Maternal hemodynamics and neonatal birth weight in pregnancies complicated by gestational diabetes: new insights from novel causal inference analysis modeling

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CONTRIBUTION

What are the novel findings of this work?
In a graphical causal inference model, maternal body mass index (BMI) at booking, cardiac output and pulse wave velocity had a significant positive influence on neonatal birth weight in normal pregnancy. Pregnancies with gestational diabetes showed a similar relationship between hemodynamics and birth weight, although only the relationship between BMI and birth weight reached statistical significance.

What are the clinical implications of this work?
Fetal growth restriction occurring in pregnancies complicated by gestational diabetes may indicate underlying maternal cardiovascular dysfunction.

ABSTRACT

Objective Normal pregnancy is characterized by significant changes in maternal hemodynamics that are associated with fetal growth. Pregnancies complicated by gestational diabetes mellitus (GDM) are associated with large-for-gestational age and macrosomia, but the relationship between maternal hemodynamic parameters and birth weight (BW) among women with GDM has not been established. Our objective was to investigate the influence of maternal hemodynamics on neonatal BW in healthy pregnancies and in those complicated by GDM.

Methods This was a prospective, cross-sectional case–control study of women aged ≥ 16 years with a singleton viable pregnancy, recruited between January 2016 and February 2021 at Leicester Royal Infirmary, Leicester, UK. GDM was defined as a fasting glucose level ≥ 5.3 mmol/L and/or serum glucose level ≥ 7.8 mmol/L, 2 h following a 75-g oral glucose load. We collected data on maternal characteristics and pregnancy outcome, including body mass index (BMI) at booking and BW centile adjusted for gestational age at delivery. Maternal hemodynamic parameters were assessed at 34–42 weeks' gestation using the Arteriograph® and bioreactance techniques. Graphical causal inference methodology was used to identify causal effects of the measured variables on neonatal BW centile.

Results Included in the analysis were 141 women with GDM and 136 normotensive non-diabetic pregnant controls. 62% of the women with GDM were managed pharmacologically, with metformin and/or insulin. Variables included in the final model were cardiac output (CO), mean arterial pressure (MAP), total peripheral resistance (TPR), aortic augmentation index (AIx), aortic pulse wave velocity (PWV) and BMI at booking. Among the controls, maternal BMI, CO and aortic PWV were significantly associated with neonatal BW. Each SD increase in booking BMI produced an increase of 8.4 BW centiles (P = 0.002), in CO produced an increase of 9.4 BW centiles (P = 0.008) and in aortic PWV produced an increase of 7.1 BW centiles (P = 0.017). We found no significant relationship between MAP, TPR or aortic AIx and neonatal BW. Maternal hemodynamics influenced neonatal BW among the women with GDM in a similar manner to that

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in the control group, but only the relationship between maternal BMI and neonatal BW reached statistical significance, with a 1-SD increase in BMI producing an increase of 6.1 BW centiles (P = 0.019).

Conclusions *Maternal BMI, CO and PWV were determinants of BW in our control group. The relationship between maternal hemodynamics and neonatal BW was similar between women with GDM and healthy controls. Our findings therefore suggest that fetal growth restriction in pregnancies complicated by GDM may indicate maternal cardiovascular dysfunction.* © 2022 The Authors. *Ultrasound in Obstetrics & Gynecology published by John Wiley & Sons Ltd on behalf of International Society of Ultrasound in Obstetrics and Gynecology.*

INTRODUCTION

Normal pregnancy is characterized by an increase in maternal cardiac output (CO)[1,2] and a decrease in mean arterial pressure (MAP)[2], total peripheral resistance (TPR)[1,2] and central arterial stiffness[3,4]. These changes to the maternal cardiovascular system sustain the increasing uteroplacental perfusion and are closely related to fetal growth.

The majority of research in this area has focused on the difference in cardiovascular adaptation in terms of the changes in healthy pregnancies compared with those affected by fetal growth restriction (FGR). Pregnancies complicated by FGR or small-for-gestational age (SGA) are characterized by lower maternal CO[5,6] and higher TPR[5–7], aortic augmentation index (AIx)[5,8,9] and aortic pulse wave velocity (PWV)[5,10], compared with pregnancies with normal birth weight. Hypertensive disorders of pregnancy are also well known to be associated with FGR[11,12].

In comparison, the volume of work which has studied maternal hemodynamics across the full spectrum of fetal growth, including pregnancies delivering large-for-gestational-age (LGA) as well as those delivering SGA infants, is much smaller. One study showed neonatal birth weight to have a positive relationship with maternal CO and a negative linear correlation with TPR and MAP[13]. Two smaller studies, each with 50 subjects, reported a negative association between birth weight and aortic AIx[14] and PWV[15].

In contrast to those with hypertensive disorders, pregnancies complicated by gestational diabetes mellitus (GDM) are associated with increased fetal growth, and GDM is considered an independent risk factor for macrosomia[16]. However, the relationship between maternal hemodynamics and neonatal birth weight in pregnancies complicated by GDM is yet to be explored.

Finally, whilst there is some evidence in the literature to describe the relationships between fetal growth and maternal cardiovascular parameters in non-diabetic populations, the study designs and statistical methods employed can conclude only association, and not causality. Causal inference is a statistical technique which utilizes domain expertise, often in the form of direct acyclic graphs (DAGs), in order to draw causal rather than associational conclusions. This method is being used increasingly to handle observational data, in studies attempting to prove hypotheses for which a randomized controlled trial is not feasible[17]. The aim of this pilot study, therefore, was to investigate the influence of maternal hemodynamics on neonatal birth weight in healthy pregnancies, compared with those complicated by GDM, using a graphical causal inference methodology. The null hypothesis was that maternal hemodynamic variables would not significantly impact neonatal birth weight.

