Arterial stiffness throughout pregnancy:

Arteriograph device-specific reference ranges based on a low-risk population

Running Title: Arterial stiffness throughout pregnancy.

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ABSTRACT

Objective

The maternal cardiovascular system undergoes significant adaptation during pregnancy. We aimed to examine the changes in arterial stiffness parameters during normal pregnancy and establish reference ranges for the general population.

Methods

We performed a prospective cross-sectional observational study at the University Hospitals of Leicester. We included low-risk healthy pregnant women with singleton and viable pregnancies with no evidence of fetal abnormality or aneuploidy. Smokers, women with pre-existing or gestational hypertensive disorders and diabetes, booking BMI ≥30, on medication that could affect cardiac function and/or those who delivered before 37 completed weeks of gestation, and/or a neonate with birthweight <10th centile were excluded. Brachial (BrAIx) and aortic augmentation indices (AoAIx), and pulse wave velocity (PWV) were assessed using the Arteriograph®. Data were analysed using a linear mixed model.

Results

We analysed a total of 555 readings from 254 women across different gestational ages and present the 10th, 25th, 50th, 75th and 90th centiles for BrAIx, AoAIx and PWV from 12^{+0} – 42^{+0} weeks' gestation. All hemodynamic variables were significantly associated with maternal age and heart rate. BrAIx, AoAIx and PWV demonstrated significant change with gestation, with all reaching their lowest value in the second trimester.

Conclusion

The current study presents reference ranges for BrAIx, AoAIx and PWV in low-risk singleton pregnancies. Further work is required to establish if women in whom measures of arterial stiffness lie above the 90th centile could be at increased risk of adverse pregnancy outcomes and to identify the optimum time for screening.

KEYWORDS: pregnancy; haemodynamics; arterial stiffness; pulse wave velocity; augmentation index; reference range; pre-eclampsia; intra-uterine growth restriction

INTRODUCTION

The maternal cardiovascular system undergoes significant change during pregnancy, in order to meet the increased metabolic demands and to sustain the utero-placental perfusion. Heart rate (HR), stroke volume (SV) and cardiac output (CO) throughout gestation, whilst blood pressure (BP) and total peripheral resistance (TPR) are, at least until the third trimester, decreased[1-3]. However, since peripheral BP measurement does not accurately convey central BP[4, 5], attention over recent years has turned towards the assessment of central hemodynamics and arterial stiffness (AS) in pregnancy, and its use in predicting adverse pregnancy outcomes.

AS refers to the rigidity of the arterial wall, and is commonly measured by the pulse wave velocity (PWV) and augmentation index (AIx). PWV, the speed at which the pulse wave travels between two points on the arterial tree is a direct marker of AS[6], with stiffer vessels transmitting the pulse wave more quickly. AIx is a measure of wave reflection, and is dependent on the ventricular ejection, the PWV and the reflection coefficient[7, 8]. It is considered a surrogate measure of AS, and represents the AS distal to the point of measurement[6]. Aortic PWV therefore describes the compliance of the central, elastic arteries, whilst aortic and brachial AIx provide information on the more peripheral muscular arteries. In non-pregnant populations, increased AIx and PWV are both associated with cardiovascular events and all-cause mortality[9, 10].

Several studies have examined the changes in central hemodynamics within a cohort of normal healthy pregnancies[11-18]. These studies have consistently concluded that AIx falls from the first trimester, reaching a nadir in the second trimester, and rising again in the third trimester. A similar pattern has been described for PWV, although the studies have disagreed as to when the nadir in PWV occurs; Robb et al. reporting the nadir to

occur at 24 weeks, with a continuous rise in PWV towards term[12], and Osman et al. finding the nadir to occur at an earlier gestation of 17 weeks, followed by a rise peaking at 35 weeks, followed by a subsequent fall again, so that the curve resembled a sine wave[13].

Evidence is accumulating suggesting that deviation from this normal pattern of adaptation is associated with increased risk of placental mediated diseases, with both AIx and PWV being elevated in pregnancies complicated by pre-eclampsia[19], pregnancy-induced hypertension[20, 21], and fetal growth restriction[22], compared to pregnancies with a normal outcome. Furthermore, these maladaptive patterns pre-date the onset of clinical disease[23], and so may have a role in screening and prevention strategies.

Despite the interest in central hemodynamics in low-risk pregnancy, normal ranges for AIx and PWV throughout the gestational period have not yet been established. In a study of over 6200 low-risk pregnancies, Khalil et al. reported the median, 5th, 10th, 90th and 95th centiles for AIx-75 and PWV multiples of the median (MoM) at 11+0 - 13+6 weeks' gestation, but did not examine the cohort beyond the first trimester[24]. Our research group has previously reported the 5th, 25th, 50th, 75th and 95th centiles for PWV and AIx from 13 - 40 weeks' gestation from a longitudinal study of maternal hemodynamics[13], but the data were limited by a small sample size of just 30 women.

Generating normal ranges for measures of maternal hemodynamics in pregnancy would enable clinicians to identify pregnant women with maladaptation of the cardiovascular system, and who could be at increased risk of placental mediated diseases. The current study aimed to establish normal ranges for central hemodynamics in a larger group of women throughout pregnancy.

METHODS

This was a prospective cross-sectional observational study of central hemodynamics in low-risk pregnant women with a singleton, viable pregnancy. Pregnant women were recruited from the antenatal and ultrasound clinics at the Leicester Royal Infirmary, a tertiary-level maternity unit in the United Kingdom.

Women who were current smokers, with body mass index (BMI) ≥30 at booking, with pre-existing disorders or on medications known to affect cardiovascular function, multiple pregnancies, and pregnancies affected by known aneuploidy or fetal abnormality were excluded. We also excluded women who subsequently developed any hypertensive disorder of pregnancy, who delivered prior to 37 completed weeks of gestation, or who delivered a neonate with birth weight <10th centile according to population-based growth charts[25]. Case notes were examined by the research team to assess eligibility, and suitable candidates were approached sequentially regarding participation. All women provided written consent to take part.

