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Midgestation cardiovascular phenotype in women who develop gestational diabetes and hypertensive disorders of pregnancy: comparative study

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KEYWORDS: cardiovascular function; gestational diabetes; HDP; hypertensive disorder; midgestation

CONTRIBUTION

What are the novel findings of this work?
In midgestation, in women who subsequently develop hypertensive disorders of pregnancy (HDP), with or without gestational diabetes mellitus (GDM), there is evidence of impaired placentation, with decreased serum placental growth factor and increased impedance to peripheral blood flow, reflected by high mean arterial pressure, ophthalmic artery peak systolic velocity (PSV) ratio and peripheral vascular resistance on echocardiography. In contrast, in women who subsequently develop GDM, in the absence of HDP, biomarkers of placental function and ophthalmic artery PSV ratio are not significantly different from those in unaffected pregnancies. In both HDP and GDM pregnancies, there was a mild subclinical reduction in left myocardial deformation and left ventricular diastolic function.

What are the clinical implications of this work?
In midgestation, women at risk of GDM and those at risk of HDP show a similar pattern of cardiac alterations. However, assessment of peripheral vascular status revealed that ophthalmic artery PSV ratio is increased only in pregnancies that subsequently develop HDP in the presence or absence of GDM.

ABSTRACT

Objective *Women with gestational diabetes mellitus (GDM) and/or hypertensive disorders of pregnancy (HDP) are at increased long-term cardiovascular risk. Mild cardiac functional alterations have been detected in women with GDM or HDP in midgestation, prior to clinical onset of the disease, but these functional alterations have not been found to be useful as screening tools. In contrast, increased impedance to peripheral blood flow, measured by echocardiography or ophthalmic artery Doppler, has been shown to provide incremental value to maternal characteristics for the prediction of pre-eclampsia. However, it is unknown whether similar changes can be detected in women at risk of GDM. In this study, we performed detailed cardiovascular phenotyping in a large, unselected population of women in midgestation to identify similarities and differences in cardiovascular adaptation in women who are at risk of GDM and/or HDP.*

Methods *This was a prospective observational study in women attending for a routine hospital visit at 19 + 1 to 23 + 3 weeks' gestation. This visit included assessment of flow velocity waveforms from the maternal ophthalmic arteries, echocardiography for assessment of maternal cardiovascular function and measurement of uterine artery pulsatility index and serum placental growth factor (PlGF) for assessment of placental perfusion and function. The measured indices were converted to either multiples of the median (MoM) values or deviation from the median (delta) after adjusting for maternal characteristics and elements of medical history. Biomarker delta or MoM values in the GDM and HDP groups were compared with those in the unaffected group using 95% CI and* t*-tests.*

Results *The study population of 5214 pregnancies contained 4429 (84.9%) that were unaffected by GDM or HDP, 509 (9.8%) complicated by GDM without HDP, 41 (0.8%) with GDM and HDP, and 235 (4.5%) with HDP without GDM. In HDP cases, with or without*

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GDM, there was evidence of impaired placentation, with a decrease in PlGF, and increased impedance to flow in the peripheral circulation, suggested by an increase in ophthalmic artery peak systolic velocity (PSV) ratio, peripheral vascular resistance assessed on echocardiography and mean arterial pressure. In the GDM group without HDP, there was no evidence of altered placental perfusion or function and ophthalmic artery PSV ratio was not significantly different from that in the unaffected group; peripheral vascular resistance and mean arterial pressure were increased but to a lesser degree than in the HDP group. In the HDP group, there was an increase in global longitudinal systolic strain and slight increase in isovolumic relaxation time, while in the GDM group, there was an increase in mitral valve E/e′, myocardial performance index and global longitudinal systolic strain.