METHODS

We conducted a prospective cross-sectional case–control study of maternal hemodynamics in the late third trimester, amongst women attending the antenatal clinic, and subsequently delivering, at Leicester Royal Infirmary. Participants were identified from women recruited to a larger longitudinal study of maternal hemodynamics between January 2016 and February 2021. Ethical approval was obtained from the East Midlands Research Ethics Committee (15/EM/0469, IRAS 182250) and all women provided written consent to participate. The study was conducted in accordance with STROBE guidelines[18].

We included women aged ≥ 16 years with a singleton viable pregnancy. Women with pre-existing hypertension, diabetes or cardiovascular disease and those taking medication known to affect cardiovascular function were excluded. Multiple pregnancies and those complicated by aneuploidy or fetal abnormality were also excluded. Women who developed pre-eclampsia (PE) or pregnancy-induced hypertension (PIH), as defined by the National Institute for Health and Care Excellence (NICE)[19], were excluded from the control group. We also excluded women who did not speak English, as funding for translation services for the study was not available. GDM was defined as a fasting glucose level ≥ 5.3 mmol/L and/or serum glucose level ≥ 7.8 mmol/L, 2 h following a 75-g oral glucose load[20].

Data regarding baseline characteristics and pregnancy outcome were obtained from the electronic maternity records. Maternal age and body mass index (BMI) were recorded at the time of booking, i.e. at initial contact with their midwife in the first trimester. Gestational age was calculated from the crown–rump length measured at ultrasound examination performed between 11 + 0 and 13 + 6 weeks' gestation. Birth-weight centiles were calculated using The Fetal Medicine Foundation's Birth Weight Calculator[21]. LGA was defined as birth weight > 90th centile and SGA as birth weight < 10th centile.

Hemodynamic assessment

We included in the analysis hemodynamic assessments performed between 34 + 0 and 42 + 0 weeks' gestation, since cardiovascular adaptations to pregnancy have already reached their peak and change only minimally

during this period[1,2]. If a participant had more than one assessment during this gestational window, the later assessment was included in the analysis. Assessments were performed in a temperature-controlled room, free from noise and 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 09.00 and 17.00 h. Previous work has shown that stroke volume, MAP, heart rate (HR), TPR, PWV and AIx are not significantly affected by the time of day at which they are measured[22].

Maternal hemodynamic parameters were measured using an Arteriograph® (TensioMed Ltd, Budapest, Hungary), which measures arterial stiffness oscillometrically, through a single, non-invasive blood-pressure cuff, and a non-invasive bioreactance method (NICOM®, Cheetah Medical, Portland, OR, USA). The Arteriograph has been validated against invasive assessment of arterial stiffness in a non-pregnant population undergoing cardiac angiography[23], and shown to have good-to-excellent repeatability amongst healthy pregnant subjects in the third trimester[22]. Recruits had a minimum of two Arteriograph readings taken at each visit. Measurements with $SD \geq 1.0$ were excluded, as recommended by the Arteriograph's user manual[24], and an average was taken of the remaining readings. The NICOM demonstrates significant correlation with transthoracic echocardiography for hemodynamic assessment and good intraobserver reproducibility[25,26].

Statistical and causal analysis

Statistical analysis was performed using Stata (Version 15.0, StataCorp LLC, College Station, TX, USA). Only cases with a complete dataset were included. Continuous data were confirmed as being normally distributed using Kolmogorov–Smirnov analysis and were compared using mean, SD and *t*-test. Categorical data were compared using the chi-square test. Results were considered statistically significant if $P < 0.05$.

Causal analysis was performed using a graphical causal inference approach, in which a causal DAG[17], based on known relationships, was used to identify systematically a set of adjustment variables to eliminate confounding and for use in regression analysis. The R package, Dagitty[27], was used to identify a suitable adjustment set for each relationship of interest. We selected the smallest set of variables sufficient to mitigate all sources of confounding bias according to the causal DAG and, before estimating the effect of each variable, computed a correlation matrix to identify and remove any highly collinear variables. Data for each variable were standardized (by subtracting the mean and dividing by the SD for all continuous prediction variables). Numerical outliers, defined as those with a value that was > 4 SD above or below the mean, were removed from the analysis. We then used linear

regression models[28] to predict the effect on the mean birth-weight centile of increasing each variable by 1 SD above its mean. Insulin and metformin have been shown to reduce endothelial dysfunction and inflammation[29–31]; however, evidence regarding the effect of hypoglycemic treatment on central hemodynamics in GDM is limited to a single pilot study[32]. We therefore did not include hypoglycemic treatment as a node on the DAG, but performed a subanalysis of the diabetic cohort, using only the women treated with diet therapy to investigate any potential confounding effect from hypoglycemic agents. A variable was considered to have a statistically significant effect on birth-weight centile if the effect estimate 95% CI did not contain zero.

RESULTS

A total of 141 women with GDM and 136 non-diabetic, normotensive pregnant controls were included in the analysis. All participants had a complete dataset.

Baseline characteristics, birth outcomes and hemodynamic profiles of the two groups are given in Table 1. Compared with controls, women with GDM were significantly older (32 ± 5.2 *vs* 29 ± 5.3 years, $P < 0.001$), had a higher BMI at booking (30 ± 6.5 *vs* 26 ± 5.6 kg/m^2, $P < 0.001$), and were less likely to be of white ethnic origin (48.9% *vs* 80.9%, $P < 0.001$). The gestational age at assessment was later in the controls (38.3 ± 2.1 *vs* 37.0 ± 1.5 weeks, $P < 0.001$). At the time of assessment, 38% of the GDM group were being treated with dietary management, 40% with metformin, 4% with insulin alone and 18% with metformin and insulin in combination. Women with GDM delivered earlier than did those in the control group (38.9 ± 1.0 *vs* 39.6 ± 1.3 weeks, $P < 0.001$). The neonatal birth weight for women with GDM was non-significantly lower than that for controls, and, after accounting for the earlier gestational age at delivery, there was no difference in the birth-weight centile (56 ± 31.3 *vs* 53 ± 29.6, $P = 0.322$) or the rate of LGA (15.6% *vs* 14.7%, $P = 0.387$).

