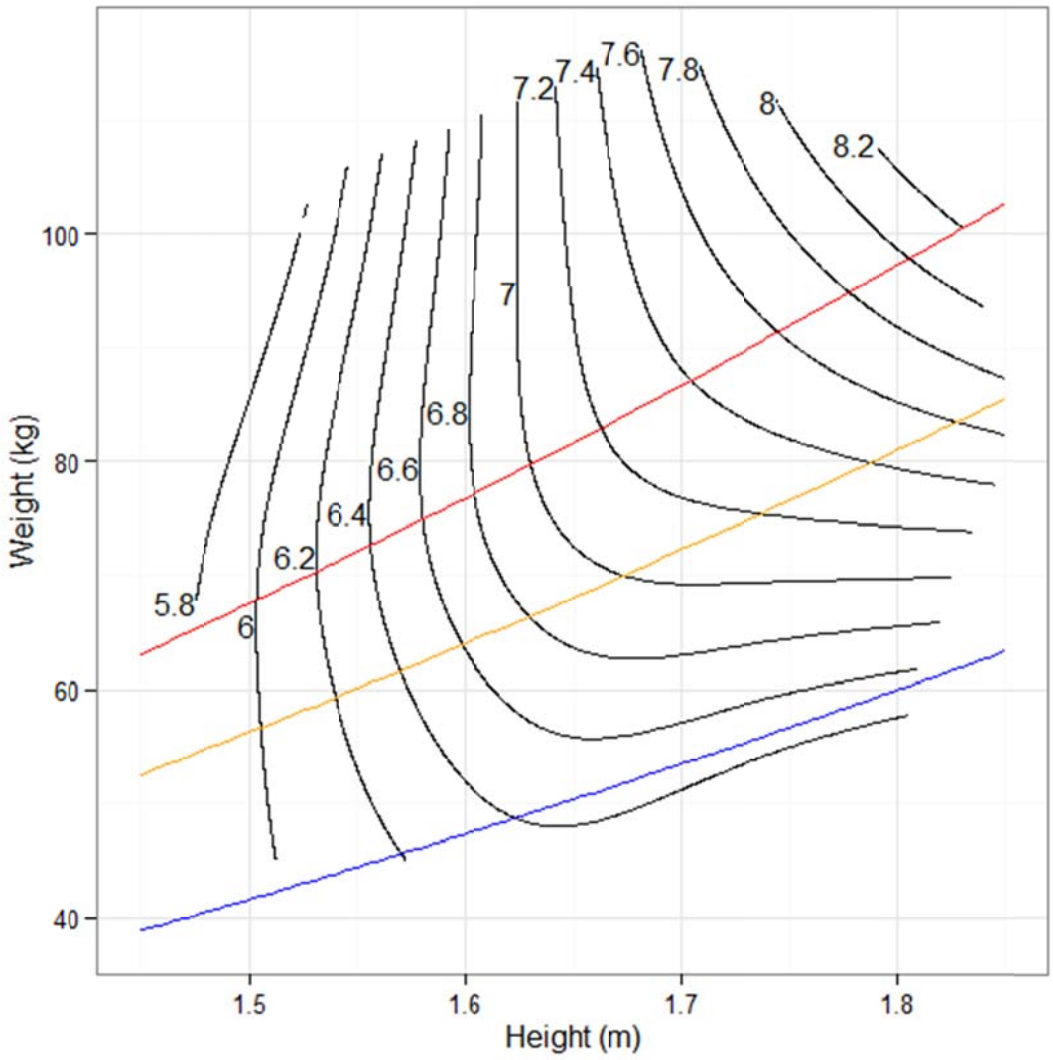


Figure 5. The estimated difference in median cardiac output (CO) (L/min) according to maternal age relative to 24 years. The 95% confidence interval is represented by the grey shaded area.