Conclusions *In midgestation, women who subsequently develop HDP or GDM have a mild subclinical reduction in left ventricular function. In HDP cases, with or without GDM, there is evidence of impaired placentation and all biomarkers of impedance to peripheral blood flow are consistently increased. In contrast, in the GDM group without HDP, biomarkers of placental function are normal and those of impedance to peripheral blood flow are either marginally increased or not significantly different from those in normal pregnancies. © 2022 International Society of Ultrasound in Obstetrics and Gynecology.*

INTRODUCTION

Epidemiological studies have shown consistently that women with gestational diabetes mellitus (GDM) and hypertensive disorders of pregnancy (HDP) are at increased risk of developing adverse cardiovascular events within the first decade after the index pregnancy[1–5]. Following this observation, several research groups have assessed the cardiovascular phenotype of women in pregnancy, aiming to explore the presence of latent disease prior to the development of pregnancy complications[6–8].

Echocardiographic studies have demonstrated that, in midgestation, women who are at risk of pre-eclampsia and those at risk of gestational hypertension have similar cardiovascular phenotype prior to the development of the outcome[6]. Left myocardial deformation was shown to be reduced, as assessed by global longitudinal systolic strain, and there was evidence of increased peripheral vascular resistance, as measured by echocardiography[6]. However, screening studies showed that assessment of these indices offers no significant benefit to routine screening which uses maternal characteristics to identify women at risk of HDP[7]. In contrast, impedance to peripheral blood flow assessed by ophthalmic artery Doppler can identify women at risk of HDP in all three trimesters of pregnancy[9–11]. Whether these findings suggest more established vascular disease in women at risk of HDP remains to be determined.

In midgestation, similar to women with HDP, women at risk of GDM have a mild reduction in their left systolic and diastolic ventricular function and mild increase in peripheral vascular resistance measured by echocardiography compared to women with uncomplicated pregnancy[12]. However, there are no data on the impedance to peripheral blood flow in these cases. Considering that women at risk of GDM share similar cardiovascular risk factors with women affected by HDP, it is reasonable to suggest that both conditions present with similar cardiovascular alterations prior to clinical development of the disease.

In the current study, we performed detailed cardiovascular phenotyping in a large, unselected population of women who attended the hospital for their routine clinical care. Our aim was to assess whether women at risk of GDM and those at risk of HDP show similar cardiovascular alterations during pregnancy, focusing in particular on measures of peripheral vascular status.

METHODS

Study design and participants

This was a prospective observational study of women attending for a routine hospital visit at 19 + 1 to 23 + 3 weeks' gestation at King's College Hospital, London, UK, between August 2019 and August 2021. This visit included recording of maternal demographic characteristics and medical history; ultrasound examination for fetal anatomy and growth; assessment of maternal cardiovascular function and flow velocity waveforms from the maternal ophthalmic arteries; measurement of mean arterial pressure (MAP) using validated automated devices (Microlife BPA2-B; Microlife AG Swiss Corporation, Widnau, Switzerland) and a standardized protocol, in which two blood pressure recordings were made in the right and left arms and the average of the four measurements was used for analysis[13]; transvaginal color Doppler ultrasound of the left and right uterine arteries and calculation of the mean uterine artery pulsatility index (UtA-PI)[14]; and measurement of serum concentration of placental growth factor (PlGF) and soluble fms-like tyrosine kinase-1 using an automated biochemical analyzer (BRAHMS KRYPTOR compact PLUS; Thermo Fisher Scientific, Hennigsdorf, Germany).

Gestational age was determined by the measurement of fetal crown–rump length at 11–13 weeks or fetal head circumference at 19–24 weeks[15,16]. The women gave written informed consent to participate in the study, which was approved by the NHS Research Ethics Committee. The inclusion criteria for this study were singleton pregnancy delivering a non-malformed liveborn or stillborn fetus. Exclusion criteria for the study were the presence of major fetal abnormality and inability to consent to the study. Women were excluded if they had breast implants, as these obscure echocardiographic windows.

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We have reported previously findings of cardiovascular function in a smaller dataset of the same cohort[12].

