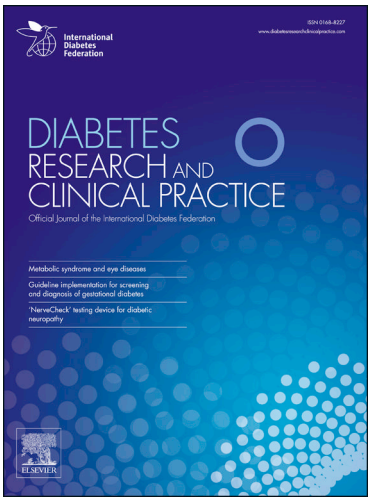

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Mohamed Waseem Osman, Mintu Nath, Asma Khalil, David R. Webb, Thompson G. Robinson, Hatem A. Mousa

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The effects of metformin on maternal haemodynamics in gestational diabetes mellitus: A pilot study

Mohamed Waseem Osman[1], Mintu Nath[2], Asma Khalil[3], David R Webb[4], Thompson G. Robinson[5], Hatem A.Mousa[6]

[1] Clinical Research Fellow, University Hospitals of Leicester, mwo3@le.ac.uk

[2] Senior Biomedical Statistician, Department of Cardiovascular Sciences and NIHR Leicester Biomedical Research Centre, University of Leicester, mn193@leicester.ac.uk

[3]Consultant/ Reader in Maternal Fetal Medicine, St George's University of London, akhalil@sgul.ac.uk

[4] Clinical Senior Lecturer and Honorary Consultant Physician in Diabetes Medicine, Diabetes Research Centre, University of Leicester, david.webb@uhl-tr.nhs.uk

[5] Professor of Stroke Medicine, Department of Cardiovascular Sciences and NIHR Leicester Biomedical Research Centre, University of Leicester, tgr2@le.ac.uk

[6]Consultant/ Honorary Senior Lecturer in Maternal and Fetal Medicine, University of Leicester, tommy.mousa@uhl-tr.nhs.uk

Contact author address:

Dr M.W Osman

University Hospitals of Leicester

Leicester Royal Infirmary

Infirmary Close

LE1 5WW

Mwo3@le.ac.uk

ABSTRACT

Background

Gestational diabetes mellitus (GDM) is a major clinical challenge and is likely to remain so as the incidence of GDM continues to increase

Aim

To assess longitudinal changes in maternal haemodynamics amongst women diagnosed with GDM requiring either metformin or dietary intervention in comparison to low-risk healthy controls.

Methodology

Fifty-six pregnant women attending their first appointment at the GDM clinic and 60 low-risk healthy pregnant controls attending their routine antenatal clinics were recruited and assigned to three groups: GDM Metformin (GDM-M), GDM Diet (GDM-D) and Control. Non-invasive assessment of maternal haemodynamics, using recognised measures of arterial stiffness and central blood pressure (Arteriograph®), were undertaken under controlled conditions within four gestational windows: antenatal; AN1 (26-28 weeks), AN2 (32-34 weeks) and AN3 (37-40 weeks), and postnatal (PN) (6-8 weeks after delivery). Data were analysed using a linear mixed model incorporating gestational age and other relevant predictors, including age, blood pressure (BP), baseline bodyweight and pulse as fixed effects, and patient as a random effect.

Results

Fitted linear mixed models showed evidence of a two-way interaction effect between groups (GDM-D, GDM-M and Control) and stages of gestation (AN1, AN2, AN3 and PN) for maternal haemodynamic parameters: brachial artery augmentation index (AIx) ($p=0.004$), aortic AIx ($p=0.008$), and central systolic BP ($p=0.001$). However, differences in respect of aortic pulse wave velocity ($p=0.001$) and heart rate ($p<0.001$) were only significant for gestational stage. At AN2, we did not observe any evidence that the mean brachial Aix in the GDM-M was different from the control group ($p=0.158$).

Conclusion

AIx and central systolic BP measures of arterial stiffness are adversely affected by GDM in comparison to controls during pregnancy. The possible beneficial effects of metformin therapy seen at 32 to 34 weeks of gestation require further exploration.

INTRODUCTION

Pregnancy is associated with significant changes in maternal haemodynamics and measures of arterial stiffness across each trimester(1). In particular, significant increases in arterial stiffness and wave reflection parameters are noted amongst pregnant women who subsequently develop pre-eclampsia and small for gestational age foetuses(2), as well as those with known pre-eclampsia(3). Cross-sectional studies(4-6) conducted in late pregnancy or immediately post-partum have suggested an independent link between arterial stiffness and gestational diabetes mellitus (GDM), with increased pulse wave velocity (PWV) and augmentation index (AIx) in GDM compared to women with normal glucose tolerance. Furthermore, GDM may be associated with chronic effects on vascular haemodynamics, impacting longer-term outcomes. Women with a history of GDM have evidence of endothelial dysfunction and are at increased risk of vascular complications independent of known risk factors(7, 8). However, these studies are limited by sample size and are cross-sectional in nature. A clearer understanding of changes in arterial stiffness throughout pregnancy and post-partum between GDM and healthy women may be of predictive value.

Pregnancy-associated diabetes has historically only been treated with dietary modification and/or insulin. Metformin was also considered unsafe, as the drug crosses the placenta, posing a potential threat to the foetus. Glyburide, a sulphonylurea, was the second line treatment after Insulin in the US for GDM. However, it has now superseded insulin as the most common treatment since 2007; being used in over 64.5% of women with GDM(9). Though this change was due to the perception that Glyburide does not cross the placenta(10), there have been reports of an increased rate of pre-eclampsia, neonatal jaundice requiring phototherapy, increased duration of stay in the neonatal unit, macrosomia and neonatal hypoglycaemia following its use(11). Results from a systematic review and meta-analysis established that glyburide is inferior to both metformin and insulin in the treatment of women with GDM(12). Results from several observational and randomised trials over the past decade have confirmed that metformin use in pregnancy is safe, with no evidence of increased birth defects or other pregnancy-related complications(13-16), though it remains unlicensed for use in pregnancy.

