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Does treatment modality affect measures of arterial stiffness in women with gestational diabetes?

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KEYWORDS: arterial stiffness; augmentation index; gestational diabetes; maternal hemodynamics; metformin

CONTRIBUTION

What are the novel findings of this work?
Brachial (BrAIx) and aortic (AoAIx) augmentation indices are higher among women with gestational diabetes mellitus (GDM) from 24 + 0 to 35 + 6 weeks' gestation compared with healthy controls regardless of treatment modality. We observed a decrease in mean AIx in all GDM treatment groups after initiation of treatment and altered longitudinal patterns of BrAIx and AoAIx in the groups treated with metformin.

What are the clinical implications of this work?
Maladaptation of the cardiovascular system may underlie the association between GDM and gestational hypertensive disorders. Our findings also suggest that treatment with metformin may attenuate the increase in BrAIx and AoAIx, although this finding requires further investigation in larger studies.

ABSTRACT

Objective *To investigate whether arterial stiffness (AS) differs between healthy women and women with gestational diabetes mellitus (GDM) managed by different treatment modalities.*

Methods *This was a prospective longitudinal cohort study comparing AS in pregnancies complicated by GDM and low-risk controls. AS was assessed by recording aortic pulse-wave velocity (AoPWV), brachial augmentation index (BrAIx) and aortic augmentation index (AoAIx) using the Arteriograph® at four gestational-age windows: 24 + 0 to 27 + 6 weeks (W1); 28 + 0 to 31 + 6 weeks (W2); 32 + 0 to 35 + 6 weeks (W3) and ≥ 36 + 0 weeks (W4). Women with GDM were considered both as a single group and as subgroups stratified by treatment modality. Data were analyzed using a linear mixed model on each AS variable (log-transformed) with group, gestational-age window, maternal age, ethnicity, parity, body mass index, mean arterial pressure and heart rate as fixed effects and individual as a random effect. We compared the group means including relevant contrasts and adjusted the P-values using Bonferroni correction.*

Results *The study population comprised 155 low-risk controls and 127 women with GDM, of whom 59 were treated with dietary intervention, 47 were treated with metformin only and 21 were treated with metformin + insulin. The two-way interaction term of study group and gestational age was significant for BrAIx and AoAIx (P < 0.001), but there was no evidence that mean AoPWV was different between the study groups (P = 0.729). Women in the control group demonstrated significantly lower BrAIx and AoAIx compared with the combined GDM group at W1–W3, but not at W4. The mean difference in log-transformed BrAIx was −0.37 (95% CI, −0.52 to −0.22), −0.23 (95% CI, −0.35 to −0.12) and −0.29 (95% CI, −0.40 to −0.18) at W1, W2 and W3, respectively. The mean difference in log-transformed AoAIx was −0.49 (95% CI, −0.69 to −0.30), −0.32 (95% CI, −0.47 to −0.18) and −0.38 (95% CI −0.52 to −0.24) at W1, W2 and W3, respectively. Similarly, women in the control*

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group also demonstrated significantly lower BrAIx and AoAIx compared with each of the GDM treatment subgroups (diet, metformin only and metformin + insulin) at W1–W3. The increase in mean BrAIx and AoAIx seen between W2 and W3 in women with GDM treated with dietary management was attenuated in the metformin-only and metformin + insulin groups. However, the mean differences in BrAIx and AoAIx between these treatment groups were not statistically significant at any gestational-age window.

Conclusions *Pregnancies complicated by GDM demonstrate significantly higher AS compared with low-risk pregnancies regardless of treatment modality. Our data provide the basis for further investigation into the association of metformin therapy with changes in AS and risk of placenta-mediated diseases.* © *2023 The Authors. Ultrasound in Obstetrics & Gynecology published by John Wiley & Sons Ltd on behalf of International Society of Ultrasound in Obstetrics and Gynecology.*

INTRODUCTION

The incidence of gestational diabetes mellitus (GDM) is rising, driven largely by an increase in maternal obesity[1]. GDM is associated with a variety of adverse fetal, neonatal and maternal outcomes[2], including placenta-mediated diseases, such as maternal hypertensive disorders of pregnancy[3], and the development of cardiovascular disease in future life[4].