Ophthalmic artery Doppler

The mother was in the supine position for the routine 19 + 1 to 23 + 3-week scan and, at the end of this procedure, a 7.5-MHz linear transducer (Canon Aplio i900 PLT-704SBT Linear Probe; Canon Medical Systems Europe BV, Zoetermeer, The Netherlands) was placed transversely and gently over her closed upper eyelid after application of conduction gel. Color flow was used to identify the ophthalmic artery, which is found superior and medial to the hypoechoic band representing the optic nerve[17]. Pulsed-wave Doppler was then used to record three to five similar waveforms; the angle of insonation was kept at < 20°, the sample gate was 2 mm, the depth was 3.0–4.5 cm, the high-pass filter was 50 Hz and the pulse repetition frequency was set at 3–6 kHz. In order to minimize any potential adverse effects on the eyes, the duration of the examination was always less than 1 min and a special preset was used with significant reduction in output power and the maximum mechanical index was 0.4.

The ultrasound scans were carried out by obstetricians or sonographers, and minimal training (five supervised scans) was necessary to visualize the ophthalmic arteries, obtain flow velocity waveforms and record the necessary indices without technical difficulties in any of the patients. Waveforms were obtained in sequence from the right eye, left eye and again from the right and then left eye. The first and second peaks of systolic velocity were measured and the ratio of the second to first peak (PSV ratio) was calculated.

Maternal cardiovascular assessment

All participants were assessed using two-dimensional conventional and tissue Doppler transthoracic echocardiography at rest in the left lateral decubitus position, and data were acquired during unforced expiration (Canon Aplio i900 scanner; Canon Medical Systems Europe BV, Zoetermeer, The Netherlands). Speckle tracking was employed to assess global longitudinal systolic strain of the left ventricle.

The protocol included standard parasternal and apical views, and systolic and diastolic left ventricular functional indices were obtained as per the American Society of Echocardiography and European Cardiovascular Imaging guidelines[18,19]. Echocardiography was performed by fetal medicine fellows who were trained in acquisition and analysis of echocardiograms. All fellows were blinded to patients' medical history when obtaining and analyzing echocardiographic data. In a previous study, we reported excellent interobserver reproducibility of various cardiac indices[20].

The measured hemodynamic parameters included cardiac output and peripheral vascular resistance, as reported previously[20,21]. Left ventricular systolic function was assessed by measuring ejection fraction, myocardial performance index and global longitudinal strain. Left ventricular diastolic function was evaluated by measuring mitral peak early (E) and late (A) diastolic flow velocities, and E/A ratio was calculated. Left ventricular filling pressure was assessed by E/e′ ratio from pulsed tissue Doppler recordings obtained at the septal and lateral aspects of the basal left ventricle at the junction with the mitral valve annulus in the apical four-chamber view. Time intervals (isovolumic contraction and relaxation time) were measured as described previously[20]. Left atrial area was measured in the apical four-chamber view at end systole in the frame just prior to mitral valve opening by tracing the left atrial border, excluding the area under the mitral valve annulus and the inlet of the pulmonary veins. Measurements were indexed to body surface area. Left ventricular mass was calculated with the Devereux formula using measurements of the anatomical M-mode applied in the parasternal long axis[20].

Outcome measure

Outcome measures were delivery with pre-eclampsia or gestational hypertension, grouped as HDP without GDM, GDM without HDP, GDM with HDP and unaffected by HDP or GDM. Data on pregnancy outcome were collected from the hospital maternity records or the general medical practitioners of the women.

Diagnosis of gestational hypertension was based on the finding of hypertension (systolic blood pressure of ≥ 140 mmHg or diastolic blood pressure of ≥ 90 mmHg on at least two occasions 4 h apart developing after 20 weeks' gestation in previously normotensive women). Diagnosis of pre-eclampsia was based on the finding of new-onset hypertension or chronic hypertension and at least one of the following: proteinuria (≥ 300 mg/24 h or protein-to-creatinine ratio ≥ 30 mg/mmol or ≥ 2+ on dipstick testing), renal insufficiency with serum creatinine > 97 μmol/L in the absence of underlying renal disease, hepatic dysfunction with blood concentration of transaminases more than twice the upper limit of normal (≥ 65 IU/L for our laboratory), thrombocytopenia (platelet count < 100 000/μL), neurological complications (e.g. cerebral or visual symptoms) and pulmonary edema[22].