GDM is now treated with dietary and lifestyle modification, metformin and if needed insulin(17). Metformin may have cardiovascular benefits(18); the UK Prospective Diabetes Study (UKPDS) demonstrating that metformin use in obese patients with type 2 diabetes is associated with beneficial effects on cardiovascular disease outcomes, with a 36% and 39% relative risk reduction in all-cause mortality and myocardial infarction, respectively(19). In a randomised, placebo controlled trial, short-term metformin therapy was found to improve arterial stiffness and endothelial function in young women with polycystic ovarian syndrome (PCOS)(20).

It is important to assess whether metformin use may be associated with potential benefits on vascular stiffness in GDM, as this may also be associated long-term cardiovascular benefit. Therefore, a pilot study was undertaken to assess i) longitudinal changes in maternal haemodynamics, including AIx and PWV parameters among pregnant women with GDM compared to healthy pregnancy; and ii) to explore whether metformin compared to diet-only modification had beneficial effects on maternal haemodynamic assessments.

METHODS

Fifty-six consecutive women with a singleton viable pregnancy attending their first appointment at the GDM clinic and a further 60 low-risk healthy pregnant women attending their routine antenatal dating ultrasound scan at the University Hospitals of Leicester NHS Trust, were invited to participate in the study. Screening for women at risk of GDM is always offered to pregnant women with: BMI greater than 30kg/m^2, previous macrosomic baby weighing more than 4.5kg, previous history of GDM, family history of diabetes in a first degree relative, or of minority ethnic origin with a high prevalence of diabetes(17). Screening was offered at 24-28 weeks of gestation and diagnosis of GDM was made if the woman had either: a fasting plasma glucose level of 5.6 mmol/litre or above OR a 2-hour plasma glucose level of 7.8 mmol/litre or above(17).

Women screening positive for GDM were included into the GDM group. Participants were excluded if they were current smokers, had a multiple pregnancy, foetal anomalies, pre-pregnancy or pregnancy-induced hypertension, pre-eclampsia, thyroid disease requiring medication, renal disease, type1 or 2 diabetes mellitus, GDM requiring insulin or were

taking any medication that could affect the cardiovascular system. In addition, eligibility into the control group required the participants to have body mass index (BMI) between 18.5-24.9Kg/m^2 at booking and not to have diabetes mellitus.

Following informed written consent (Stanmore National Research Ethics Committee, Reference 12/LO/0810), maternal characteristics, including medical history, were obtained. Participants were separated into two groups, GDM and control. The GDM group was further divided into two groups according to GDM management: diet modification (GDM-D) or metformin therapy (GDM-M). Upon diagnosis of GDM, women were reviewed in a multidisciplinary GDM clinic with a diabetes nurse and dietician, and were counselled on the diagnosis and dietary changes needed. They were then reviewed two weeks later at around 30 to 31 weeks of gestation to review the effects of dietary adjustments on blood sugar control. Women with poor control were then immediately started on metformin (500mg po bd) and therefore all women in the GDM-M group were on metformin during the AN2 and AN3 measurements. Compliance was monitored by checking the electronic readings stored on the glucometer by the diabetic physician and women requiring insulin were excluded (n=4).

Participants were assessed at four gestational windows: antenatal 26-28 [AN1], 32-34 [AN2] and 37-40 weeks [AN3]) and post-natal at 6-8 weeks after delivery [PN]. They were assessed in a temperature-controlled room (22°C) in a semi recumbent position. Participants were rested for a minimum of ten minutes, and were free from distraction, including speaking and moving, during the assessments. Assessments were not carried out following a large meal or caffeine intake. Arterial stiffness measurements of PWV and AIx were obtained with the Arteriograph® (Tensiomed Ltd, Hungary). The Arteriograph® cuff was applied to the right arm over the brachial artery for an estimation of central systolic blood pressure (BP), aortic PWV and AIx, as previously described(21). Recordings were made by one observer (MWO), who had received appropriate training in use of the Arteriograph®.

Statistical analysis

We modelled the changes at gestational and post-natal stages for brachial and aortic AIx, and PWV, by separate linear mixed models, incorporating group (three levels: Diet [GDM-D],

Metformin [GDM-M] and Control), and gestational stage (four levels: AN1, AN2, AN3, PN), as fixed effects and individual participant as a random effect. If statistically significant ($p<0.05$), the final model also included the two-way interaction term of group and gestational stage. The final models for brachial and aortic Aix also included baseline body weight, heart rate and central mean arterial pressure as additional fixed effects, while baseline body weight, heart rate and systolic blood pressure were included as fixed effects for PWV. The variables height and age did not demonstrate a significant effect either in single or multi-variable models; hence were not considered in the final model. Since the two-way interaction effect of group and gestational stage for brachial and aortic AIx and central systolic BP was statistically significant, we compared the mean differences between Control, GDM-D and GDM-M groups at each of the four gestational windows and the estimated probabilities of 12 mean differences were subsequently adjusted by Bonferroni correction to account for multiple comparisons. For variables where the two-way interaction effect was not statistically significant, we did not conduct any treatment group comparison at the predefined time points.

All statistical tests were two-sided with type 1 error rate (p-value) of 0.05 to determine statistical significance. All statistical analyses were carried out using the R software version 3.3 with appropriate R packages (nlme, multcomp, ggplot2) (R Core Team, 2016).

RESULTS

A total of one hundred and sixteen women were recruited to the study; 56 women with GDM, of whom 33 of mean age 31.7 years (SD 5.4 years) were in the GDM-M group and 23 of mean age 33.1 years (4.7 years) were in the GDM-D group, and 60 women of mean age 29.7 years (SD 5.3 years) in the control group. Baseline characteristics are described in Table 1.