Only a handful of studies have investigated changes in central hemodynamics in pregnancies complicated by GDM and they produced conflicting results. Three studies[5–7] reported no difference in pulse-wave velocity (PWV) between women with GDM and low-risk controls in the third trimester, whereas Mansukhani *et al.*[8] found PWV to be 3.7% higher among women with GDM at 35–37 weeks' gestation. Similarly, three studies found no difference in third-trimester augmentation index (AIx) between women with GDM and healthy controls[6,8,9], whereas Savvidou *et al.*[7] and Kintiraki *et al.*[10] both reported increased AIx among women with GDM compared with controls ($13.1 \pm 8.9\%$ *vs* $0.7 \pm 11.4\%$ ($P < 0.001$) and $3.77 \pm 2.22\%$ *vs* $1.51 \pm 3.35\%$ ($P = 0.021$), respectively). A limitation of these studies is that they evaluated AIx at a single time-point only, rather than throughout the third trimester. Additionally, with the exception of the study of Mansukhani *et al.*[8], the studies involved fewer than 50 women in each group and evaluated pregnant women with GDM as a single group without considering the potential impact of different treatment modalities on maternal cardiovascular adaptation.

Metformin is a glyburide recommended for the treatment of hyperglycemia in GDM that does not respond to dietary and lifestyle changes[11]. Its use is associated with a reduction in the risk of gestational hypertension among pregnant women with GDM and polycystic ovary syndrome (PCOS)[12–14] and a reduction in the incidence of pre-eclampsia in obese pregnant women[14]. In non-pregnant populations, metformin has been shown to improve markers of arterial stiffness (AS) in populations with non-alcoholic fatty liver disease[15] and PCOS[16–18], although the effect of metformin on AS in pregnant women has not yet been fully established. In a pilot study assessing longitudinal changes in AS in pregnancies complicated by GDM[19], brachial AIx (BrAIx) and aortic AIx (AoAIx) were significantly higher among women with GDM managed with dietary intervention at 32–34 weeks and among those managed with metformin at 26–28 weeks compared with women with low-risk pregnancies, but there was no difference at other gestational ages. Although this study was limited by the small number of women included, it indicated that different treatment modalities for GDM may have different effects on AS.

The aims of our study were to examine longitudinal changes in AS among women with GDM and to investigate if these changes are affected by treatment modality.

METHODS

This was a prospective longitudinal cohort study of central hemodynamics in women with GDM compared with low-risk controls. Pregnant women were recruited from the antenatal and ultrasound clinics at the Leicester Royal Infirmary, a tertiary-level maternity unit in the UK. Ethical approval was obtained from the East Midlands Research Ethics Committee (15/EM/0469, IRAS 182250) and the University Hospitals of Leicester (UHL) National Health Service Trust 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[20]. All women provided written consent to take part.

Study population

Women over 16 years of age with a viable singleton pregnancy were eligible for inclusion in the study. Women with pre-existing diabetes and/or cardiovascular disease and those with a pregnancy complicated by aneuploidy or fetal abnormality were excluded. Because funding for translation services was not available, women who did not speak or read English were also excluded. In addition, women in the low-risk control group were excluded if they developed any hypertensive disorder of pregnancy, delivered prior to 37 completed weeks' gestation or delivered a neonate with birth weight $< 10^{th}$ centile according to population-based growth charts[21].

GDM was defined as fasting glucose levels ≥ 5.6 mmol/L and/or serum glucose levels ≥ 7.8 mmol/L 2 h after a 75-g oral glucose load. The screening protocol for GDM was adapted from UK national guidance[11] (Table S1). Women with GDM were managed by a multidisciplinary team of midwives, obstetricians and endocrinologists at UHL. Adequate glucose control was defined as a fasting glucose level of < 5.3 mmol/L and

a 1-h postprandial glucose level of < 7.8 mmol/L[11]. In accordance with UK national guidance[11], women who did not achieve and subsequently maintain these levels within 2 weeks of the start of dietary intervention were commenced on metformin therapy by the managing physician, starting at 500 mg and increasing up to a maximum of 2000 mg daily. Supplemental insulin therapy was commenced if adequate glycemic control had not been achieved within 2 weeks of commencing metformin.

Power calculation based on data available from Osman *et al.*[19] indicated that, for $> 80\%$ statistical power, a sample size of 100 was required to detect a difference in AoAIx of $\geq 35\%$ and a difference in PWV of $\geq 7\%$ between women with GDM and healthy controls.