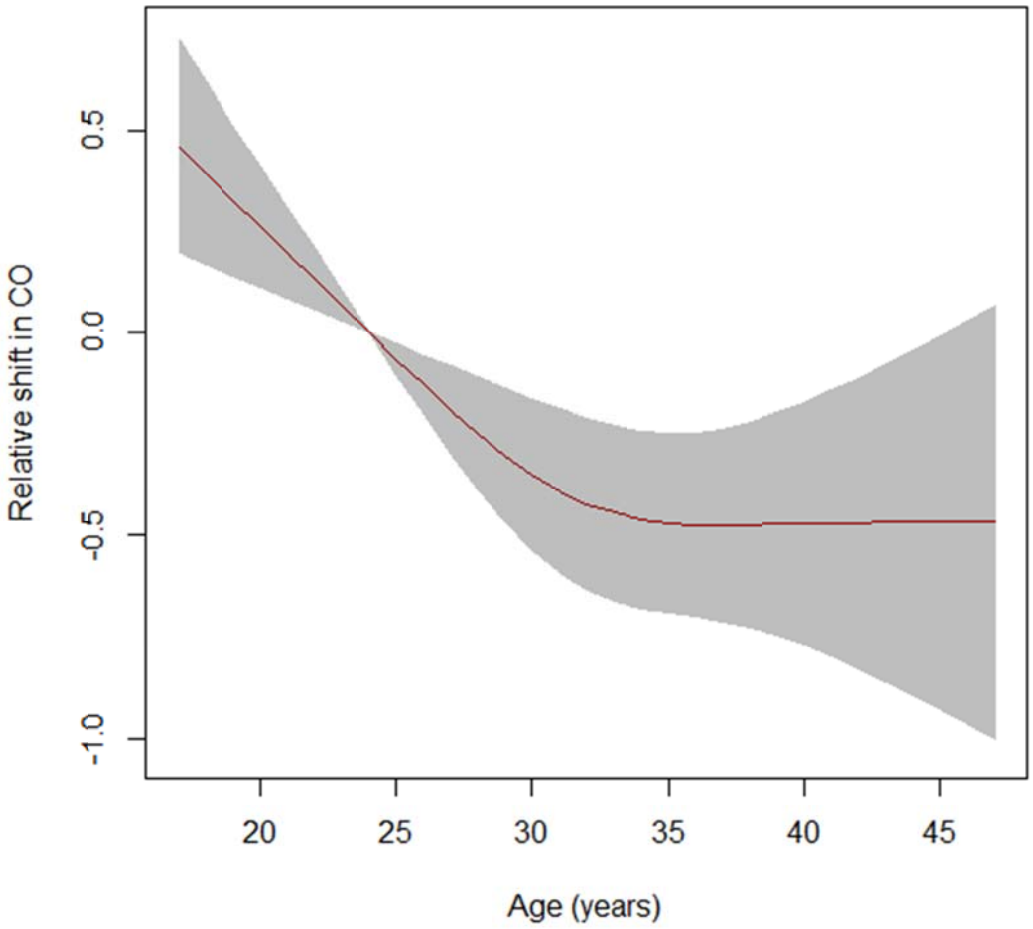


Figure 6. Contour plot of stroke volume in a woman at 20 weeks' gestation. The labelled black lines show the median stroke volume (ml) according to the maternal height and weight, while the coloured lines represent the body mass index values of 18.5Kg/m^2 (blue), 25Kg/m^2 (orange) and 30Kg/m^2 (red).