Brachial Augmentation index

The fitted linear mixed model showed strong evidence of a two-way interaction effect between group (Control, GDM-D and GDM-M) and gestational stage (AN1, AN2, AN3 and PN) for brachial AIx (p=0.004) and aortic AIx (p=0.008) after adjusting for heart rate, central mean arterial pressure and baseline body weight.(Table 2 and Supplementary Tables 1 and 2, Figure 1). At AN1, the mean (±SE) brachial AIx (%) of GDM-M (-58.20±2.41) was significantly different (adjusted p = 0.020) from the control group (-68.15±1.78). The mean difference between brachial AIx (%) GDM-D (-59.02±2.65) although showed statistically significance (p=0.005) before Bonferonni correction, the adjusted p-value (0.055), however, exceeded the pre-assigned type 1 error of 0.05. There was no evidence that mean brachial AIx were significantly different between two GDM groups at AN1 (p=0.817). At AN2, only the mean difference between GDM-D (-46.53±3.80) and control (-68.91±2.32) groups was statistically significant (adjusted p<0.001). We did not observe mean brachial AIx values were significantly different between groups at AN3, however, postnatally, both GDM-M (-24.25±8.23) and GDM-D(-24.21±6.90) were significantly different from the control (-44.10±3.76) group (adjusted p=0.023 and 0.034, respectively). There was no evidence that mean brachial AIx differed between GDM-M and GDM-D postnatally (p=0.790).

Aortic augmentation index

Similar to brachial AIx , we also found strong evidence (p=0.008) of a two-way interaction effect between group (Control, GDM-D and GDM-M) and gestational stage (AN1, AN2, AN3 and PN) for aortic AIx following adjustment for baseline body weight, heart rate and central mean arterial pressure (Table 2 and Supplementary Tables 1 and 2 , Figure 2). At AN1, the mean (±SE) aortic AIx (%) of GDM-M (8.08±1.25) was significantly different (adjusted p = 0.033) from the control group (3.18±0.92). The mean difference between aortic AIx (%) GDM-D (6.99±1.38) was statistically significant (p=0.023), but following Bonferroni correction, the adjusted p-value (0.277) exceeded the pre-assigned type 1 error of 0.05. On the other hand, only the mean difference of aortic AIx between GDM-D (12.72±1.97) and control (2.84±1.20) groups was statistically significant (adjusted p<0.001) at AN2. We did not observe mean aortic AIx values were significantly different between groups at AN3.

Postnatally, both GDM-M (17.53±2.39) and GDM-D (16.86±2.21) were significantly different from the control (8.94±1.75) group (adjusted p=0.036 and 0.030, respectively). There was no evidence that mean aortic AIx differed between GDM-M and GDM-D postnatally (p=0.828).

Pulse wave velocity

Only mean differences between gestational stages (p=0.003), not between groups (p=0.511), were statistically significant for PWV, after adjusting for baseline body weight, heart rate and systolic blood pressure (Table 2 and Supplementary Tables 1 and 2, Figure 3). The mean PWV values were significantly higher at AN2 (p=0.005) and PN (p=0.003) compared with the value at AN1, but the mean PWV at AN3 was not significantly different from the mean PWV at AN1 (p=0.458).

DISCUSSION

This longitudinal pilot study has demonstrated that pregnancies affected by GDM may be associated with significant alterations in maternal haemodynamics, as demonstrated by temporal changes in AIx, BP and PWV. Exploring the effect of metformin on maternal haemodynamics, we observed a potential interaction effect suggesting that metformin may attenuate the GDM associated AIx rise during the second trimester as demonstrated between 32-34 weeks of pregnancy.

Our study describes differences in arterial stiffness measurements over the course of GDM and normal glucose tolerant pregnancies. However, apart from AIx, there was no significant difference in arterial stiffness parameters between the GDM and control groups in pregnancy or postpartum. Further merit is given to this finding when the comparison is performed at PN. The GDM-M group would now not be on any therapy, as metformin is stopped on the day of delivery, yet we found a significant mean difference between the GDM-D and GDM-M vs the control group, with a marked increase in AIx in the GDM metformin group at PN. This trend could mean that metformin may offer a protective effect on the vasculature and once stopped, the protection ceases. This is in keeping with the understanding that AIx may reflect the early changes of arterial stiffness, as the changes are more prevalent in younger individuals (age<50years), whereas, PWV may reflect the later or chronic changes in arterial stiffness as age related changes are more marked in individuals over the age of 50(22). In addition, our results are in keeping with previous work demonstrating that AIx, increases with advancing gestational from 28 weeks of gestation to term(23-25). The pattern of AIx in this study, however, demonstrates a unique alteration in the expected pattern, i.e., the metformin group had an improvement in the AIx at AN3. This potential atypical trend was only present during the time of metformin treatment and reverted to the expected pattern at PN when metformin was stopped. This further strengthens the proposed effects of metformin in this population group.

Savidou et al(6) found that in patients with GDM, mean (SD) AIx (a measure of arterial wave reflection) was significantly higher compared to healthy controls, (13.1 ± 8.9% vs 0.7 ± 11.4%; p<0.001), similarly, this study found a significant difference in the AIx values in

women with GDM managed with metformin or diet modification in comparison to the control group . Our study found that at AN1, mean AIx was higher in the GDM-M group, 4.90% (11.02), in comparison to controls.

Savidou et al(6) also found that in patients with GDM the mean (SD) PWV was marginally increased compared to healthy controls (6.0 ± 1.5 vs 5.4 ± 0.6 m/s; p =0.070). Similarly, in our study we found that the mean PWV is higher in women with GDM, with the mean value in the GDM-D group being 8.54 m/s (1.51) and in the GDM-M group being 8.97 m/s (1.71), in comparison to 8.28m/s in the healthy control group. However, the differences were not statistically significant, p=0.494 (Figure2). This re-affirms the findings from two previous studies(4, 5) which found that there was no significant difference in PWV between GDM and control groups. Additionally, we found that the mean difference between the stages of pregnancy was significant and observed that the pattern of PWV in the diet and healthy control group followed a pattern, grossly resembling a sine wave, similar to the findings of other studies of longitudinal changes of PWV during pregnancy(26, 27) .However, the metformin group did not demonstrate any such pattern. The PWV in the metformin group did not exhibit the characteristic reduction in the third trimester of pregnancy, remaining higher at AN3 and PN.