The maternal aortic PWV was significantly higher (8.7 ± 1.4 *vs* 8.2 ± 1.2, $P = 0.003$) amongst women with GDM, but there was no difference in maternal CO ($P = 0.266$), TPR ($P = 0.808$), HR ($P = 0.366$), stroke volume ($P = 0.473$), systolic blood pressure (BP) ($P = 0.965$), diastolic BP (DBP) ($P = 0.784$), MAP ($P = 0.854$) or aortic AIx ($P = 0.098$) between the two groups.

Variables included in the model

The initial graphical model (i.e. the DAG), showing the variables of interest (nodes) and the relationships between them (edges), is given in Figure S1 and the final DAG is in Figure S2. After removal of variables showing a high degree of collinearity (demonstrated in Figure S3), the variables retained in the model were CO, MAP, TPR, aortic AIx, PWV and BMI at booking. Our initial DAG did not include an edge between gestational age and CO, PWV or aortic AIx, since the change in these variables during late gestation is less than that at earlier

Table 1 Comparison of maternal baseline characteristics, hemodynamic assessment and pregnancy outcome between pregnancies complicated by gestational diabetes mellitus (GDM) and healthy controls

Parameter	Controls (n = 136)	GDM (n = 141)	P
Maternal characteristics			
Age (years)	29 ± 5.3	32 ± 5.2	< 0.001
Height (cm)	164 ± 7.1	163 ± 7.0	0.252
Weight (kg)	69 ± 17.0	79 ± 21.1	< 0.001*
BMI (kg/m²)	26 ± 5.6	30 ± 6.5	< 0.001*
Parity			0.225
0	61 (44.9)	55 (39.0)	
1	43 (31.6)	50 (35.5)	
2	23 (16.9)	18 (12.8)	
≥ 3	9 (6.6)	18 (12.8)	
Ethnicity			< 0.001
African/Afro-Caribbean	7 (5.1)	16 (11.3)	
South Asian	15 (11.0)	42 (29.8)	
White British/European	110 (80.9)	69 (48.9)	
Other	4 (2.9)	14 (9.9)	
Current smoker (n)	4 (2.9)	7 (5.0)	0.389
Maternal hemodynamic assessment			
GA at assessment (weeks)	38.3 ± 2.1	37.0 ± 1.5	< 0.001
CO (L/min)	7.0 ± 1.37	7.2 ± 1.54	0.266
SV (mL)	77 ± 15.3	79 ± 18.4	0.473
HR (bpm)	92 ± 12.9	93 ± 13.5	0.366
TPR (dynes × s/cm²)	1085 ± 230.6	1078 ± 238.4	0.808
SBP (mmHg)	117 ± 10.2	118 ± 12.4	0.965
DBP (mmHg)	68 ± 7.9	68 ± 9.9	0.784
MAP (mmHg)	84 ± 8.0	85 ± 10.2	0.854
Ao_AIx (%)	9.5 ± 9.25	11.3 ± 9.4	0.098
Ao_PWV (m/s)	8.2 ± 1.2	8.7 ± 1.4	0.003
Pregnancy outcome			
GA at delivery (weeks)	39.6 ± 1.3	38.9 ± 1.0	< 0.001*
BW (g)	3442 ± 518	3372 ± 461	0.238
BW centile	53 ± 29.6	56 ± 31.3	0.322*
BW category			0.387
SGA	10 (7.4)	17 (12.1)	
AGA	106 (77.9)	102 (72.3)	
LGA	20 (14.7)	22 (15.6)	

Data are presented as mean ± SD or *n* (%). *Mann–Whitney *U*-test; all other data were analyzed by *t*-test (continuous data) or chi-square test (categorical data). *P* < 0.05 was considered statistically significant. AGA, appropriate-for-gestational age; Ao_AIx, aortic augmentation index; Ao_PWV, aortic pulse wave velocity; BMI, body mass index at booking; BW, birth weight; CO, cardiac output; DBP, diastolic blood pressure; GA, gestational age; HR, heart rate; LGA, large-for-gestational age; MAP, mean arterial blood pressure; SBP, systolic blood pressure; SGA, small-for-gestational age; SV, stroke volume; TPR, total peripheral resistance.

stages of pregnancy[1]. Incorporating an adjustment of these variables for gestational age did not change the results significantly, supporting our initial decision not to include this association.

Determinants of neonatal birth weight

Figure 1 shows the relationships between the variables included in the model and birth-weight centile in the GDM and control groups. Figure 2 shows the mean overall effect of each variable on birth-weight centile, with 95% CIs, in the two groups and Figure 3 shows

the relative effect of each variable on the birth-weight centile.

Among the non-diabetic, normotensive controls, maternal BMI at booking, CO and aortic PWV were significantly associated with neonatal birth weight. Each SD increase in booking BMI produced an increase of 8.4 BW centiles (*P* = 0.002), in CO produced an increase of 9.4 BW centiles (*P* = 0.008) and in PWV produced an increase of 7.1 BW centiles (*P* = 0.017). We found no significant relationship between MAP, TPR or aortic AIx and neonatal birth weight.