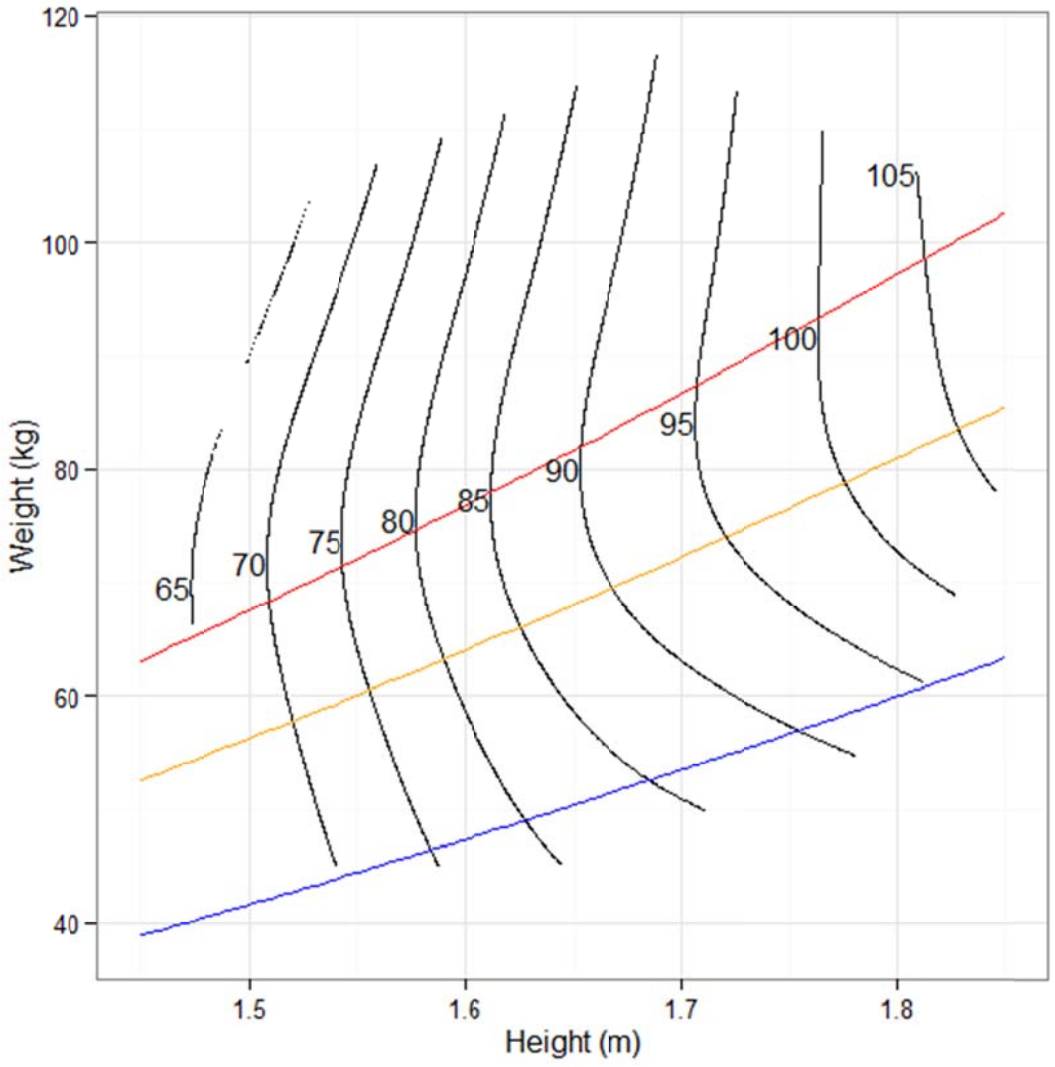


Figure 7. The estimated difference in the median systemic vascular resistance (dynes·sec·cm^5) according to the maternal height relative to 1.56m. The 95% confidence interval is represented by the grey shaded area.