The current study has several strengths. We have used a well-defined inclusion and exclusion criteria to limit the effect of any maternal condition on haemodynamic parameters. We have longitudinal follow-up to make sure that changes are directly related to the same group. In comparison, Savvidou et al(6) , however, had a GDM population that had a significantly higher blood pressure than the control subjects, and this may have influenced the results within the GDM group, as it is understood that PWV in known to increase with BP, and BP is a recognised determinant of aortic PWV(28-30). Equally, the control group in the study of Bulzico et al(5) had a higher prevalence of T2DM and cardiovascular disease in their first degree relatives(31), which may be associated with higher aortic stiffness(31). Throughout our study, BP in both groups over all the four time points remained within the normal range, however Central mean (SD) BP was significantly higher in the GDM group in comparison to the healthy control, 67.02mmHG (13.25) vs 61.25mmHG (9.57), p=0.02. Furthermore, Central diastolic BP and Central mean BP were significantly higher in the GDM metformin group compared to the healthy control group,

p=0.01 and p=0.06, respectively. Therefore, it could be argued that the findings of an increased PWV in the GDM groups are a result of an increase in BP and possibly age.

We cannot fully explain the cause of this interesting observation which may allude to Metformin having pleiotrophic actions yet unknown to us, therefore more research is necessary. Even though we did not find that metformin had a significant effect on all maternal haemodynamic parameters in women with GDM, the mean difference (SD) between the GDM-M and GDM-D groups for aortic AIx at AN3 was statistically significant (p=0.033), the AIx in the GDM-M group changed more than in the GDM-D group, -54.54%(22.85) vs -41.04 (31.48), respectively. This may be attributed to a possible beneficial effect of metformin on the vascular walls of arteries. Further work with larger studies are required to explore this pattern more closely.

The study has certain limitations. The small number of participants (n=56), however, an attempt to overcome this was made with the longitudinal assessment of women on four separate occasions. Unfortunately, loss to follow-up is an understood weakness of a longitudinal study, and the authors found a higher loss to follow up in the postnatal period. This was attributed to the practical difficulties to a new mother in the puerperium. We employed the mixed effects model to account for the missing values. Ideally, a randomised controlled trial having defined arterial stiffness outcomes with a larger population and consistent methodological designs are required to further explore these findings. One could argue that the current observation may only be applicable to this population with a distinct ethnic mix. It was also noted that the GDM-M group had a greater mean (SD) fasting and 2hr OGTT plasma glucose level in comparison to the GDM-D group, (4.53[0.62] vs. 5.11[0.70]) and (8.07[0.92] vs. 8.54[1.22]), respectively. These findings demonstrate the potentially significant effect hyperglycaemia has on the vascular wall, even over a short duration in pregnancy, and highlighting the beneficial effects of metformin. This study did not evaluate women prior to 26 weeks of pregnancy, and therefore, women in the GDM group may have prior undiagnosed diabetes. However, as much as there is a case for glycaemic memory(32) influencing the haemodynamic measurements for the worse, there is a stronger case displaying the early and beneficial effects of metformin. There are numerous studies(33-36) recommending that early intensive control of hyperglycaemia is able to reduce the risk of diabetic micro- and macro-vascular complications, therefore, the work

done demonstrating the pleiotrophic effects of metformin are welcome. It is important to stress that the current study did not examine the risk of placental-mediated diseases. It is generally understood that arterial stiffness increases with age(30); however, our GDM-M group were younger than the GDM-D group and demonstrated an improvement in their AIx after metformin therapy.

Even though there are no validation studies of the Arteriograph® in pregnancy, it has been extensively used in pregnancy research(21, 37, 38). The accuracy of SBP, PWV and AIx determination have been validated against invasive and non-invasive measurements(21, 39), in non-pregnant populations. Furthermore, triplicate measurements in a previous repeatability study performed by the authors showed moderate-to-high correlation between observations on the same woman for all Arteriograph variables (estimates of intra-class correlation ranged from 0.49 to 0.91)(40).

CONCLUSION

In conclusion, our study documented that that AIx and central systolic BP measures are adversely affected by GDM in comparison to controls during pregnancy. Metformin intake may influence changes in AIx over the course of pregnancy. The possible beneficial effects of metformin therapy seen at 32 to 34 weeks of gestation require further exploration in a future intervention trial.

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Table 1: Baseline characteristics for all study participants at time of recruitment at AN1

		Control	GDM diet	GDM metformin
		n=60	n=23	n=33
Age (years)		29.71 (5.33)	33.13(4.72)	31.76(5.43)
Height at booking (cm)		162.80 (7.09)	159.26(6.54)	163.33 (6.31)
Baseline body weight at booking(kg)		66.1(9.6)	71.87(16.86)	82.48 (19.99)
Body weight at recruitment (kg)		69.26 (16.79)	78.11(14.81)	88.00 (32.80)
Body surface area **(BSA)** at booking (m^2)		1.79(0.19)	1.80 (0.17)	1.93 (0.2)
Body mass index **(BMI)** at booking (kg/m^2)		24.16(5.36)	27.96 (6.03)	32.13 (9.74)
Body mass index **(BMI)** at recruitment (kg/m^2)		24.56(3.10)	30.76 (5.37)	32.80 (5.17)
Gestational age at recruitment (weeks + days)		28+2 (1.1)	28+3 (1.6)	27+2 (1.8)
Gestational age at OGTT (weeks + days)		Not Available	28+3 (1.6)	27+2 (1.8)
	Normal OGTT			
OGTT fasting	≥5.6mmol/litre		4.53(0.62)	5.11(0.70)
OGTT 2hrs	≥7.8mmol/litre		8.07 (0.92)	8.54 (1.22)
HBA1c at AN2 (%)		Not available	5.26 (0.36)	5.57(0.43)
HBA1c at AN2 (mmol/mol)		Not available	33.90 (4.04)	37.38(4.63)
Parity	P0	27 (45%)	8 (34.8%)	15 (45.4%)
	P1	26 (43.3%)	11(47.9)	9 (27.3%)
	P2	6 (10.0%)	2 (8.7%)	5 (15.3%)
	P3	0	1 (4.3%)	2 (6.0%)
	P4	1 (1.7%)	1 (4.3%)	0
	P5	0	0	2 (6.0%)
Ethnicity	Asian	2 (3.3%)	9 (39.1%)	7 (21.2%)
	Caucasian	53 (88.3%)	8 (34.8%)	15 (45.5%)
	African	4 (6.8%)	1 (4.4%)	8 (24.3%)
	Far East	0	3 (13%)	1 (3%)
	Middle East	1 (1.7%)	2 (8.7%)	2 (6%)