Ethical approval was obtained from the East Midlands Research Ethics Committee (15/EM/0469, IRAS 182250) and the University Hospitals of Leicester Research and Innovation Department prior to commencement. The study was conducted in accordance with the principles of Good Clinical Practice, and the Declaration of Helsinki[26]. Recruitment to the study was impacted by COVID-19 pandemic restrictions and the limitation of research activities.

Study Measurements

Women between 11^{+0} and 42^{+0} weeks of gestation were eligible for inclusion. We collected demographic details including maternal age, ethnicity, height, parity, BMI and

smoking status at booking. Gestational age at each visit was calculated based on the dating scan performed between 11^{+0} and 13^{+3} weeks gestation.

Maternal hemodynamics were assessed in a temperature-controlled room, free from noise or any other distractions. Patients were positioned in the semi-recumbent position, and were asked not to move or talk during the assessment. All measurements were performed by a researcher who had received appropriate training. The assessments were performed at scheduled appointments between 0900 and 1700. Our group has previously shown that measurements of PWV and AIx are not significantly affected by the time of day at which they are measured[27].

Brachial (BrAIx) and aortic augmentation indices (AoAIx), and PWV were measured using the Arteriograph® (TensioMed Ltd, Budapest, Hungary), which estimates arterial stiffness oscillometrically, through a single, non-invasive blood pressure cuff. The Arteriograph® has been validated against invasive assessment of arterial stiffness in a non-pregnant population undergoing cardiac angiography[28]. It has been used previously in research in pregnant populations[11, 13, 15, 29], and shown to have good to excellent repeatability amongst healthy pregnant subjects in the third trimester[27]. Recruits had a minimum of two Arteriograph® readings taken at each visit. Measurements with a standard deviation of ≥1.0 were excluded, as recommended by the Arteriograph® user manual[30], and an average taken of the remaining readings.

Statistical analysis

We modelled each of the Arteriograph® hemodynamic measurements (BrAIx, AoAIx and PWV) by separate linear mixed models incorporating gestational age (GA) as a fixed effect and tested the statistical significance ($p<0.05$) of linear, quadratic and cubic terms of GA with hemodynamic measurements.

The initial models evaluated the effects of maternal age, BMI, central mean arterial pressure (MAP), heart rate (HR), parity (0 and 1 or more) and ethnicity (White and Non-White). All final models included maternal age and heart rate, and the model on PWV additionally included MAP, as fixed effects. To account for the heterogeneity of residuals with GA, the model on brachial AIx and PWV considered a fixed variance structure, and the model on aortic AIx allowed an exponential variance structure with GA. All models incorporated a random intercept of individuals, and if statistically significant ($p<0.05$), a random time-specific slope for each individual. The model selection within a set of candidate models was assessed by comparing the log-likelihood of the nested models along with the Akaike information criterion and Schwarz Bayesian information criterion, and the fitted models were checked for their underlying model assumptions. We also conducted sensitivity analyses to evaluate the influence of a few outlying values. All statistical tests were two-sided with the type 1 error rate (p-value) of 0.05 to determine the statistical significance. The final fitted model for each hemodynamic measurement was used to predict different centiles (10th, 25th, 50th, 75th, 90th), across different points of GA. All statistical analyses were carried out using the R software version 3.6 (R Core Team, 2019) with appropriate R packages (nlme, multcomp) and plots were created by ggplot2[31].

RESULTS

The study included 254 pregnant women. The characteristics of the study population are described in Table 1.

The study recorded 555 readings in total. 89 readings were between 11^{+0} and 19^{+6} weeks, 104 between 20^{+0} and 27^{+6}, 94 between 28^{+0} and 31^{+6} weeks, 133 between 32^{+0} and 35^{+6} weeks and 135 between 36^{+0} and 42^{+0} weeks of gestation. The earliest reading was obtained at 11^{+4} weeks, and the latest at 42^{+0} weeks of gestation.

Association with maternal characteristics

Brachial AIx and Aortic AIx) showed significant association ($p<0.05$) with maternal age and HR. PWV was significantly associated with HR ($p<0.001$) but not maternal age ($p=0.055$). When adjusted for maternal age and HR, PWV did not show a significant variation with MAP in our cohort ($p=0.083$); however, MAP was retained in our model for PWV, as recommended by the American Heart Association[32]. Maternal parity and ethnicity did not show significant association with any of the measured variables ($p>0.05$). The effect sizes and the overall conclusions did not show substantial change when we conducted sensitivity analysis by removing a few outlying values.

Association with gestational age

Aortic AIx, brachial AIx and aortic PWV all showed significant change throughout gestation. The relationship with gestational age for each variable is demonstrated in Figures one to three, and the estimates for the 10^{th}, 25^{th}, 50^{th}, 75^{th} and 90^{th} centiles from 12 to 42 weeks gestation are shown in Tables two - four.

All variables demonstrated a modest U-shaped relationship with gestational age, with the curve being most pronounced for brachial AIx, and almost flattened for PWV. The

nadir of the curve reached at 26 weeks of gestation for brachial AIx, and 25-27 weeks of gestation for aortic AIx. For PWV, the nadir depended on the centile, occurring at 18-19 weeks for the 90^{th} centile, 21-22 weeks for the 50^{th}, and 24-25 weeks for the 10^{th} centile.

The correlation coefficient between Brachial Aix with Aortic AIx was positive and statistically significant ($r = 0.978$, $p<0.001$). However, estimates of correlation coefficients between Aortic AIx and Brachial AIx with PWV were not significantly different ($p=0.713$ and $p=0.253$, respectively).