Maternal hemodynamics influenced neonatal birth weight among the women with GDM in a similar manner to that in the control group, but only the relationship between maternal BMI and neonatal birth weight reached statistical significance, with a 1-SD increase in BMI producing an increase of 6.1 birth-weight centiles (*P* = 0.019).

With the exception of MAP, the direction of association between all variables and neonatal birth-weight centile remained the same in the subgroup analysis of the dietary-controlled GDM patients, although none of the associations reached statistical significance (Figure 4).

DISCUSSION

Summary of main findings

We conducted a prospective case–control study using graphical causal inference modeling. Amongst the controls, maternal BMI at booking, CO and aortic PWV showed a significant positive causal relationship with birth weight. In the GDM group, maternal hemodynamics influenced neonatal birth weight in a similar manner, although only the relationship between maternal BMI and birth weight reached statistical significance.

Interpretation of main findings and comparison with the literature

Previous work in non-diabetic women has demonstrated a positive relationship between maternal CO, BMI and neonatal birth weight, with neonatal birth weight correlating positively with $\log_{10}$ multiples of the median CO ($r = 0.117$, $P < 0.001$)[13], and increasing by 14.7 g for every unit increase in maternal BMI[33].

Our findings of a positive relationship between aortic PWV and neonatal birth weight in the control group contrast with the findings of a smaller study[15], which reported that each 1 m/s increase in PWV was associated with a 17.6% decrease in birth-weight centile. Also, we did not find a significant relationship between MAP or TPR and birth-weight centile in either group, whereas Guy *et al.*[13] reported a negative association between neonatal birth weight and both MAP ($r = -0.067$, $P < 0.0001$) and TPR ($r = -0.133$, $P < 0.0001$). This contrast might be explained by the differences between our population and that examined by Guy *et al.*[13]; whilst women who developed PE or PIH were excluded from their population, they did not exclude women with other conditions known

to affect maternal hemodynamics, including chronic hypertension, diabetes, systemic lupus erythematosus and antiphospholipid syndrome. The MAP for Guy *et al.*'s[13] study population as a whole was not reported, but data presented for subgroups of their cohort show that the lowest observed median and interquartile range for MAP occurred in the appropriate-for-gestational-age (AGA) group, not the LGA group. The data also suggest that our cohort had a lower BP than theirs, since the median MAP in our cohort was equal to the 25th centile in their AGA group (84.0 mmHg), and the 75th centile in our cohort (89.5 mmHg) was similar to the median MAP in their AGA group (89.7 mmHg).

DBP has an inverted U-shaped relationship with birth weight, which increases as DBP increases up to 70 mmHg, plateaus until a DBP of 90 mmHg and then falls as DBP increases further[34]. Maternal chronic hypotension has also been associated with low neonatal birth weight[35,36]. Since DBP is a function of MAP, we propose that MAP could also be related to birth weight in a non-linear manner. An inverted U-shaped relationship would explain why the population of Guy *et al.*[13], with higher MAPs, showed a negative relationship with birth weight, while our cohort, with a lower distribution of MAP, demonstrated both positive and negative relationships, producing an indeterminate effect overall.

We found that the relationships between neonatal birth weight and maternal hemodynamics in pregnancies complicated by GDM were similar to those in the normotensive, non-diabetic controls. However, there was no difference between the two groups in most of the hemodynamic measurements, the birth-weight centile and the rate of LGA. This homogeneity of the two groups may explain the similarity in behavior
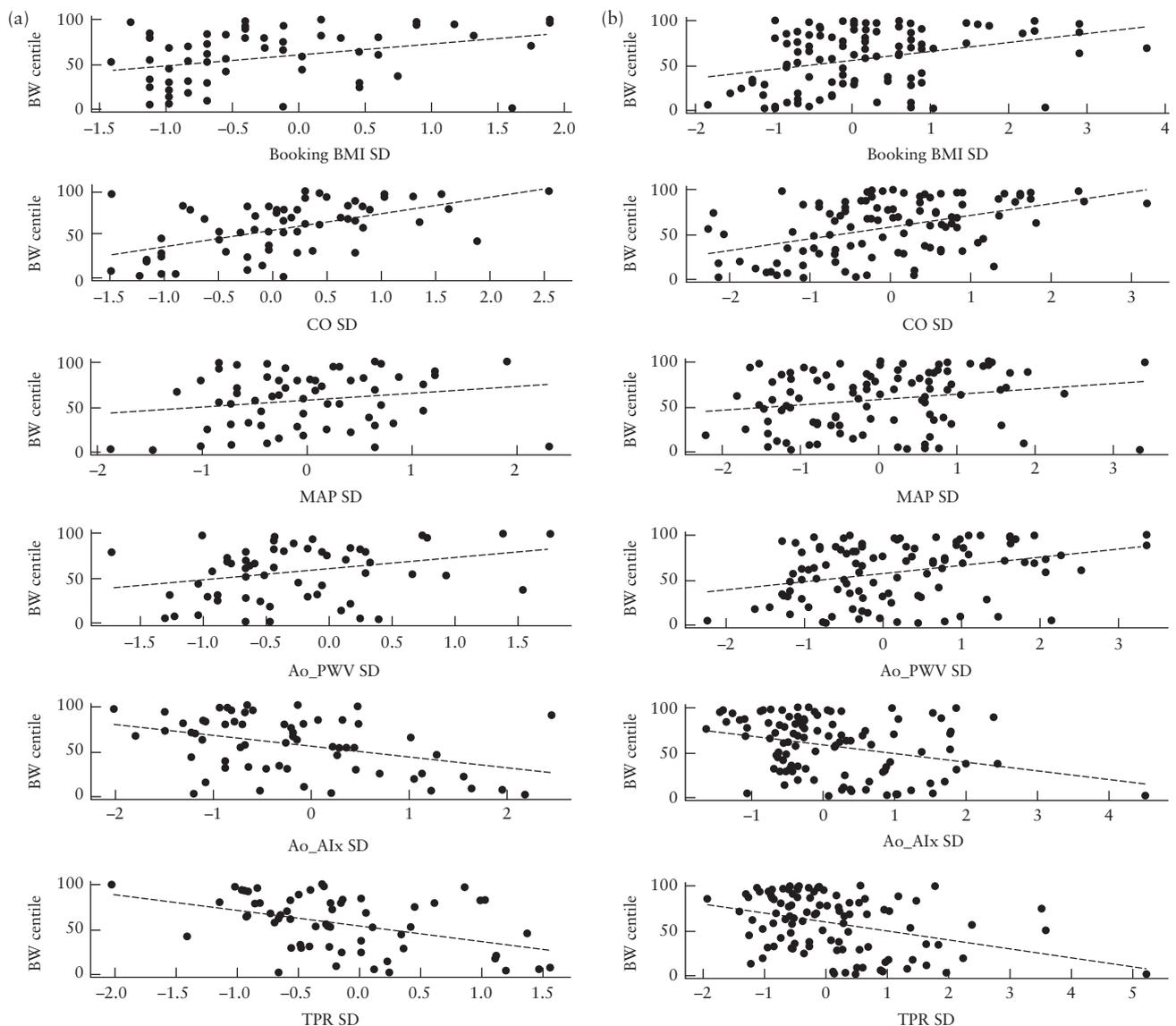
Figure 1 Scatterplots showing relationship between maternal hemodynamic variables and birth-weight (BW) centile in healthy control pregnancies (a) and in those affected by gestational diabetes mellitus (b). Ao_AIx, aortic augmentation index; Ao_PWV, aortic pulse wave velocity; BMI, body mass index; CO, cardiac output; MAP, mean arterial pressure; TPR, total peripheral resistance.