Study measurements

All women attended a minimum of two study visits during the third trimester. Demographic details, including maternal age, ethnicity, height, parity, body mass index (BMI) and smoking status at booking, were collected. Gestational age at each visit was calculated based on the dating scan performed between $11 + 0$ and $13 + 6$ weeks. For women in the GDM group, treatment modality (diet, metformin only or metformin + insulin) and gestational age at commencement of treatment were also recorded. Women who changed treatment modality after recruitment into the study were excluded so that only women who remained in the same treatment group at each study visit were included in the analysis.

Maternal hemodynamics were measured in four gestational-age windows: $24 + 0$ to $27 + 6$ weeks (W1), $28 + 0$ to $31 + 6$ weeks (W2), $32 + 0$ to $35 + 6$ weeks (W3) and $\geq 36 + 0$ weeks (W4). Assessment was performed in a temperature-controlled room, free from noise or any other distractions. Patients were positioned in the semirecumbent position and were asked not to move or talk during the assessment. All measurements were performed by a researcher (A.R.A. or M.W.O.) who had received appropriate training. Assessment was performed at scheduled appointments between 09:00 and 17:00. 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[22].

BrAIx, AoAIx and aortic PWV (AoPWV) were measured using the Arteriograph® (TensioMed Ltd, Budapest, Hungary), which estimates AS oscillometrically using a single, non-invasive blood pressure cuff. The Arteriograph has been validated against invasive assessment of AS in a non-pregnant population undergoing cardiac angiography[23] and has been shown to have good-to-excellent repeatability among healthy pregnant subjects in the third trimester[22]. The women had a minimum of two Arteriograph readings taken at each visit. Measurements with a SD of ≥ 1.0 m/s were excluded, as recommended by the Arteriograph user manual[24], and an average of the remaining readings was obtained.

Statistical analysis

All AS variables (BrAIx, AoAIx and AoPWV) were log-transformed. We fitted a linear mixed model for each log-transformed AS variable with group, gestational-age window (W1, W2, W3 and W4), maternal age, ethnicity, parity, BMI, mean arterial pressure (MAP) and heart rate (HR) as fixed effects and the individual participant as a random effect. We evaluated each model for the two-way interaction effect of group and gestational-age window and retained the interaction term if it was statistically significant ($P < 0.05$). All models estimated the variance at different gestational-age windows to account for the heterogeneity of variance at different periods. For comparison of AS, the contrast estimated the difference in means between the control group and all women with GDM (i.e. those on a dietary intervention, metformin only and metformin + insulin combined into a single group) and between the control group and women with GDM in each individual treatment subgroup.

All statistical tests were two-sided with a Type-I error rate (P-value) of 0.05 to determine statistical significance. P-values obtained from all group comparisons were adjusted using the Bonferroni correction to account for multiple comparisons. Statistical analysis was performed using R software version 4.0.3 and R packages nlme, emmeans and ggplot2 (R Core Team, 2020).

RESULTS

Baseline characteristics

In total, 211 women with GDM were recruited into the study. Among them, 84 women were later excluded; 45 changed treatment modality during the study period, 31 attended only a single study visit, five patients did not meet the study criteria (later diagnosed with having a fetal abnormality or pre-existing diabetes) and three women were treated with insulin only. After exclusion of these women, 127 women with GDM and 155 low-risk controls were included in the analysis. Of women with GDM, 59 were treated with dietary management, 47 were treated with metformin only and 21 were treated with metformin + insulin.

Baseline characteristics and pregnancy outcomes of the control group and women with GDM are given in Table 1. Compared with low-risk controls, pregnant women in the combined GDM group were older, had higher BMI and more often had non-white ethnicity (all $P < 0.05$). Among women with GDM, fasting oral glucose tolerance test (OGTT) levels were significantly lower in women controlled by dietary management compared with those requiring metformin only and metformin + insulin ($P < 0.001$ for both comparisons). 2-h OGTT levels were significantly lower in the diet group compared with the metformin + insulin group ($P = 0.002$) but not when compared with the metformin-only group ($P = 0.07$).

Women with GDM delivered at an earlier gestational age than did women in the control group ($P < 0.001$). After adjusting for gestational age at delivery, women with GDM controlled by dietary intervention delivered neonates in a lower birth-weight centile compared with low-risk controls ($P < 0.001$), but there was no statistically significant difference in birth-weight centile between controls and women with GDM controlled pharmacologically ($P > 0.05$). Women with GDM controlled by dietary intervention delivered neonates in a lower birth-weight centile compared with women with GDM requiring metformin ($P = 0.037$) and those on metformin + insulin ($P = 0.001$).