DISCUSSION

Summary of main findings

Using data from a prospective cross-sectional observational study of arterial stiffness in healthy pregnant women with singleton pregnancies, we demonstrated that brachial AIx, aortic AIx and aortic PWV change significantly throughout pregnancy. We presented the estimates of 10th, 25th, 50th, 75th and 90th centiles for these variables from 12 to 42 weeks gestation.

Interpretation of findings and comparison with the literature

Our findings confirm that the compliance of both the central elastic (demonstrated by PWV), and the more peripheral muscular arteries (demonstrated by AoAIx and BrAIx) changes significantly in normal pregnancy. Our results agree with other studies that reported decreased aortic AIx in pregnancy, with the lowest values occurring in the second trimester[11 -18]. Furthermore, the 50th centile values for aortic AIx are also comparable to the mean values that we reported previously[13] and that of Macedo et. al[17].

We have shown that PWV falls in normal pregnancy, reaching its lowest point at 18-25 weeks, depending on centile. Other studies examining arterial stiffness in normal pregnancy have investigated this parameter at discrete gestational windows, rather than continuously throughout gestation as we reported here – but have also reported the lowest PWV in the mid-trimester[12 -15, 18]. Interestingly, the only other study to investigate PWV continuously during pregnancy[17] did not find any significant change across gestation. This study was smaller in size (193 readings), and compared to ours, the study population had a higher risk profile, with a larger BMI (27 vs 23 kg/m^2) and an increased number of smokers (19.7%). We also found a continuous increase in PWV towards term, in contrast to Franz et al.[15] and the normograms previously produced by

our group[13] which found a decrease in PWV after 37 weeks gestation. Again, this difference might be explained by the significantly larger size of the current study.

We did not find a significant association between aortic PWV and aortic or brachial AIx. Similarly, several other studies[7, 33, 34] have also reported a lack of significant association between PWV and AIx, which reflects that AIx is dependent on added factors such as the ventricular ejection, distance to the reflection site and reflection coefficient of the vessels[7, 8], in addition to the PWV.

Strengths and Limitations

To our knowledge, this is the largest study to investigate arterial stiffness in healthy, low-risk women throughout pregnancy. A major strength of this work is that we collected data throughout the gestational period, meaning we produced centile charts for all time points between 12 and 42 weeks of gestation. We used strict inclusion and exclusion criteria to define our population. In contrast to previous studies which either did not consider exclusion based on birth weight centile[12, 13, 15, 18], or only excluded pregnancies delivering neonates <5th centile[11, 14, 24], we excluded all pregnancies delivering neonates <10th centile and pregnancies complicated by placental-mediated disease, and preterm delivery.

A limitation of this work is that it is a relatively small, single centre study. Whilst we did not find any evidence of a difference on average for all hemodynamics variables between white and non-white women, an increased sample size with the representation of diverse ethnicities might help a better understanding of the trends in arterial stiffness between ethnic groups during the pregnancy. We were also unable to compare the hemodynamics variables at pre and postnatal stages due to the restriction and limitation of research activities as a result of COVID-19 pandemic.

Clinical and Research Implications

Current UK screening protocols[35] for preeclampsia utilise maternal characteristics in early pregnancy, but only detect 31.6% of all preeclampsia and 42.8% of preterm preeclampsia[36]. Over 90 potential screening markers for preeclampsia have been identified, but none achieve a sensitivity and specificity of >90%[37]. For fetal growth restriction, first-trimester pregnancy-associated plasma protein A (Papp-A) levels, and second-trimester uterine artery Doppler resistance profiles in high-risk women are recommended for screening, but only achieve moderate predictive value[38].

Predictive models employing maternal characteristics, biochemical markers and uterine artery Doppler in combination with maternal BP have achieved more promising detection rates for both preeclampsia[39, 40] and fetal growth restriction. Since PWV and AIx are elevated prior to the onset of the placental-mediated disease[23], they could also have a role in screening regimes.

Our results therefore allow identification of women in whom measures of arterial stiffness lie at or beyond the extremes of the normal range. Further work is needed to examine whether women with measures of PWV or AIx above the 90th centile identified in our study are at a high risk of developing preeclampsia and/or fetal growth restriction, and whether the use of these normograms could improve the detection rates offered by current protocols. Our results demonstrated a significant change in parameters of central haemodynamics as gestation advances, and so it will also be important to identify the optimum time point (first trimester versus second trimester) for screening utilising these measurements.

Finally, maternal central haemodynamics have been shown to correlate with downstream haemodynamics within the utero-placental circulation. Increased PWV in

the central elastic arteries is associated with increased pulsatility index in both the uterine[41, 42] and umbilical[41] arteries in women at high risk of, or established PET. Further work is therefore warranted to establish if the normal ranges for PWV and AIx identified from our data correlate with normal ranges of resistance in the utero-placental circulation.

Conclusions

We investigated physiological changes of parameters of arterial stiffness in low-risk healthy pregnancy and observed significant changes in PWV, brachial AIx and aortic AIX as gestation advances. We present the 10th, 25th, 50th, 75th and 90th centiles for these variables between 12 and 42 weeks of gestation. Further work is needed to investigate the potential applications of the current centile ranges for identifying optimum time for screening for placental mediated and cardiovascular diseases.

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Conflicts of interest.

The authors have no conflicts of interest to declare.