of their hemodynamics in relation to neonatal birth weight.

There was no significant interaction between maternal hemodynamic variables and neonatal birth weight amongst women with GDM controlled with diet alone, due to the larger 95% CIs for the effect estimates, likely because of the smaller sample size of patients in this subanalysis. With the exception of MAP, the directions of the associations did not change with the removal of patients controlled by pharmacological management. Thus, we did not observe an effect of pharmacological treatment of GDM on the relationship between maternal hemodynamics and birth weight in this cohort.
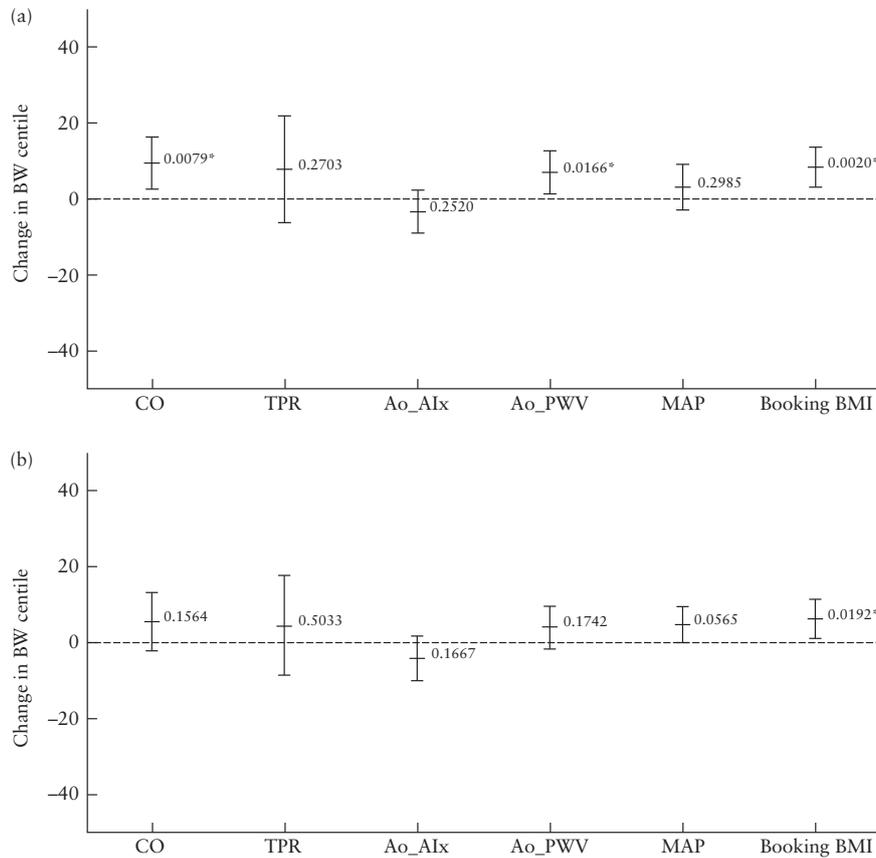
Figure 2 Effects of maternal hemodynamic variables on birth-weight (BW) centile in healthy control pregnancies (a) and in those affected by gestational diabetes mellitus (b). Plots represent mean and 95% CI change in BW centile for each SD increase in hemodynamic variable. *Results are significant if 95% CI does not include 0. *P*-values for significance are provided adjacent to each plot. Ao_AIx, aortic augmentation index; Ao_PWV, aortic pulse wave velocity; BMI, body mass index; CO, cardiac output; MAP, mean arterial pressure; TPR, total peripheral resistance.
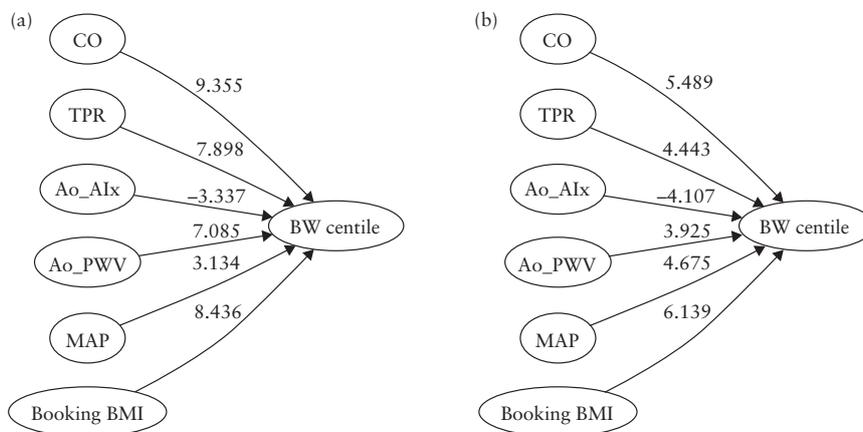
Figure 3 Quantitative effects of maternal hemodynamic variables on birth-weight (BW) centile in healthy control pregnancies (a) and in those affected by gestational diabetes mellitus (b). Numbers represent change in BW centile for an increase of 1 SD in the corresponding variable. Ao_AIx, aortic augmentation index; Ao_PWV, aortic pulse wave velocity; BMI, body mass index; CO, cardiac output; MAP, mean arterial pressure; TPR, total peripheral resistance.
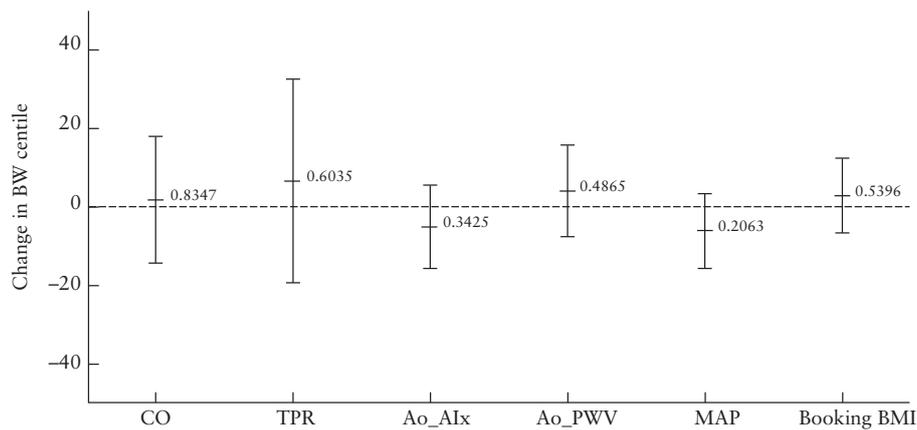
Figure 4 Effects of maternal hemodynamic variables on birth-weight (BW) centile amongst women with gestational diabetes mellitus controlled by dietary management. Plots represent mean and 95% CI change in BW centile for each SD increase in hemodynamic variable. Results would be significant if 95% CI did not include 0. *P*-values for significance are provided adjacent to each plot. Ao_AIx, aortic augmentation index; Ao_PWV, aortic pulse wave velocity; BMI, body mass index; CO, cardiac output; MAP, mean arterial pressure; TPR, total peripheral resistance.