Continuous data are presented as mean (standard deviation) and categorical data are presented as count (% of total).

Weight, height, BSA and BMI are reported at time of recruitment to the study which is AN1

Table 2: Mean (standard deviation) of maternal haemodynamic and arterial stiffness measurements in healthy pregnant (control) and gestational diabetes mellitus populations managed by diet or metformin at three antenatal and one post-partum gestational time-points

		AN1 26-28 weeks			AN2 32-34 weeks			AN3 37-40 weeks			PN 6-8 weeks			Group	Stage	Group: Stage interaction
	Units	**Control**	**GDM-D**	**GDM-M**	**Control**	**GDM-D**	**GDM-M**	**Control**	**GDM-D**	**GDM-M**	**Control**	**GDM-D**	**GDM-M**	**Global p value**	**Global p value**	**Global p value**
Heart rate	*Bpm*	90.89 (11.91)	90.14 (11.70)	92.19 (9.45)	93.57 (11.20)	88.17 (11.71)	93.31 (11.50)	86.21 (14.02)	79.94 (11.56)	85.28 (15.72)	76.15 (9.35)	73.79 (10.21)	71.87 (11.73)	*0.190*	*<0.001*	*NS*
Central Systolic BP	*mmHg*	104.72 (12.89)	107.04 (11.35)	114.88 (21.38)	111.49 (13.41)	111.23 (12.45)	117.39 (15.89)	111.79 (12.16)	108.40 (11.53)	116.21 (15.41)	110.33 (10.84)	118.16 (14.91)	120.29 (15.59)	*0.040*	*<0.001*	*0.001*
Central Diastolic BP	*mmHg*	34.49 (8.72)	35.63 (7.73)	40.71 (12.31)	37.09 (7.77)	37.28 (8.58)	40.78 (12.31)	39.31 (9.58)	39.71 (5.89)	44.93 (12.11)	39.92 (8.52)	43.58 (9.75)	43.96 (8.93)	*0.022*	*<0.001*	*NS*
Central mean BP	*mmHg*	57.90 (9.58)	59.53 (8.31)	65.43 (14.82)	37.09 (7.77)	62.69 (9.32)	66.32 (12.54)	63.47 (9.69)	62.61 (6.72)	68.69 (13.99)	63.38 (8.75)	68.44 (11.13)	69.40 (10.67)	*0.011*	*<0.001*	*NS*
Brachial AIx	**%**	-69.52 (13.16)	-61.19 (15.92)	-55.61 (21.80)	-65.49 (16.21)	-46.26 (29.99)	-56.63 (19.35)	-51.01 (17.93)	-41.04 (31.48)	-54.54 (22.85)	-44.10 (19.16)	-24.21 (27.59)	-24.25 (30.78)	0.002	<0.001	0.004
Aortic AIx	**%**	2.73 (6.39)	5.93 (7.98)	9.48 (11.02)	4.49 (8.21)	13.22 (15.89)	9.04 (9.83)	12.12 (9.92)	16.86 (15.94)	10.02 (11.57)	15.33 (9.69)	25.38 (13.97)	25.36 (15.59)	0.007	0.0002	0.007

PWV	**m/s**		8.13 (1.41)	8.05 (1.11)	8.93 (1.99)		8.58 (1.25)	9.23 (2.05)	9.27 (1.42)		8.13 (1.36)	8.39 (1.45)	8.72 (1.41)		8.19 (1.49)	8.58 (1.32)	8.80 (1.97)		*0.502*	*0.0008*	*NS*

Group: The p-value for the global main effect of group

Stage: The p-value for the global main effect of gestational stage

Group:Stage interaction: Statistical significance of the global two-way interaction of group and gestational stage.

The global p-value indicates the p-value obtained from the F-statistics based on the type 3 analysis of variance. We considered the statistical significance as $p<0.05$.

NS: Not Significant, i.e. the two-way interaction effect of group and gestational stage was not statistically significant ($p>0.05$)

BP: blood pressure; AIx: augmentation index; PWV: pulse wave velocity; AN: ante-natal; PN: post-natal; GDM-D: gestational diabetes, diet controlled; GDM-M: gestational diabetes, metformin controlled;

Supplementary Table 1: Mean (standard deviation) of maternal haemodynamic and arterial stiffness measurements in **healthy pregnant (control)** and **gestational diabetes mellitus managed by diet modification (GDM-D)** groups at three antenatal and one postpartum gestational time-points.