REFERENCES

1. Ouzounian JG, Elkayam U. Physiologic Changes During Normal Pregnancy and Delivery. Cardiol Clin 2012; 30(3):317–29.
2. Sanghavi M, Rutherford JD. Cardiovascular physiology of pregnancy. Circulation 2014; 130(12): 1003–8.
3. Karamermer Y, Roos-Hesselink JW. Pregnancy and adult congenital heart disease. Expert Rev Cardiovasc Ther 2007; 5(5): 859-69.
4. McEniery CM, Yasmin, McDonnell B, Munnery M, Wallace SM, Rowe C V et al. Central pressure: Variability and impact of cardiovascular risk factors the anglo-cardiff collaborative trial II. Hypertension. 2008; 51(6): 1476–82.
5. Sharman JE, Stowasser M, Fassett RG, Marwick TH, Franklin SS. Central blood pressure measurement may improve risk stratification. J Hum Hypertens. 2008; 22(12): 838–44.
6. Laurent S, Cockcroft J, Van Bortel L, Boutouyrie P, Giannattasio C, Hayoz D et al. Expert consensus document on arterial stiffness: methodological issues and clinical applications. Eur Heart J. 2006; 27 (21): 2588–605.
7. Sakurai M, Yamakado T, Kurachi H, Kato T, Kuroda K, Ishisu R et al. The relationship between aortic augmentation index and pulse wave velocity: an invasive study. J Hypertens. 2007; 25(2): 391-7.
8. Kohara K, Tabara Y, Oshiumi A, Miyawaki Y, Kobayashi T, Miki T. Radial augmentation index: A useful and easily obtainable parameter for vascular aging. Am J Hypertens. 2005; 18(1 Pt 2): 11S-14S.
9. Vlachopoulos C, Aznaouridis K, Stefanadis C. Prediction of Cardiovascular Events and All-Cause Mortality With Arterial Stiffness. A Systematic Review and Meta-Analysis. Eur Heart J 2010; 31(15): 1865-71.
10. Li W-F, Huang Y-Q, Feng Y-Q. Association between central haemodynamics and risk of all-cause mortality and cardiovascular disease: a systematic review and meta-analysis. J Hum Hypertens. 2019. 33(7): 531-541.
11. Khalil A, Jauniaux E, Cooper D, Harrington K. Pulse wave analysis in normal pregnancy: A prospective longitudinal study. PLoS One 2009; 4(7): 1–7.
12. Robb AO, Mills NL, Din JN, Smith IBJ, Paterson F, Newby DE et al. Influence of the menstrual cycle, pregnancy, and preeclampsia on arterial stiffness. Hypertension 2009; 53(6): 952–8.
13. Osman MW, Nath M, Khalil A, Webb DR, Robinson TG, Mousa HA.

Longitudinal study to assess changes in arterial stiffness and cardiac output parameters among low-risk pregnant women. Pregnancy Hypertens 2017; 10:256–61.

14. Iacobaeus C, Andolf E, Thorsell M, Bremme K, Jörneskog G, Östlund E et al. Longitudinal study of vascular structure and function during normal pregnancy. Ultrasound Obstet Gynecol 2017; 49(1): 46–53.
15. Franz MB, Burgmann M, Neubauer A, Zeisler H, Sanani R, Gottsauner-Wolf M et al. Augmentation index and pulse wave velocity in normotensive and pre-eclamptic pregnancies. Acta Obstet Gynecol Scand 2013; 92: 960-6
16. Mahendru AA, Everett TR, Wilkinson IB, Lees CC, McEniery CM. A longitudinal study of maternal cardiovascular function from preconception to the postpartum period. J Hypertens 2014; 32: 849-56
17. Macedo ML, Luminoso D, Savvidou MD, McEniery CM, Nicolaides KH. Maternal wave reflections anda rterial stiffness in normal pregnnacy as assessed by applanation tonometry. Hypertension 2008; 51: 1047-1051.
18. O'Callaghan KM, Hennessy A, Malvisi L, Kiely M. Central haemodynamics in normal pregnancy: a prospective longitudinal study. J Hypertens 2018; 36: 2102-2108.
19. Hausvater A, Giannone T, Sandoval YHG, Doonan RJ, Antonopoulos CN, Matsoukis IL et al. The association between preeclampsia and arterial stiffness. J Hypertens 20129; 30(1): 17-33.
20. Khalil A, Jauniaux E, Harrington K. Antihypertensive therapy and central hemodynamics in women with hypertensive disorders in pregnancy. Obstet Gynecol 2009; 113(3): 646–54.
21. Elvan-Taşpinar A, Franx A, Bots ML, Bruinse HW, Koomans HA. Central hemodynamics of hypertensive disorders in pregnancy. Am J Hypertens 2004; 17(10): 941–6.
22. Tay J, Foo L, Masini G, Bennett PR, McEniery CM, Wilkinson IB et al. Early and late preeclampsia are characterized by high cardiac output, but in the presence of fetal growth restriction, cardiac output is low: insights from a prospective study. Am J Obstet Gynecol 2018; 218(5): 517e1-517.e12.
23. Osman MW, Nath M, Breslin E, Khalil A, Webb DR, Robinson TG et al. Association between arterial stiffness and wave reflection with subsequent development of placental-mediated diseases during pregnancy: Findings of a systematic review and meta-analysis. J Hypertens 2018; 36(5): 1005-1014.