Among women treated pharmacologically, all were first commenced on metformin and then insulin if required. The mean gestational age at the commencement of metformin therapy was significantly lower in the metformin + insulin group compared with the metformin-only group (21.1 ± 6.3 *vs* 27.1 ± 5.6 weeks; $P < 0.001$). The median duration of metformin treatment prior to the first and final hemodynamic assessment was significantly greater in the metformin + insulin group compared with the metformin-only group: 7.3 (interquartile range (IQR), 5.0–11.3) weeks *vs* 3.1 (IQR, 1.7–5.7) weeks ($P < 0.001$) and 12.4 (IQR, 10.1–22.3) weeks *vs* 8.1 (IQR, 6.0–13.1) weeks ($P < 0.001$), respectively.

Changes in AS

Association of AS with maternal characteristics

Maternal BMI at booking was negatively associated with BrAIx ($P = 0.012$) and AoAIx ($P = 0.010$) but positively associated with AoPWV ($P = 0.029$). All AS variables (BrAIx, AoAIx, AoPWV) demonstrated a positive association with maternal MAP ($P < 0.001$). Both maternal age ($P = 0.008$) and HR ($P < 0.001$) showed a positive association with AoPWV. Maternal age was positively associated with BrAIx ($P = 0.003$) but not AoAIx ($P > 0.05$). Maternal HR was negatively associated with AoAIx and BrAIx (both $P < 0.001$). There was no association of maternal ethnicity (white *vs* non-white) or parity (nulliparous *vs* parous) with AS variables ($P > 0.05$). Detailed outputs of the fitted linear mixed models are presented in Tables S2–S4.

Low-risk controls vs *women with GDM*

Mean AoPWV demonstrated significant interaction with gestational age ($P < 0.001$) but was not different between study groups ($P = 0.729$). The two-way interaction term of study group and gestational age was significant for BrAIx and AoAIx ($P < 0.001$). Mean differences between the control group and women with GDM (as a combined group) in log-transformed BrAIx and AoAIx at each

Table 1 Baseline characteristics and pregnancy outcomes of study population

		GDM group			
Characteristic	*Controls (n = 155)*	*Total (n = 127)*	*Dietary treatment (n = 59)*	*Metformin treatment (n = 47)*	*Metformin + insulin treatment (n = 21)*
Baseline (at presentation)					
Maternal age (years)	29.5 ± 5.32	32.0 ± 5.19	31.5 ± 5.45	32.0 ± 4.96	33.7 ± 4.83
Maternal height (cm)	164.6 ± 7.07	161.8 ± 6.09	161.2 ± 5.67	161.2 ± 6.12	164.9 ± 6.54
Maternal weight (kg)	68.7 ± 15.67	77.1 ± 21.58	69.9 ± 16.16	81.4 ± 24.7	89.7 ± 19.36
Maternal BMI (kg/m^2)	25.3 ± 5.03	29.3 ± 7.54	26.5 ± 5.60	31.2 ± 9.03	32.8 ± 5.92
Parity					
Nulliparous	64 (41.3)	52 (40.9)	24 (40.7)	22 (46.8)	6 (28.6)
Parous	91 (58.7)	75 (59.1)	35 (59.3)	25 (53.2)	15 (71.4)
Maternal ethnicity					
White British/European	124 (80.0)	55 (43.3)	30 (50.8)	16 (34.0)	9 (42.9)
Non-white	31 (20.0)	72 (56.7)	29 (49.2)	31 (66.0)	12 (57.1)
Current smoker	5 (3.2)	3 (2.4)	2 (3.4)	1 (2.1)	0 (0)
OGTT fasting glucose (mmol/L)	NA	4.8 ± 0.84	4.4 ± 0.71	5.0 ± 0.72	5.5 ± 0.9
OGTT 2-h glucose (mmol/L)	NA	8.8 ± 1.51	8.4 ± 0.97	8.8 ± 1.35	9.7 ± 2.52
Pregnancy outcome					
GA at delivery (weeks)	39.8 ± 1.1	38.8 ± 1.1	39.1 ± 1.3	38.8 ± 0.9	38.3 ± 0.7
Hypertensive disorder of pregnancy	0 (0)	10 (7.9)	5 (8.5)	2 (4.3)	3 (14.3)
Birth weight (g)	3558 ± 419	3280 ± 468	3190 ± 463	3320 ± 459	3446 ± 467
Birth-weight centile	58.4 ± 26.7	49.5 ± 31.9	40.5 ± 30.5	53.2 ± 30.8	66.5 ± 31.1
Birth-weight category					
Small-for-gestational age	0 (0)	20 (15.7)	13 (22.0)	6 (12.8)	1 (4.8)
Large-for-gestational age	23 (14.8)	13 (10.2)	3 (5.1)	5 (10.6)	5 (23.8)