The diagnosis of GDM was based on a 75-g oral glucose tolerance test (OGTT). The diagnostic criteria were fasting plasma glucose level ≥ 5.6 mmol/L and/or 2-h plasma glucose level ≥ 7.8 mmol/L[23]. There was a two-stage screening policy for GDM. First, women with at least one risk factor (body mass index > 30 kg/m^2, previous birth of a macrosomic baby weighing > 4.5 kg, previous GDM, first-degree relative with diabetes or persistent glucosuria) were offered measurement of glycosylated hemoglobin (HbA1c) at booking and, if the value was ≥ 5.7%, then they had an OGTT, usually at around 12 weeks' gestation. Second, in all women at 26–28 weeks' gestation, plasma glucose level was measured 1–2 h after eating ≥ 50 g of carbohydrate, and, if the concentration was ≥ 6.7 mmol/L, an OGTT was carried out. An OGTT was also performed if there was polyhydramnios or the fetus became macrosomic.

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Statistical analysis

Data are expressed as median (interquartile range (IQR)) for continuous variables and *n* (%) for categorical variables. Mann–Whitney *U*-test and chi-square test or Fisher's exact test were used to compare outcome groups for continuous and categorical data, respectively.

The measured values of MAP, UtA-PI, PlGF and the cardiovascular indices were converted to multiples of the median (MoM) or deviation from the median (delta) to remove the effects of characteristics such as gestational age, weight, race, method of conception, medical conditions and elements from the obstetric history associated with the individual being measured, as described previously[6]. Similarly, the measured ophthalmic artery PSV ratio was converted to delta. Biomarker delta or MoM values in the HDP and GDM groups were compared with those in the unaffected group by means of 95% CI and *t*-tests. The statistical software package R was used for data analysis[24].

RESULTS

Study participants

The study population of 5214 pregnancies contained 4429 (84.9%) that were unaffected by GDM or HDP, 509 (9.8%) complicated by GDM without HDP, 41 (0.8%) with GDM and HDP, and 235 (4.5%) with HDP without GDM. Maternal and pregnancy characteristics of the study population are summarized in Table 1. In the group with GDM without HDP, compared with unaffected pregnancies, there was a higher median maternal age, weight and body mass index, higher proportions of non-white women, those with chronic hypertension and parous women. In the group with HDP in the absence of GDM, compared with unaffected pregnancies, there was a higher median maternal weight and body mass index, and higher proportion of non-white women, those with chronic hypertension, pre-existing diabetes mellitus, autoimmune disease, use of assisted reproduction, nulliparous women and parous women with pre-eclampsia in a previous pregnancy.

Table 1 Maternal and pregnancy characteristics of study population

Characteristic	*Unaffected* (n = *4429*)	*HDP only* (n = *235*)	*GDM only* (n = *509*)	*GDM with HDP* (n = *41*)
Age (years)	33.2 (30.1–36.2)	33.5 (30.8–36.9)	34.2 (30.7–37.4)*	32.5 (28.6–39.1)
Weight (kg)	70.0 (63.0–78.4)	76.0 (67.0–84.0)*	87.7 (66.4–89.0)*	85.0 (76.0–96.0)*
Height (cm)	166 (162–170)	167 (162–171)	165 (160–169)*	164 (158–170)
Body mass index (kg/m^2)	25.3 (23.0–28.4)	27.1 (24.3–30.8)*	28.1 (25.0–33.3)*	31.5 (29.3–35.4)*
Gestational age (weeks)	21.3 (20.9–21.6)	21.3 (21.0–21.6)*	21.3 (20.9–21.6)*	21.3 (20.9–21.6)*
Racial origin				
White	3376 (76.2)	174 (74.0)	289 (56.8)	16 (39.0)
Black	537 (12.1)	43 (18.3)	106 (20.8)	16 (39.0)
South Asian	260 (5.9)	10 (4.3)	57 (11.2)	5 (12.2)
East Asian	105 (2.4)	2 (0.9)	35 (6.9)	3 (7.3)
Mixed	151 (3.4)	6 (2.6)	22 (4.3)	1 (2.4)
Medical history				
Chronic hypertension	54 (1.2)	9 (3.8)*	15 (2.9)*	3 (7.3)*
Type-I DM	11 (0.2)	4 (1.7)*	0 (0)	0 (0)
Type-II DM	13 (0.3)	1 (0.4)*	0 (0)	0 (0)
SLE/APS	10 (0.2)	3 (1.3)*	0 (0)	0 (0)
Smoker	54 (1.2)	6 (2.6)*	4 (0.8)	0 (0)*
Method of conception				
Spontaneous	4153 (93.8)	210 (89.4)	481 (94.5)*	34 (82.9)*
In-vitro fertilization	245 (5.5)	24 (10.2)*	28 (5.5)	7 (17.1)
Ovulation induction drugs	31 (0.7)	1 (0.4)*	0 (0)	0 (0)
Parity				
Nulliparous	2414 (54.5)	155 (66.0)*	225 (44.2)	23 (56.1)
Parous, no previous PE	1935 (43.7)	58 (24.7)	260 (51.1)	12 (29.3)
Parous, previous PE	80 (1.8)	22 (9.4)*	24 (4.7)	6 (14.6)
Interpregnancy interval (years)	2.4 (1.5–4.1)	3.2 (2.1–5.9)*	2.8 (1.6–5.0)	4.5 (2.2–6.2)