24. Khalil A, Akolekar R, Syngelaki A, Elkhouli M, Nicolaides KH. Maternal hemodynamics in normal pregnancies at 11-13 weeks' gestation. Fetal Diag Ther 2012; 32: 179-185.
25. Fetal Medicine Foundation: Birth Weight assessment. Available at https://fetalmedicine.org/research/assess/bw [Last accessed 28th February 2021]
26. World Medical Association. World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. J Am Coll Dent. 2014;81(3):14–8.
27. Osman MW, Leone F, Nath M, Khalil A, Webb DR, Robinson TG et al. Diurnal variation and repeatability of arterial stiffness and cardiac output measurements in the third trimester of uncomplicated pregnancy. J Hypertens. 2017; 35(12): 2436–42.
28. Horváth IG, Németh Á, Lenkey Z, Alessandri N, Tufano F, Kis P et al. Invasive validation of a new oscillometric device (Arteriograph) for measuring augmentation index, central blood pressure and aortic pulse wave velocity. J Hypertens. 2010; 28(10): 2068–75.
29. Khalil A, Sodre D, Syngelaki A, Akolekar R, Nicolaides KH. Maternal hemodynamics at 11-13 weeks of gestation in pregnancies delivering small for gestational age neonates. Fetal Diagn Ther 2012; 32(4): 231–8.
30. Tensiomed. Arteriograph Users Manual. Available from: https://www.tensiomed.com/assets/images/download-pdf/Tensiomed_arteriograph-02v4-00.pdf
31. Wickham H. ggplot2: Elegant Graphics for Data Analysis. New York: Springer; 2016.
32. Townsend RR, Wilkinson IB, Schiffrin EL, Avolio AP, Chirinos JA, Cockcroft JR et al. Recommendations for improving and standardizing vascular research on arterial stiffness. Hypertension 2015; 66(3): 698-722.
33. Lemogoum D, Flores G, Van den Abeele W, Ciarka A, Leeman M, Degaute JP et al. Validity of pulse pressure and augmentation index as surrogate measures of arterial stiffness during beta-adrenergic stimulation. J Hypertens. 2004; 22: 511-517.
34. Kelly RP, Hayward CS, Avolio AP, O'Rourke MF. Non-invasive determination of age-related changes in the human arterial pulse. Circulation. 1989; 80: 1852 – 1859.

35. National Institute for Health and Care Excellence (NICE). Hypertension in pregnancy: diagnosis and management [NICE Guideline NG 133]. 2019. https://www.nice.org.uk/guidance/ng133
36. Poon LC, Wright D, Thornton S, Akolekar R, Brocklehurst P, Nicolaides KH. Mini-combined test compared with NICE guidelines for early risk-assessment for pre-eclampsia: the SPREE diagnostic accuracy study. Efficacy and Mechanistic Evaluation, No. 7.8. 2020; NIHR Journal Library (Southampton).
37. Townsend R, Khalil A, Premakumar Y, Allotey J, Snell KIE, Chan C et al. Prediction of pre-eclampsia: review of reviews. Ultrasound Obstet Gynecol 2019; 54(1): 16-27.
38. Royal College of Obstetricians. The investigation and management of small-for-gestational-age fetus. 2013. Available at https://www.rcog.org.uk/globalassets/documents/guidelines/gtg_31.pdf
39. O'Gorman N, Wright D, Poon LC, Rolnik DL, Syngelaki A, de Alvarado M et al. Multicenter screening for pre-eclampsia by maternal factors and biomarkers at 11-13 weeks' gestation: comparison with NICE guidelines and ACOG recommendations. Ultrasound Obstet Gynecol 2017; 49(6): 756-760.
40. Crovetto F, Crispi F, Scazzocchio E, Mercade I, Meler E, Figueras F et al. First-trimester screening for early and late small-for-gestational-age neonates using maternal serum biochemistry, blood pressure and uterine artery Doppler. Ultrasound Obstet Gynecol 2014; 43(1): 34-40.
41. Li J, Wang B, Cai A, Yuan Q, Ding H, Zhao D. Carotid arterial wall stiffness correlates positively with impedance of the umbilical and uterine arteries in women with preeclampsia. J Clin Ultrasound. 2019; 47: 27-35.
42. Everett TR, Mahendru AA, McEniery CM, Wilkinson IB, Lees CC. Raised uterine artery impedance is associated with increased maternal arterial stiffness in the alte second trimester. Placenta. 2012; 33(7): 572-2.

Table 1. Characteristics of the study population.

Baseline Demographics		
Maternal age (years)		30 (26 – 33)
Maternal Height (cm)		165 (160 – 169)
Booking body mass index (kg/m^2)		23 (21 – 25)
Current Smoker		3 (1.2)
Ethnicity:	Black African/ Caribbean	12 (4.9)
	East Asian	3 (1.2)
	Middle Eastern	2 (0.8)
	South Asian	34 (13.9)
	White British/ European	193 (79.1)
Parity:	0	111 (45.5)
	1	91 (37.3)
	2	34 (13.9)
	≥3	8 (3.3)
Pregnancy Outcomes		
Gestational age at delivery (days)		279 (259 – 285)
Birth weight centile		57 (32 – 79.75)

Data presented as number (percentage), or median (interquartile range).

Table 2. Brachial Augmentation Index (%) by gestational age (GA) and centile.

Gestational age (weeks)	10th	25th	50th	75th	90th
12	-73.26	-64.44	-54.63	-44.82	-36.00
13	-74.77	-66.08	-56.42	-46.76	-38.06
14	-76.17	-67.60	-58.07	-48.55	-39.97
15	-77.46	-68.99	-59.59	-50.19	-41.73
16	-78.64	-70.27	-60.98	-51.69	-43.32
17	-79.71	-71.43	-62.24	-53.04	-44.76
18	-80.68	-72.47	-63.36	-54.24	-46.04
19	-81.54	-73.40	-64.35	-55.30	-47.16
20	-82.29	-74.20	-65.21	-56.21	-48.12
21	-82.93	-74.88	-65.93	-56.98	-48.93
22	-83.47	-75.44	-66.52	-57.60	-49.57
23	-83.90	-75.88	-66.98	-58.08	-50.06
24	-84.22	-76.21	-67.31	-58.40	-50.39
25	-84.43	-76.41	-67.50	-58.59	-50.57
26	-84.54	-76.49	-67.56	-58.62	-50.58
27	-84.53	-76.46	-67.49	-58.52	-50.44
28	-84.42	-76.30	-67.28	-58.26	-50.15
29	-84.20	-76.02	-66.94	-57.86	-49.69
30	-83.86	-75.63	-66.47	-57.32	-49.08
31	-83.42	-75.11	-65.87	-56.63	-48.32
32	-82.87	-74.47	-65.13	-55.80	-47.40
33	-82.20	-73.71	-64.26	-54.82	-46.32
34	-81.43	-72.82	-63.26	-53.70	-45.09
35	-80.54	-71.82	-62.13	-52.43	-43.71
36	-79.55	-70.69	-60.86	-51.02	-42.17
37	-78.43	-69.44	-59.46	-49.47	-40.48
38	-77.21	-68.07	-57.92	-47.77	-38.64
39	-75.87	-66.58	-56.26	-45.93	-36.64
40	-74.42	-64.97	-54.46	-43.95	-34.49
41	-72.86	-63.23	-52.53	-41.82	-32.19
42	-71.18	-61.37	-50.46	-39.56	-29.74

The estimates of centiles are based on the linear mixed model of Brachial Augmentation Index (BrAIx) for different values of gestational age (week) at the mean maternal age (29.6 weeks) and heart rate (87.4).