Data are given as mean ± SD or *n* (%). Small-for-gestational age was defined as birth weight < 10th centile and large-for-gestational age was defined as birth weight > 90th centile according to population-based growth charts[21]. BMI, body mass index; GA, gestational age; GDM, gestational diabetes mellitus; NA, not applicable; OGTT, oral glucose tolerance test.

gestational-age window are presented in Table 2. Women in the GDM group had significantly higher mean BrAIx and AoAIx compared with low-risk controls at W1, W2 and W3 ($P < 0.05$) but not at W4.

Low-risk controls vs *women with GDM according to treatment modality*

Estimated mean and 95% CIs for BrAIx, AoAIx and AoPWV for control and individual treatment groups at each gestational-age window are presented in Table 3 and Figure 1. Women in each GDM treatment group (dietary management, metformin only and metformin + insulin) demonstrated significantly higher mean BrAIx and AoAIx compared with the control group at W1, W2 and W3 ($P < 0.05$). There was no difference in BrAIx and AoAIx between GDM treatment groups and low-risk controls at W4 ($P > 0.05$). There was no difference in AoPWV between the control group and GDM treatment groups at any gestational-age window ($P > 0.05$).

Women with GDM managed with dietary intervention vs *metformin*

Among women with GDM, the differences in BrAIx, AoAIx and AoPWV in the dietary-intervention, metformin-only or metformin + insulin groups were not statistically significant at any gestational-age window. However, we did observe differences in patterns of BrAIx and AoAIx across advancing gestation between

Table 2 Mean difference in log-transformed brachial augmentation index (BrAIx) and aortic augmentation index (AoAIx) between controls and all women with gestational diabetes according to gestational age

	Gestational age:							
	24 + 0 to 27 + 6 weeks (W1)		*28 + 0 to 31 + 6 weeks (W2)*		*32 + 0 to 35 + 6 weeks (W3)*		*≥ 36 weeks (W4)*	
Parameter	*Mean difference*	*Adjusted* P	*Mean difference*	*Adjusted* P	*Mean difference*	*Adjusted* P	*Mean difference*	*Adjusted* P
BrAIx	−0.37 (−0.52 to −0.22)	< 0.001	−0.23 (−0.35 to −0.12)	0.001	−0.29 (−0.40 to −0.18)	< 0.001	−0.11 (−0.22 to 0.00)	> 0.999
AoAIx	−0.49 (−0.69 to −0.30)	< 0.001	−0.32 (−0.47 to −0.18)	< 0.001	−0.38 (−0.52 to −0.24)	< 0.001	−0.17 (−0.32 to −0.03)	0.405

Values in parentheses are 95% CI. *P*-values were adjusted using Bonferroni correction.

Table 3 Estimated mean of brachial augmentation index, aortic augmentation index and aortic pulse-wave velocity according to gestational age and treatment group