Strengths and limitations

Causal inference has been used previously to investigate relationships between neonatal birth weight, smoking and perinatal morbidity[37,38], but, to our knowledge, this study is the first to employ graphical causal inference methodology to investigate the effect of hemodynamics on birth weight. It is a strength of this analysis that significant results can be interpreted not just as associations between the variables, but also as causal relationships, in which the change in the hemodynamic variable produces the change in birth weight.

A potential limitation is that the gestational age at hemodynamic assessment was earlier in the GDM group compared with the control group, but, since the change in maternal hemodynamics in the late third trimester is relatively small[1,2], this is unlikely to have impacted the final results. Our study was limited by the inclusion of only English-speaking women, which had an impact on the number of subjects included in the study and thus the sample size, and by the similarity in hemodynamics and birth weight between the control and study groups.

Clinical and research implications

Our results demonstrate the significant contribution of maternal BMI to neonatal birth weight, and highlight the importance of prepregnancy lifestyle interventions to improve weight loss among overweight and obese women[39].

Since the influence of hemodynamics on neonatal birth weight was similar between both groups, our findings suggest that FGR in pregnancies complicated by GDM could indicate maladaptation of the maternal cardiovascular system. GDM is associated with cardiovascular dysfunction[40,41] which predates the onset of clinical disease[42,43], and our results demonstrate the potential impact of this on neonatal birth weight.

Finally, we propose that the contrasting findings regarding MAP and birth weight between our current and a previous study[13] may be explained by a non-linear relationship between these variables. Larger studies involving women with MAP at both the upper and lower extremes are required to test this hypothesis, which has significant implications for BP targets during pregnancy. The Control of Hypertension in Pregnancy Study[44] demonstrated that, among women with chronic hypertension and PIH, tight BP control was not associated with an increase in SGA. However, the mean DBP in the tight and 'less tight' groups were 85.3 mmHg and 89.9 mmHg, respectively – both of which would sit within the plateaued portion of the DBP/birth-weight curve proposed by Steer *et al.*[34]. NICE guidelines[19] propose a BP of $< 135/85$ mmHg as a goal in the management of gestational hypertensive disorders, but also acknowledge that there is 'no evidence on target BP levels for PE'. Defining an inverse U-shaped relationship between MAP and neonatal birth weight would enable identification of optimal 'windows' for target BP in pregnancy, in which lower, as well as upper, boundaries of ideal values are defined.