Table 3. Aortic Augmentation Index (%) by gestational age (GA) and centile

Gestational age (weeks)	10th	25th	50th	75th	90th
12	-0.68	4.07	9.35	14.63	19.39
13	-1.24	3.42	8.60	13.77	18.43
14	-1.74	2.82	7.90	12.97	17.54
15	-2.20	2.28	7.26	12.24	16.72
16	-2.62	1.78	6.67	11.56	15.97
17	-2.99	1.34	6.14	10.95	15.28
18	-3.32	0.94	5.67	10.41	14.67
19	-3.61	0.59	5.26	9.93	14.13
20	-3.86	0.29	4.90	9.52	13.67
21	-4.06	0.04	4.61	9.17	13.27
22	-4.23	-0.16	4.36	8.89	12.96
23	-4.37	-0.32	4.18	8.67	12.72
24	-4.46	-0.43	4.05	8.53	12.56
25	-4.53	-0.50	3.98	8.45	12.48
26	-4.56	-0.52	3.96	8.45	12.49
27	-4.56	-0.50	4.01	8.52	12.57
28	-4.53	-0.44	4.11	8.65	12.74
29	-4.47	-0.33	4.26	8.86	13.00
30	-4.39	-0.19	4.48	9.14	13.34
31	-4.27	0.00	4.75	9.50	13.77
32	-4.14	0.23	5.08	9.93	14.29
33	-3.98	0.50	5.46	10.43	14.90
34	-3.79	0.80	5.90	11.01	15.60
35	-3.58	1.15	6.40	11.66	16.39
36	-3.35	1.54	6.96	12.38	17.27
37	-3.09	1.96	7.57	13.18	18.24
38	-2.81	2.43	8.24	14.06	19.30
39	-2.51	2.93	8.97	15.01	20.45
40	-2.18	3.47	9.75	16.04	21.69
41	-1.84	4.05	10.60	17.14	23.03
42	-1.47	4.67	11.49	18.32	24.46

The estimates of centiles are based on the linear mixed model of Aortic Augmentation Index (AoAIx) for different values of gestational age (week) at the mean maternal age (29.6 weeks) and heart rate (87.4).

Table 4. Aortic pulse wave velocity (m/s) by gestational age (GA) and centile

Gestational age (weeks)	10th	25th	50th	75th	90th
12	6.59	7.11	7.69	8.26	8.78
13	6.51	7.04	7.63	8.22	8.75
14	6.44	6.98	7.58	8.18	8.72
15	6.37	6.92	7.53	8.15	8.69
16	6.32	6.87	7.50	8.12	8.68
17	6.26	6.83	7.47	8.10	8.67
18	6.22	6.80	7.44	8.08	8.66
19	6.18	6.77	7.42	8.08	8.67
20	6.15	6.74	7.41	8.08	8.68
21	6.12	6.73	7.41	8.08	8.69
22	6.10	6.72	7.41	8.09	8.71
23	6.09	6.72	7.41	8.11	8.74
24	6.08	6.72	7.43	8.14	8.77
25	6.08	6.73	7.45	8.17	8.81
26	6.09	6.75	7.48	8.20	8.86
27	6.11	6.77	7.51	8.25	8.91
28	6.13	6.80	7.55	8.30	8.97
29	6.16	6.84	7.60	8.35	9.03
30	6.19	6.88	7.65	8.41	9.10
31	6.23	6.93	7.71	8.48	9.18
32	6.28	6.99	7.77	8.56	9.26
33	6.34	7.05	7.85	8.64	9.35
34	6.40	7.12	7.92	8.73	9.45
35	6.47	7.20	8.01	8.82	9.55
36	6.54	7.28	8.10	8.92	9.66
37	6.62	7.37	8.20	9.03	9.78
38	6.71	7.47	8.30	9.14	9.90
39	6.80	7.57	8.41	9.26	10.03
40	6.90	7.68	8.53	9.39	10.16
41	7.01	7.79	8.66	9.52	10.30
42	7.12	7.91	8.79	9.66	10.45

The estimates of centiles are based on the linear mixed model of Pulse wave velocity (PWV) for different values of gestational age (week) at the mean maternal age (29.6 weeks), heart rate (87.4) and mean arterial pressure (82.0 mmHg).

FIGURES

FIGURE 1 Brachial augmentation index throughout gestation.

FIGURE 2 Aortic augmentation index throughout gestation.

FIGURE 3 Aortic pulse wave velocity throughout gestation.