	Gestational age:			
Group	*24 + 0 to 27 + 6 weeks (W1)*	*28 + 0 to 31 + 6 weeks (W2)*	*32 + 0 to 35 + 6 weeks (W3)*	*≥ 36 weeks (W4)*
Brachial augmentation index (%)				
Controls	−70.94 (−73.31 to −68.36)	−69.46 (−71.53 to −67.25)	−68.23 (−70.38 to −65.92)	−60.84 (−63.55 to −57.94)
Dietary treatment	−60.71 (−66.59 to −53.80)*	−62.64 (−66.37 to −58.51)*	−53.07 (−58.07 to −47.48)*	−53.73 (−58.61 to −48.28)
Metformin treatment	−57.25 (−65.15 to −47.56)*	−58.14 (−63.90 to −51.47)*	−57.89 (−62.77 to −52.38)*	−53.28 (−58.72 to −47.12)
Metformin + insulin treatment	−50.53 (−61.88 to −35.80)*	−58.87 (−65.63 to −50.77)*	−56.74 (−64.49 to −47.29)*	−56.97 (−64.42 to −47.96)
Aortic augmentation index (%)				
Controls	1.65 (0.44 to 3.01)	2.16 (1.08 to 3.35)	2.59 (1.53 to 3.75)	6.10 (4.68 to 7.67)
Dietary treatment	6.77 (3.59 to 10.69)*	5.52 (3.51 to 7.84)*	9.86 (7.26 to 12.85*	10.40 (7.67 to 13.56)
Metformin treatment	8.70 (4.33 to 14.39)*	8.30 (5.02 to 12.31)*	8.49 (5.86 to 11.54)*	10.88 (7.78 to 14.52)
Metformin + insulin treatment	14.31 (7.32 to 24.10)*	8.28 (4.41 to 13.20)*	8.63 (4.56 to 13.85)*	7.95 (4.02 to 12.97)
Aortic pulse-wave velocity (m/s)				
Controls	7.73 (7.51 to 7.96)	8.01 (7.83 to 8.19)	8.19 (8.00 to 8.38)	8.43 (8.24 to 8.62)
Dietary treatment	7.76 (7.47 to 8.06)	8.04 (7.79 to 8.29)	8.22 (7.96 to 8.49)	8.46 (8.20 to 8.72)
Metformin treatment	7.90 (7.57 to 8.24)	8.18 (7.88 to 8.49)	8.37 (8.07 to 8.68)	8.61 (8.31 to 8.92)
Metformin + insulin treatment	7.89 (7.46 to 8.34)	8.17 (7.76 to 8.61)	8.35 (7.93 to 8.80)	8.59 (8.16 to 9.05)

Values in parentheses are 95% CI. *Indicates significant difference from control group at same gestational age ($P < 0.05$).