Conclusions

Using a graphical causal inference methodology, we have demonstrated that maternal hemodynamics influence neonatal birth weight among women with GDM in a similar manner to that in non-diabetic, normotensive controls. Our findings suggest that FGR in pregnancies complicated by GDM could indicate maladaptation of the maternal cardiovascular system. Differences between our findings and those of previous work could be reconciled by the presence of a non-linear relationship between MAP and birth weight; this warrants further investigation.

REFERENCES

1. Mulder EG, de Haas S, Mohseni Z, Schartmann N, Hasson A, Alsadah F, van Kuijk SMJ, van Drongelen J, Spaanderman MEA, Ghossein-Doha C. Cardiac output and peripheral vascular resistance during normotensive and hypertensive pregnancy – a systematic review and mata-analysis. *BJOG* 2022; **129**: 696–707.
2. Meah VL, Cockroft JR, Backx K, Shave R, Stöhr. Cardiac output and related haemdynamics during pregnancy: a series of meta-analyses. *Heart* 2016; **102**: 518–526.
3. Robb AO, Mills NL, Din JN, Smith IBJ, Paterson F, Newby DE, Denison F. Influence of the menstrual cycle, pregnancy, and preeclampsia on arterial stiffness. *Hypertension* 2009; **53**: 952–958.
4. 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**: 256–261.
5. Tay J, Foo L, Masini G, Bennett PR, McEniery CM, Wilkinson IB, Lees CC. Early and late preeclampsia are characterized by high cardiac output, but in presence of fetal growth restriction, cardiac output is low: insights from a prospective study. *Am J Obstet Gynecol* 2018; **218**: 517.e1–e12.
6. Stott D, Papastefanou I, Paraschiv D, Clark K, Kametas NA. Longitudinal maternal hemodynamics in pregnancies affected by fetal growth restriction. *Ultrasound Obstet Gynecol* 2017; **49**: 761–768.
7. Roberts LA, Ling HZ, Poon LC, Nicolaides KH, Kametas NA. Maternal haemodynamics, fetal biometry and Doppler indices in pregnancies follwed up for suspected fetal growth restriction. *Ultrasound Obstet Gynecol* 2018; **52**: 507–514.
8. Perry H, Gutierrez J, Binder J, Thilaganathan B, Khalil A. Maternal arterial stiffness in hypertensive pregnancies with and without small-for-gestational-age neonate. *Ultrasound Obstet Gynecol* 2020; **56**: 44–50.
9. Osman MW, Nath M, Breslin E, Khalil A, Webb DR, Robinson TG, Mousa HA. 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**: 1005–1014.
10. Webster LM, Myers JE, Nelson-Piercy C, Mills C, Watt-Coote I, Khalil A, Seed PT, Cruickshank JK, Chappell LC. Longitudinal changes in vascular function parameters in pregnant women with chronic hypertension and association with adverse outcome: a cohort study. *Ultrasound Obstet Gynecol* 2019; **53**: 638–648.
11. Bramham K, Parnell B, Nelson-Piercy C, Seed PT, Poston L, Chappell LC. Chronic hypertension and pregnancy outcomes: systematic review and meta-analysis. *BMJ* 2014; **348**: g2301.
12. Odegård RA, Vatten LJ, Nilseon ST, Salvesen KA, Austgulen R. Preeclampsia and fetal growth. *Obstet Gynecol* 2000; **96**: 950–955.
13. Guy GP, Ling HZ, Machuca M, Poon LC, Nicolaides KH. Maternal cardiac function at 35–37 weeks' gestation: relationship with birth weight. *Ultrasound Obstet Gynecol* 2017; **49**: 67–72.
14. Khan F, Mires G, Macleod M, Belch JJF. Relationship between maternal arterial wave reflection, microvascular function and fetal growth in normal pregnancy. *Microcirculation* 2010; **17**: 608–614.
15. Elvan-Taspinar A, Franx A, Bots ML, Koomans HA, Bruinse HW. Arterial stiffness and fetal growth in normotensive pregnancy. *Am J Hypertens* 2005; **18**: 337–341.
16. He XJ, Qin FY, Hu CL, Zhu M, Tian CQ, Li L. Is gestational diabetic mellitus an independent risk factor for macrosomia: a meta-analysis? *Arch Gynecol Obstet* 2015; **291**: 729–735.
17. Tennant PWG, Murray EJ, Arnold KF, Berrie L, Fox MP, Gadd SC, Harrison WJ, Keeble C, Ranker LR, Textor J, Tomova GD, Gilthorpe MS, Ellison GTH. Use of directed acyclic graphs (DAGs) to identify confounders in applied health research: review and recommendations. *Int J Epidemiol* 2021; **50**: 620–632.
18. Von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP; STROBE Initiative. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *J Clin Epidemiol* 2008; **61**: 344–349.
19. 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.
20. National Institute for Health and Care Excellence (NICE). Diabetes in pregnancy: management from preconception to the postnatal period [NICE Guideline NG3]. 2015. https://www.nice.org.uk/guidance/ng3.
21. Fetal Medicine Foundation: Birth weight assessment. https://fetalmedicine.org/research/assess/bw.
22. Osman MW, Leone F, Nath M, Khalil A, Webb DR, Robinson TG, Mousa HA. Diurnal variation and repeatability of arterial stiffness and cardiac output measurements in the third trimester of uncomplicated pregnancy. *J Hypertens* 2017; **35**: 2436–2442.