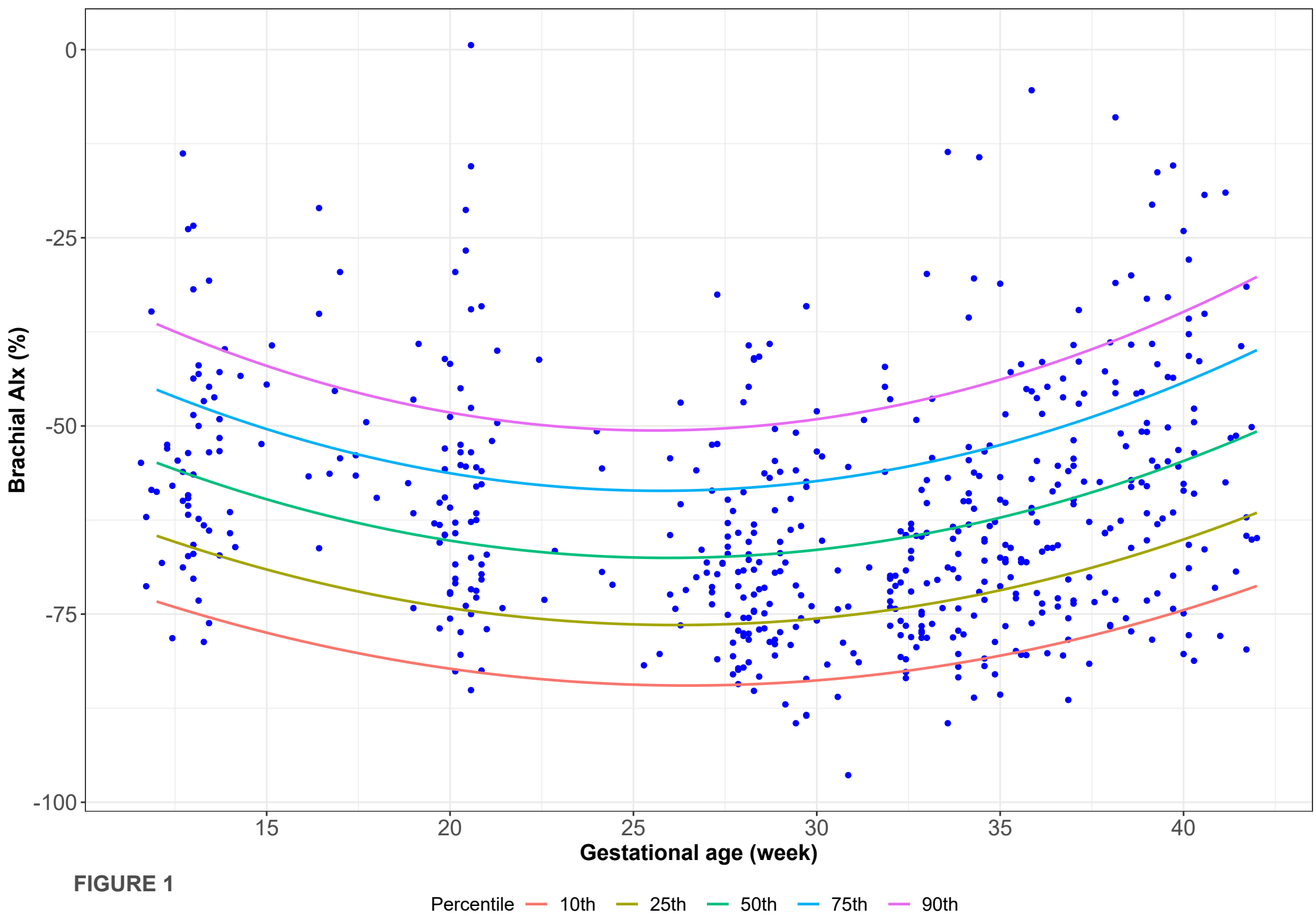
0
-25
-50
-75
-100
Brachial AIx (%)
15
20
25
30
35
40
Gestational age (week)
Percentile
10th
25th
50th
75th
90th

FIGURE 1

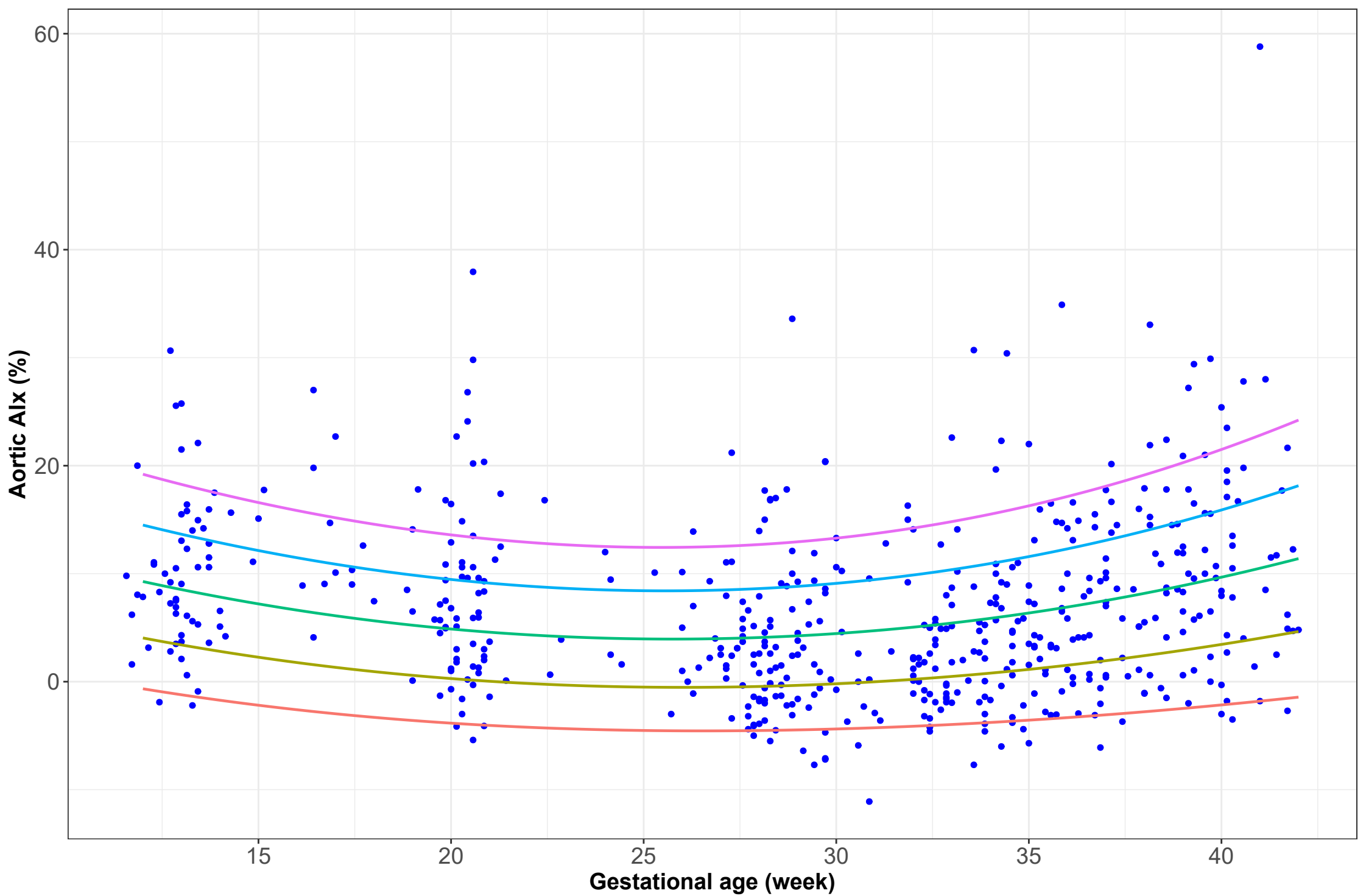
60
40
20
0
Aortic AIx (%)
15
20
25
30
35
40
Gestational age (week)
Percentile
10th
25th
50th
75th
90th