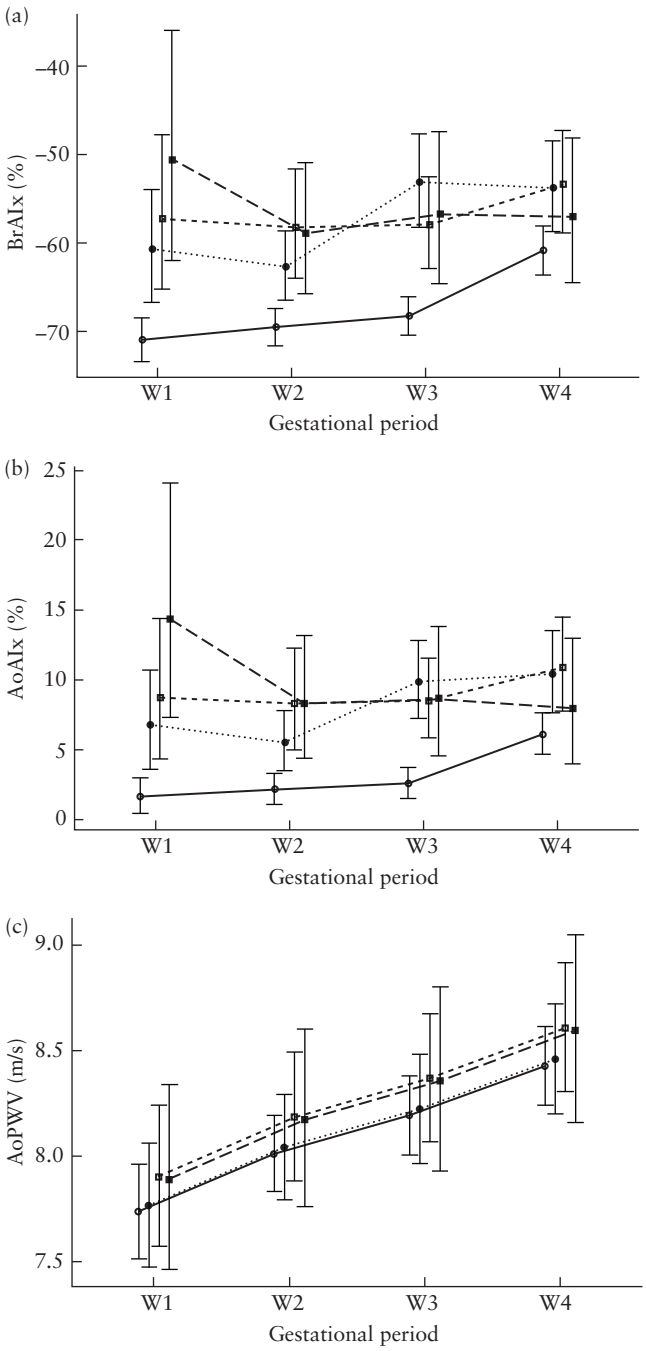

Figure 1 Mean brachial augmentation index (BrAIx) (a), aortic augmentation index (AoAIx) (b) and aortic pulse-wave velocity (AoPWV) (c) according to gestational age and study group. W1, 24 + 0 to 27 + 6 weeks; W2, 28 + 0 to 31 + 6 weeks; W3, 32 + 0 to 35 + 6 weeks; W4, ≥ 36 + 0 weeks; —o—, controls; ···•···, dietary-intervention group; -·-▪-·-, metformin-treatment group; - - ▪ - -, metformin + insulin-treatment group. Error bars are 95% CI.

groups. Among women with GDM treated with dietary intervention, the estimated mean BrAIx fell from −60.71% to −62.64% between W1 and W2, then rose to −53.07% at W3 and remained stable at −53.73% at W4. In women with GDM taking metformin only, estimated mean BrAIx also fell between W1 and W2 from −57.25% to −58.14% but then remained stable at −57.89% at W3 before rising to −53.28% at W4. In women with GDM taking metformin + insulin, estimated mean BrAIx fell between W1 and W2 from −50.53% to −58.87% and then remained stable at −56.74% at W3 and −56.97% at W4.

Similarly, among women with GDM treated with dietary intervention, estimated mean AoAIx fell from 6.77% to 5.52% between W1 and W2 and then rose to 9.86% at W3 and 10.40% at W4. In women with GDM taking metformin only, estimated mean AoAIx also fell between W1 and W2, from 8.70% to 8.30%, but then remained stable at 8.49% at W3 before rising to 10.88% at W4. In women with GDM taking metformin + insulin, estimated mean AoAIx fell between W1 and W2 from 14.31% to 8.28% and then remained stable at 8.63% at W3 and 7.95% at W4.

DISCUSSION

Summary of main findings

In this prospective longitudinal study, we observed increased AoAIx and BrAIx among women with GDM compared with low-risk controls, irrespective of treatment modality. BrAIx and AoAIx did not differ between individual treatment groups, but there was a trend towards an altered longitudinal pattern of AS between the metformin and diet-controlled groups.

Interpretation of main findings and comparison with the literature

The finding of a negative association of maternal BMI with BrAIx and AoAIx was unexpected, given that systemic vascular resistance (SVR) has been reported previously to be higher in morbidly obese women compared with non-obese pregnant women, although the difference was significant only in SVR index and not SVR[25]. In the current study, the majority (84.4%) of participants were not obese; therefore, the observed effect may be limited to our study population and may not be applicable to a wider population. It should also be noted that the effect size of BMI was small compared with the effect of the study group and, therefore, the variability of BrAIx and AoAIx due to variation in maternal BMI was minimal. A negative association between BMI and AIx has been reported previously in certain populations[26,27]. The relationship between these variables is therefore not fully understood and warrants further investigation with a large dataset and adequate distribution of participants across all BMI categories.

In keeping with several previous studies[5–7] we found no difference in PWV between women with GDM and healthy pregnancies. The only study that reported higher PWV among women with GDM had a larger population (218 women) and examined PWV at a single timepoint (35–37 weeks' gestation)[8].

Our finding of increased AIx among women with GDM is in agreement with a number of previous studies[7,10] but is at odds with others[6,8,9]. This contrast in findings may

be explained by differences in study design. The three studies whose findings are at odds with those of our study examined AS at a single timepoint in the third trimester and two of them[6,9] included fewer than 35 women with GDM. Mansukhani *et al.*[8] included a larger number of women but examined AIx at 35–37 weeks, which straddles two gestational-age windows of our study, including the ≥ 36 + 0-week window, at which we also found no significant difference between women with GDM and healthy controls.

An important finding of our study is that BrAIx and AoAIx were higher in women with GDM compared with healthy controls regardless of treatment type. A longitudinal pilot study found a significant difference in BrAIx and AoAIx in women with GDM treated with metformin at 26–28 weeks and in those managed with dietary intervention at 32–34 weeks compared with controls[19]. The current study was larger, and we found a significant difference between controls and women with GDM in all treatment modality groups in three gestational-age windows, from 24 + 0 to 35 + 6 weeks.