		AN1 26-28 weeks			AN2 32-34 weeks			AN3 37-40 weeks			PN 6-8 weeks			Group: Stage interaction
	Units	**Control**	**GDM-D**	**P value**	**Control**	**GDM-D**	**P value**	**Control**	**GDM-D**	**P value**	**Control**	**GDM-D**	**P value**	**Global p value**
Heart rate	*Bpm*	90.89 (11.91)	90.14 (11.70)	*NA*	93.57 (11.20)	88.17 (11.71)	*NA*	86.21 (14.02)	79.94 (11.56)	*NA*	76.15 (9.35)	73.79 (10.21)	NA	*NA*
Central Systolic BP	*mmHg*	104.72 (12.89)	107.04 (11.35)	*1*	111.49 (13.41)	111.23 (12.45)	*1*	111.79 (12.16)	108.40 (11.53)	*0.43*	110.33 (10.84)	118.16 (14.91)	0.17	*0.001*
Central Diastolic BP	*mmHg*	34.49 (8.72)	35.63 (7.73)	*NA*	37.09 (7.77)	37.28 (8.58)	*NA*	39.31 (9.58)	39.71 (5.89)	*NA*	39.92 (8.52)	43.58 (9.75)	NA	*NA*
Central mean BP	*mmHg*	57.90 (9.58)	59.53 (8.31)	*NA*	37.09 (7.77)	62.69 (9.32)	*NA*	63.47 (9.69)	62.61 (6.72)	*NA*	63.38 (8.75)	68.44 (11.13)	NA	*NA*
Brachial AIx	**%**	-69.52 (13.16)	-61.19 (15.92)	*0.06*	-65.49 (16.21)	-46.26 (29.99)	*<0.001*	-51.01 (17.93)	-41.04 (31.48)	*0.305*	-44.10 (19.16)	-24.21 (27.59)	0.03	*0.004*
Aortic AIx	**%**	2.73 (6.39)	5.93 (7.98)	*0.28*	4.49 (8.21)	13.22 (15.89)	*<0.001*	12.12 (9.92)	16.86 (15.94)	0.429	15.33 (9.69)	25.38 (13.97)	0.04	*0.007*
PWV	*m/s*	8.13 (1.41)	8.05 (1.11)	*NA*	8.58 (1.25)	9.23 (2.05)	*NA*	8.13 (1.36)	8.39 (1.45)	NA	8.19 (1.49)	8.58 (1.32)	NA	*NA*

Data are mean (standard deviation). P value refers to group interaction, p<0.05 indicating significance.

Group:Stage interaction: Statistical significance of the two-way interaction of group and gestational stage.

The global p-value indicates the p-value obtained from the F-statistics based on the type 3 analysis of variance. We considered the statistical significance as $p<0.05$.

NS: Not Significant, i.e. the two-way interaction effect of group and gestational stage was not statistically significant ($p>0.05$)

NA: Not available, i.e. mean values between two groups at a given time point were not compared when the two-way interaction effect of group and gestational stage was not statistically significant ($p>0.05$).

BP: blood pressure; AIx: augmentation index; PWV: pulse wave velocity; AN: antenatal; PN: postnatal; GDM-D: gestational diabetes diet controlled;

Supplementary Table 2: Maternal haemodynamic and arterial stiffness measurements in **healthy pregnant (control)** and **gestational diabetes mellitus managed with metformin (GDM-M)** groups at three antenatal and one postpartum gestational time-points.

		AN1 26-28 weeks			AN2 32-34 weeks			AN3 37-40 weeks			PN 6-8 weeks			Group:Stage interaction
	Units	**Control**	**GDM-M**	***P value***	**Control**	**GDM-M**	***P value***	**Control**	**GDM-M**	***P value***	**Normal**	**GDM-M**	**P value**	***Global p value***
Heart rate	*Bpm*	90.89 (11.91)	92.19 (9.45)	*NA*	93.57 (11.20)	93.31 (11.50)	*NA*	86.21 (14.02)	85.28 (15.72)	*NA*	76.15 (9.35)	71.87 (11.73)	*NA*	*NA*
Central Systolic BP	*mmHg*	104.72 (12.89)	114.88 (21.38)	*0.121*	111.49 (13.41)	117.39 (15.89)	*1*	111.79 (12.16)	116.21 (15.41)	*1*	110.33 (10.84)	120.29 (15.59)	*0.228*	*0.0006*
Central Diastolic BP	*mmHg*	34.49 (8.72)	40.71 (12.31)	*NA*	37.09 (7.77)	40.78 (12.31)	*NA*	39.31 (9.58)	44.93 (12.11)	*NA*	39.92 (8.52)	43.96 (8.93)	*NA*	*NA*
Central Mean BP	*mmHg*	57.90 (9.58)	65.43 (14.82)	*NA*	37.09 (7.77)	66.32 (12.54)	*NA*	63.47 (9.69)	68.69 (13.99)	*NA*	63.38 (8.75)	69.40 (10.67)	*NA*	*NA*
Brachial AIx	**%**	-69.52 (13.16)	-55.61 (21.80)	*0.020*	-65.49 (16.21)	-56.63 (19.35)	*0.158*	-51.01 (17.93)	-54.54 (22.85)	*1*	-44.10 (19.16)	-24.25 (30.78)	*0.023*	*0.04*
Aortic AIx	**%**	2.73 (6.39)	9.48 (11.02)	*0.034*	4.49 (8.21)	9.04 (9.83)	*0.22*	12.12 (9.92)	10.02 (11.57)	*1*	15.33 (9.69)	25.36 (15.59)	*0.036*	*0.007*
PWV	**m/s**	8.13 (1.41)	8.93 (1.99)	*NA*	8.58 (1.25)	9.27 (1.42)	*NA*	8.13 (1.36)	8.72 (1.41)	*NA*	8.19 (1.49)	8.80 (1.97)	*NA*	*NA*

Data are mean (standard deviation). P value refers to group: gestational stage interaction for measurements at four time-points, $p<0.05$ indicating significance.

BP: blood pressure; AIx: augmentation index; PWV: pulse wave velocity; AN: ante-natal; PN: post-natal; GDM-D: gestational diabetes, diet controlled; GDM-M: gestational diabetes, metformin controlled;

NA: Not available, i.e. mean values between two groups at a given time point were not compared when the two-way interaction effect of group and gestational stage was not statistically significant ($p>0.05$).