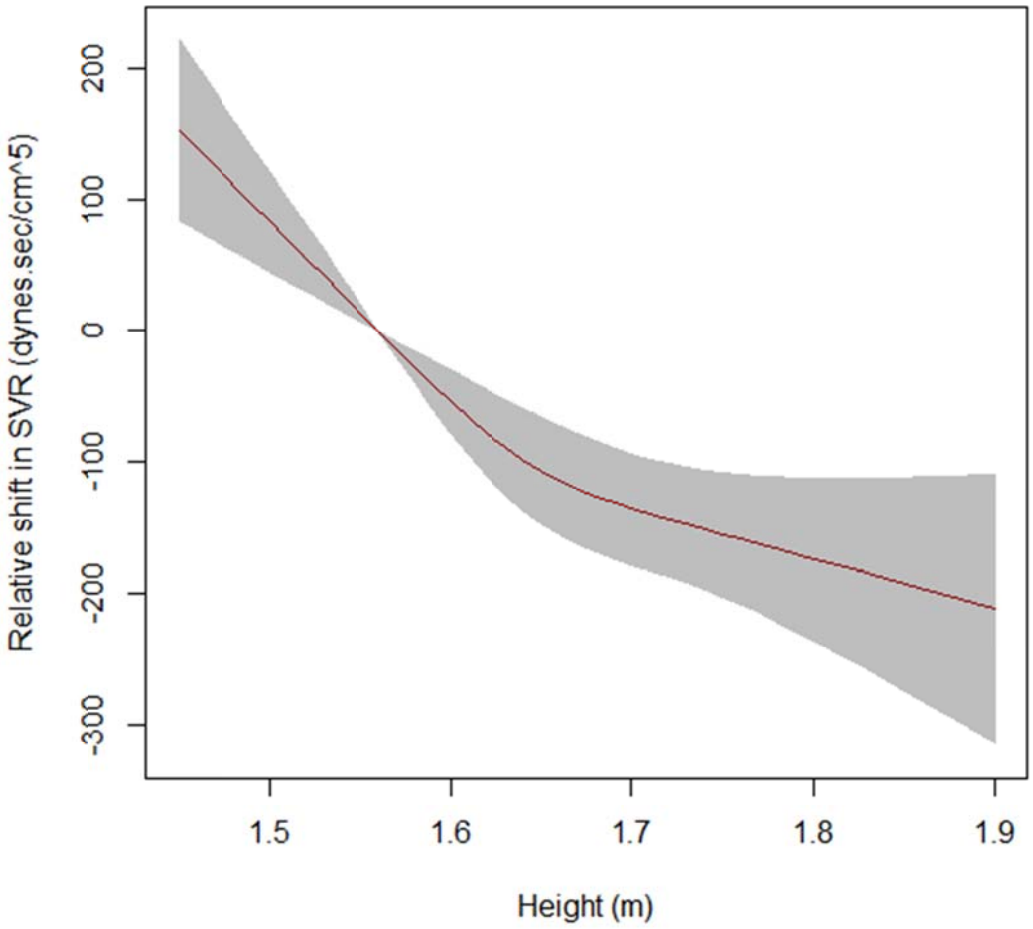
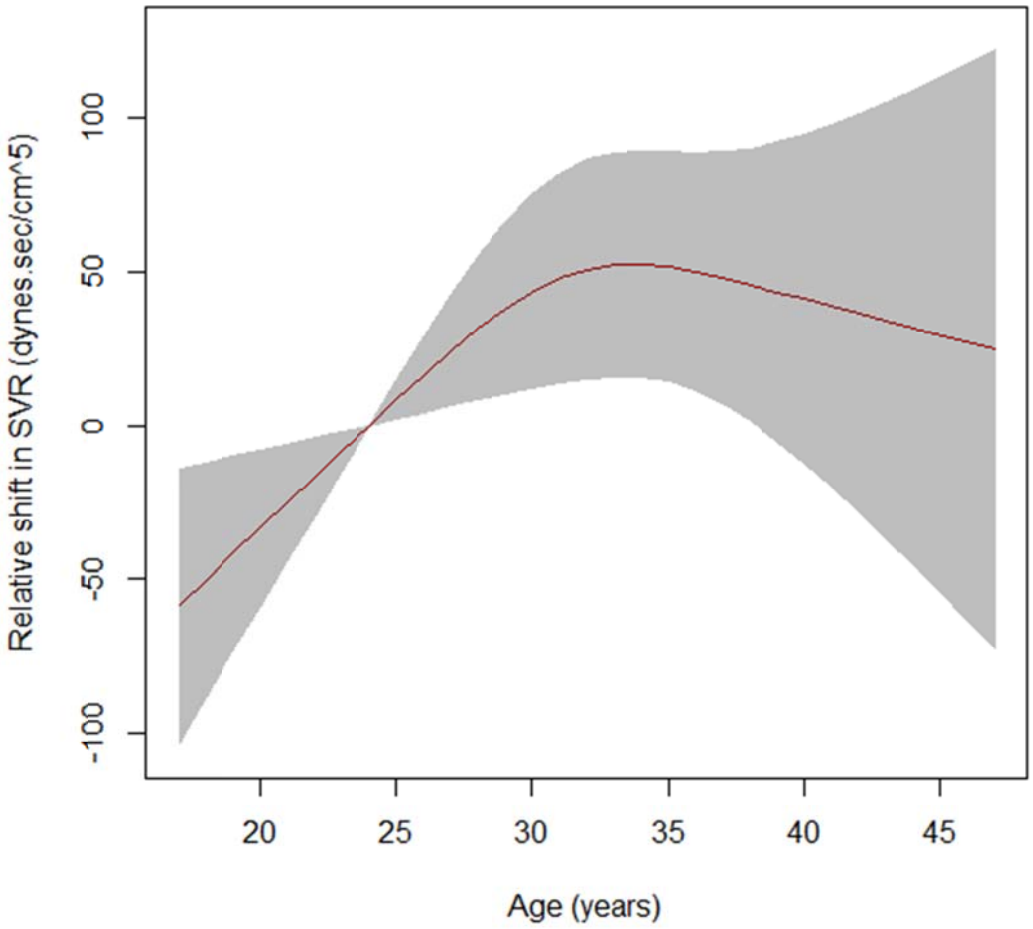


Figure 8. The estimated difference in the median systemic vascular resistance (dynes·sec·cm^5) according to the maternal age relative to 24 years. The 95% confidence interval is represented by the grey shaded area.



SUPPLEMENTARY MATERIAL (ONLINE)

Supplementary File S1: Excel spreadsheet to calculate centile positions of USCOM-1A®measurements dependant on either gestational age alone (sheet 1) or on all significant predictors of each variable (sheet 2). Gestational age is limited to ≥10 and ≤40 weeks. The expected median value is also reported conditional on the set of patient characteristics entered.