23. Horváth IG, Németh Á, Lenkey Z, Alessandri N, Tufano F, Kis P, Gaszner B, Cziráki A. Invasive validation of a new oscillometric device (Arteriograph) for measuring augmentation index, central blood pressure and aortic pulse wave velocity. *J Hypertens* 2010; **28**: 2068–2075.
24. Tensiomed: Arteriograph User Manual. https://www.tensiomed.com/app/download/8273664556/Arteriograph+User+Manual.pdf?t=1641383959
25. Vinayagam D, Patey O, Thilaganathan B, Khalil A. Cardiac output assessment in pregnancy: comparison of two automated monitors with echocardiography. *Ultrasound Obstet Gynecol* 2017; **49**: 32–38.
26. Doherty A, El-Khuffash A, Monteith C, McSweeney L, Breatnach C, Kent E, Tully E, Malone F, Thornton P. Comparison of bioreactance and echocardiographic non-invasive cardiac output monitoring and myocardial function assessment in primigravida women. *Br J Anaesth* 2017; **118**: 527–532.
27. Textor J, Ven der Zander B, Gilthorpe MS, Liśkiewicz M, Ellison GTH. Robust causal inference using directed acyclic graphs: the R package 'dagitty'. *Int J Epidemiol* 2016; **45**: 1887–1894.
28. Sharma A, Kiciman E. DoWhy: An end-to-end library for causal inference. https://arxiv.org/abs/2011.04216.
29. Ding Y, Zhou Y, Ling P, Feng X, Luo S, Zheng X, Little PJ, Xu S, Weng J. Metformin in cardiovascular diabetology: a focused review of its impact on endothelial function. *Theranostics* 2021; **11**: 9376–9396.
30. Potenza MA, Addabbo F, Montagnani M. Vascular actions of insulin with implications for endothelial dysfunction. *Am J Physiol Endocrinol Metab* 2009; **297**: E568–577.
31. Anness AR, Baldo A, Webb DR, Khalil A, Robinson TG, Mousa HA. Effect of metformin on biomarkers of placental-mediated disease: A systematic review and meta-analysis. *Placenta* 2021; **107**: 51–58.
32. Osman MW, Nath M, Khalil A, Webb DR, Robinson TG, Mousa HA. The effects of metformin on maternal haemodynamics in gestational diabetes: A pilot study. *Diabetes Res Clin Pract* 2018; **139**: 170–178.
33. Strøm-Roum EM, Tanbo TG, Eskild A. The associations of maternal body mass index with birthweight and placental weight. Does maternal diabetes matter? A population study of 106 191 pregnancies. *Acta Obstet Gynecol Scand* 2016; **95**: 1162–1170.
34. Steer PJ, Little MP, Kold-Jensen T, Chapple J, Elliot P. Maternal blood pressure in pregnancy, birth weight, and perinatal mortality in first births: prospective study. *BMJ* 2004; **329**: 1312.
35. Ng PH, Walters WAW. The effects of chronic maternal hypotension during pregnancy. *Aus NZ J Obstet Gynaecol* 1992; **32**: 14–16.
36. Grünberger W, Leodolter S, Parschalk O. Maternal hypotension: fetal outcome in treated and untreated cases. *Gynecol Obstet Invest* 1979; **10**: 32–38.
37. Hernández-Diaz S, Schisterman EF, Hernán MA. The Birth Weight "Paradox" Uncovered? *Am J Epidemiol* 2006; **164**: 1115–1120.
38. Brand JS, Gaillard R, West J, McEachan RRC, Wright J, Voerman E, Felix JF, Tilling K, Lawlor DA. Associations of maternal quitting, reducing, and continuing smoking during pregnancy with longitudinal fetal growth: Findings from Mendelian randomization and parental negative control studies. *PLoS Med* 2019; **16**: e1002972.
39. Lan L, Harrison CL, Misso M, Hill B, Teede HJ, Mol BW, Moran LJ. Systematic review and meta-analysis of the impact of preconception lifestyle interventions on fertility, obstetric, fetal, anthropometric and metabolic outcomes in men and women. *Hum Reprod* 2017; **32**: 1925–1940.
40. Buddeberg BS, Sharma R, O'Driscoll JM, Kaelin Agten A, Khalil A, Thilaganathan B. Impact of gestational diabetes mellitus on maternal cardiac adaptation to pregnancy. *Ultrasound Obstet Gynecol* 2020; **56**: 240–246.
41. Aguilera J, Sanchez Sierra A, Abdel Azim S, Georgiopoulos G, Nicolaides KH, Charakida M. Maternal cardiac function in gestational diabetes mellitus at 35–36 weeks' gestation and 6 months postpartum. *Ultrasound Obstet Gynecol* 2020; **56**: 247–254.
42. Khalil A, Garcia-Mandujano R, Chiriac R, Akolekar R, Nicolaides KH. Maternal hemodynamics at 11–13 weeks' gestation in gestational diabetes mellitus. *Fetal Diagn Ther* 2012; **31**: 216–220.
43. Gibbone E, Wright A, Vallenas Campos R, Anzoategui S, Nicolaides KH, Charakida M. Maternal cardiac function at 19–23 weeks' gestation in prediction of gestational diabetes mellitus. *Ultrasound Obstet Gynecol* 2021; **58**: 77–82.
44. Magee LA, von Dadelszen P, Rey E, Ross S, Asztalos E, Murphy KE, Menzies J, Sanchez J, Singer J, Gafni A, Gruslin A, Helewa M, Hutton E, Lee SK, Lee T, Logan AG, Ganzevoort W, Welch R, Thornton JG, Moutquin J-M. Less-tight versus tight control of hypertension in pregnancy. *N Eng J Med* 2015; **372**: 407–417.

SUPPORTING INFORMATION ON THE INTERNET

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

Figure S1 Initial direct acyclic graph (DAG), representing causal relationships amongst various hemodynamic variables, baseline characteristics and birth weight.

Figure S2 Final direct acyclic graph (DAG), following removal of highly collinear variables from the initial DAG.

Figure S3 Heat map of collinearity of variables.