FIGURE 2

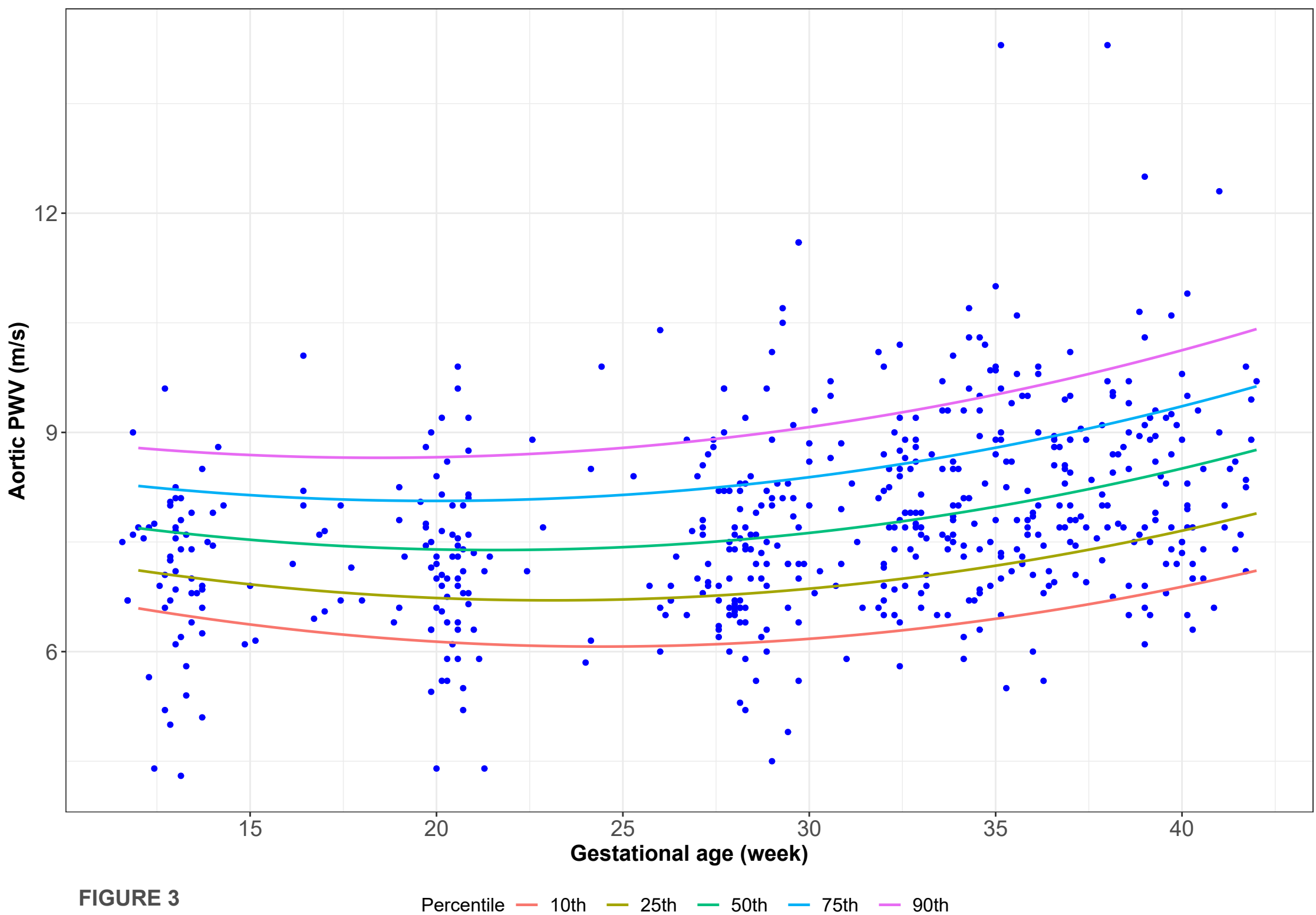
Aortic PWV (m/s)
12
9
6
15
20
25
30
35
40
Gestational age (week)
Percentile
10th
25th
50th
75th
90th

FIGURE 3