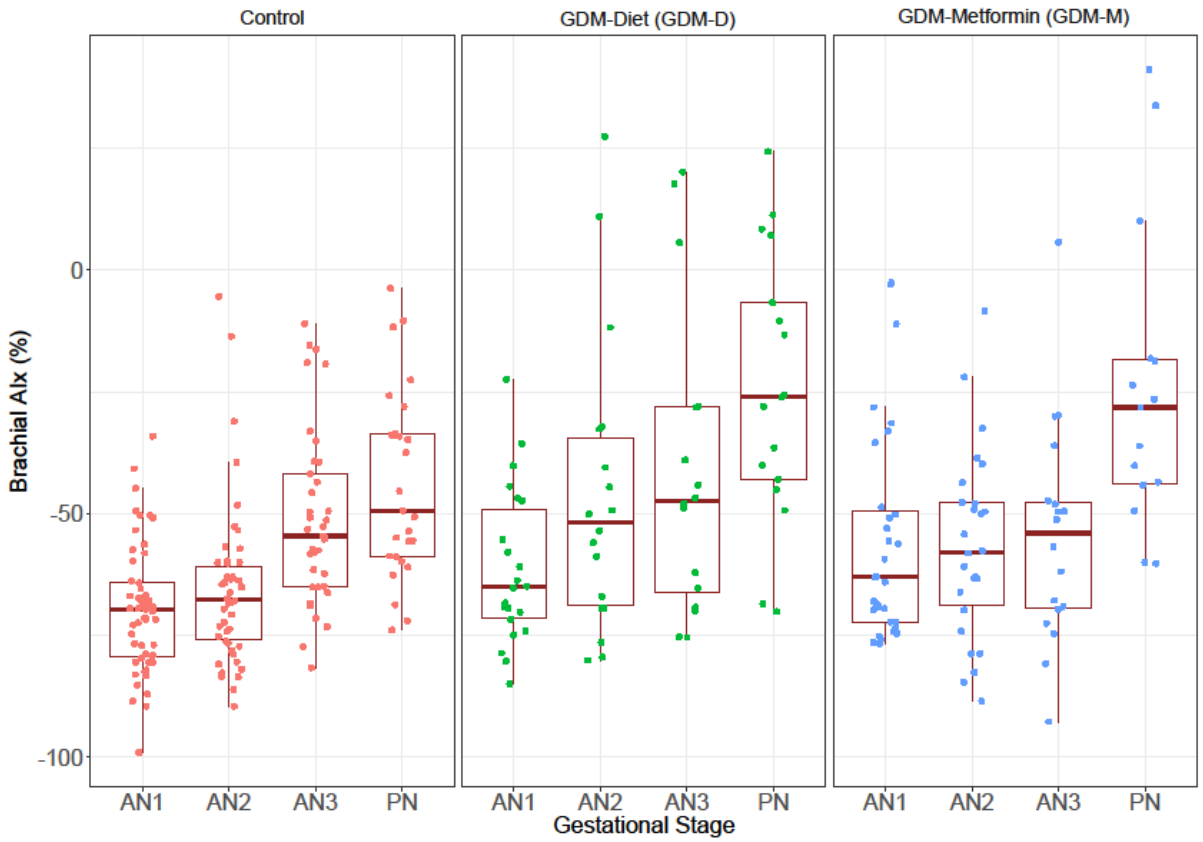

Figure 1: Measurements of Brachial AIx for participants in all three groups (points) at four time points (AN1, AN2, AN3, and PN) with the corresponding box plots showing the median and interquartile range.

AN1: 26-28 weeks: Control (n=52), GDM-D (n=22) and GDM-M (n=33)

AN2: 32-34 weeks: Control (n=51), GDM-D (n=18) and GDM-M (n=29)

AN3: 37-40 weeks: Control (n=38), GDM-D (n=17) and GDM-M (n=18)

PN: 6-8 weeks after delivery: Control (n=26), GDM-D (n=17) and GDM-M (n=15)