Monitoring glycemic response to the treatment of GDM in each gestational-age window was beyond the scope of this study. However, since pharmacological treatment was initiated based on self-monitored blood glucose levels of the participants, the different treatment groups as well as the birth weight and birth-weight centiles can be interpreted as indirect markers of glycemic control. There was no difference in the rate of large-for-gestational age babies between controls and any of the GDM groups, implying that our cohort of women with GDM were generally well controlled. It is therefore interesting to note that we found increased BrAIx and AoAIx among women with GDM despite apparently adequate treatment.

The increase in BrAIx and AoAIx seen in the GDM group managed with dietary intervention and in the healthy control group was suppressed until 35 + 6 weeks in the GDM group treated with metformin only and until ≥ 36 + 0 weeks for those treated with metformin + insulin. Birth-weight centile was significantly higher in the metformin-treated groups compared with the dietary management group; therefore, we consider it unlikely that this observation represents tighter glycemic control in the groups treated pharmacologically. Several studies conducted in non-pregnant populations have reported a significant reduction in AIx associated with treatment with metformin[15–17]. At a molecular level, metformin treatment decreases inflammation and promotes angiogenesis in pregnant populations[28], and improves oxidative stress and endothelial function in animal models[29]. Our findings suggest that metformin may play a role in attenuating the physiological increase in AS seen during pregnancy in healthy controls and the GDM-diet group in the mid-to-late third trimester. However, it is important to note that the difference in BrAIx and AoAIx between the different GDM treatment groups was not significant at any gestational-age window and that the study was underpowered for this comparison. This observation, therefore, remains a hypothesis that warrants further investigation.

Clinical and research implications

Our findings demonstrate that women with GDM have altered BrAIx and AoAIx during the third trimester compared with healthy pregnant women. Women with metabolic syndrome have increased AIx[30]; therefore, it is possible that our findings reflect preclinical risk factors and predisposition to the development of GDM. Since increased AS predicts the development of gestational hypertensive disorders[31,32], our findings also suggest that maladaptation of the cardiovascular system in pregnancies complicated by GDM may underlie the association between GDM and pregnancy-induced hypertension and pre-eclampsia. Further research assessing the association between increased AIx and these clinical outcomes in pregnant women with GDM is needed.

Our findings also suggest that treatment with metformin may attenuate the changes in BrAIx and AoAIx in the mid-to-late third trimester in low-risk and GDM diet-controlled pregnancies, which may explain why metformin therapy has been associated with decreased rates of pregnancy-induced hypertension and pre-eclampsia in obese pregnant women[12]. Prospective interventional studies are therefore needed to further investigate this effect of metformin and its association with the risk of developing placenta-mediated diseases.

Strengths and limitations

This is the largest study to investigate maternal hemodynamics in GDM throughout the third trimester rather than at a single timepoint. We also considered women with GDM on different treatments separately and as a combined group, allowing more detailed characterization of AS in pregnancies complicated by GDM compared to that described previously in the literature.

A limitation of the study is that we were unable to assess hemodynamics prior to the initiation of treatment or collect data regarding glycemic control after diagnosis. Although birth weight and the need for pharmacological treatment act as indirect markers of glycemic control, we are unable to conclude or exclude that glycometabolic decompensation accounted for the difference in hemodynamics between the groups. Second, while this study is among the largest to look at AS among women with GDM, the treatment subgroups were still relatively small. Finally, we were unable to invite women for postnatal follow-up due to the COVID-19 pandemic and, therefore, our study did not assess whether the differences in AS observed in pregnancy persisted after delivery.

Conclusions

Pregnancies complicated by GDM demonstrate significantly higher AS compared with low-risk pregnancies

regardless of treatment modality. Our data provide the basis for further investigation into the association of metformin therapy with changes in AS and risk of placenta-mediated diseases.

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SUPPORTING INFORMATION ON THE INTERNET

The following supporting information may be found in the online version of this article:

Table S1 Screening protocol for gestational diabetes mellitus at the Leicester Royal Infirmary

Table S2 Descriptors and outputs of linear mixed model for brachial augmentation index

Table S3 Descriptors and outputs of linear mixed model for aortic augmentation index

Table S4 Descriptors and outputs of linear mixed model for aortic pulse-wave velocity