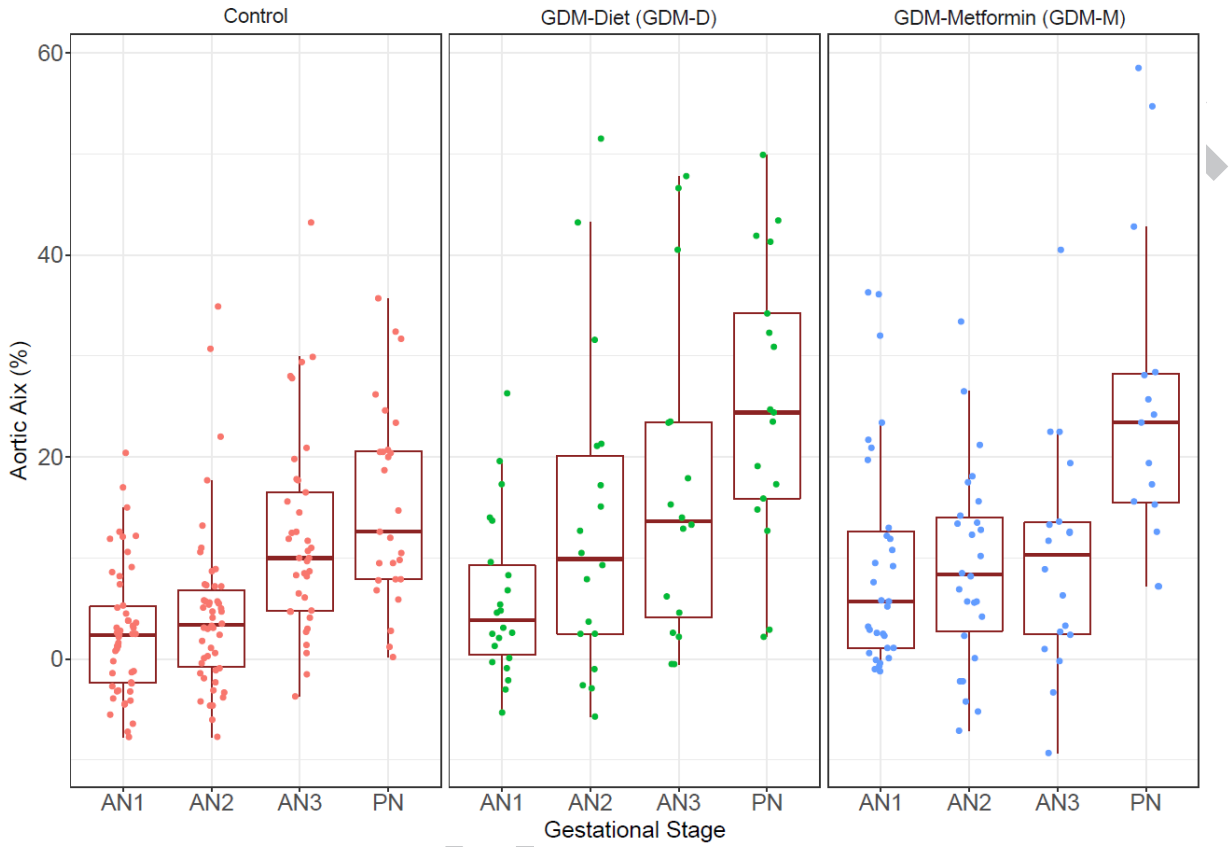

Figure 2: Measurements of Aortic AIx for participants in all three groups (points) at four time points (AN1, AN2, AN3, and PN) with the corresponding box plots showing the median and interquartile range.

AN1: 26-28 weeks: Control (n=52), GDM-D (n=22) and GDM-M (n=33)

AN2: 32-34 weeks: Control (n=51), GDM-D (n=18) and GDM-M (n=29)

AN3: 37-40 weeks: Control (n=38), GDM-D (n=17) and GDM-M (n=18)

PN: 6-8 weeks after delivery: Control (n=26), GDM-D (n=17) and GDM-M (n=15)

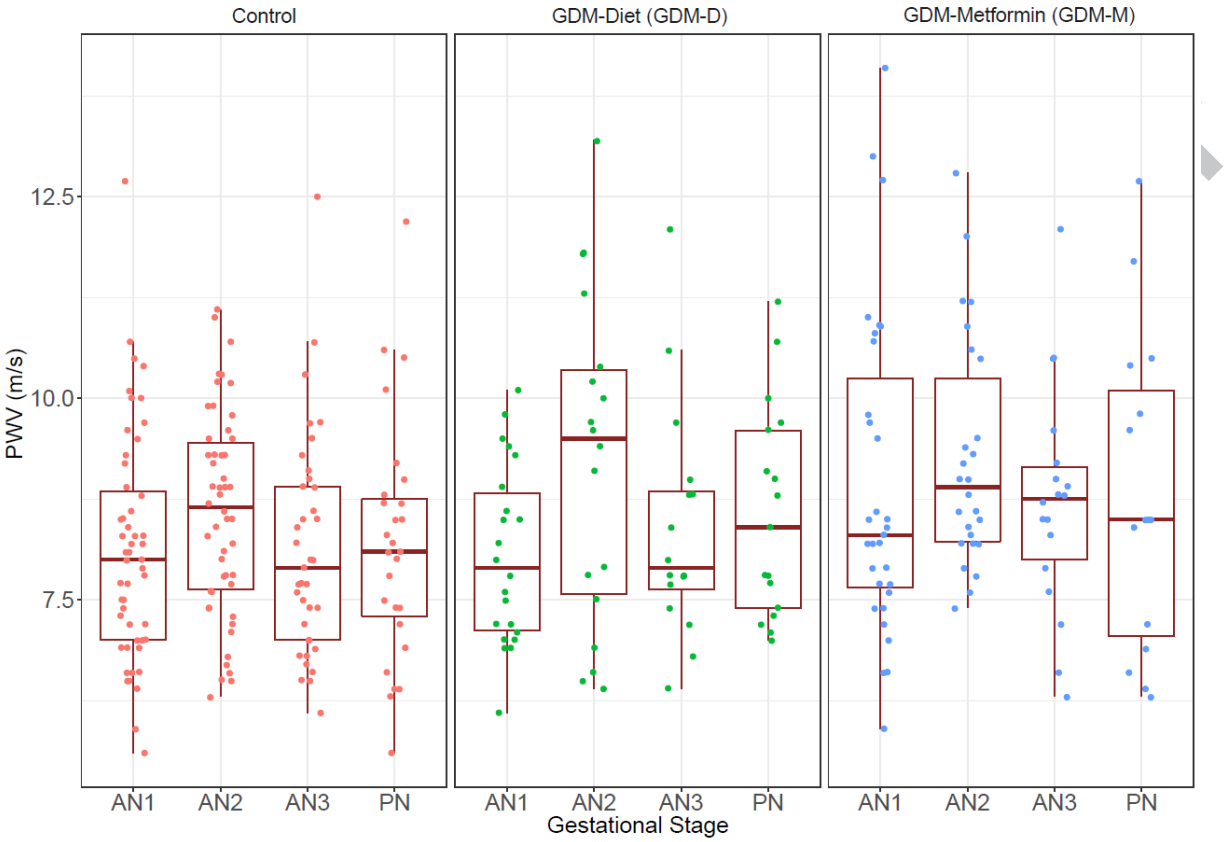

Figure 2: Measurements of PWV for participants in all three groups (points) at four time points (AN1, AN2, AN3, and PN) with the corresponding box plots showing the median and interquartile range.

AN1: 26-28 weeks: Control (n=52), GDM-D (n=22) and GDM-M (n=33)

AN2: 32-34 weeks: Control (n=51), GDM-D (n=18) and GDM-M (n=29)

AN3: 37-40 weeks: Control (n=38), GDM-D (n=17) and GDM-M (n=18)

PN: 6-8 weeks after delivery: Control (n=26), GDM-D (n=17) and GDM-M (n=15)