Data are given as median (interquartile range) or *n* (%). Comparisons between outcome groups were carried out using chi-square or Fisher's exact test for categorical variables and Mann–Whitney *U*-test for continuous variables. *Significantly different from unaffected pregnancies. DM, diabetes mellitus; GDM, gestational diabetes mellitus; HDP, hypertensive disorders of pregnancy; PE, pre-eclampsia; SLE/APS, systemic lupus erythematosus/antiphospholipid syndrome.

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Distribution of biomarkers in GDM, HDP and unaffected pregnancies

The means, with 95% CI, of biomarkers delta or MoM values of placental perfusion and function, ophthalmic artery Doppler and cardiovascular indices in the GDM and HDP groups, compared with unaffected pregnancies, are presented in Table 2 and some of them are illustrated in Figure 1.

In HDP cases, with or without GDM, there was evidence of impaired placentation, with a decrease in PlGF, and increased impedance to flow in the peripheral circulation, suggested by an increase in ophthalmic artery PSV ratio, peripheral vascular resistance assessed on echocardiography and MAP. In the GDM group without HDP, there was no evidence of altered placental perfusion or function and ophthalmic artery PSV ratio was not significantly different from that in the unaffected group;

Table 2 Mean (95% CI) multiples of the median (MoM) or deltas of biomarkers in adverse-outcome and unaffected groups

Parameter	*Unaffected (n = 4429)*	*HDP only (n = 235)*	*GDM only (n = 509)*	*GDM with HDP (n = 41)*
Placental perfusion and function				
Uterine artery pulsatility index MoM	1.000 (0.991–1.009)	1.102 (1.061–1.144)*	0.995 (0.969–1.020)	1.082 (0.988–1.184)
Placental growth factor MoM	1.002 (0.988–1.016)	0.789 (0.742–0.839)*	1.005 (0.964–1.048)	0.792 (0.685–0.915)*
Ophthalmic artery peak systolic velocity ratio delta	0.002 (−0.001 to 0.005)	0.051 (0.039–0.063)*	0.0004 (−0.008 to 0.008)	0.0464 (0.018–0.075)*
Left ventricular diastolic function				
Mitral valve E delta	0.006 (−0.483 to 0.495)	−0.149 (−2.268 to 1.970)	0.115 (−1.328 to 1.557)	−1.271 (−6.462 to 3.920)
Mitral valve A MoM	0.998 (0.990–1.007)	0.996 (0.960–1.033)	1.020 (0.995–1.046)	0.964 (0.882–1.053)
Mitral valve E/A MoM	1.002 (0.993–1.012)	0.998 (0.958–1.041)	0.980 (0.953–1.009)	1.004 (0.907–1.112)
Mitral valve E/e′ MoM	0.999 (0.992–1.005)	1.023 (0.995–1.053)	1.037 (1.017–1.058)*	1.037 (0.967–1.113)
Isovolumic relaxation time delta	−0.114 (−0.490 to 0.262)	1.972 (0.343–3.601)*	0.913 (−0.195 to 2.022)	0.973 (−3.017 to 4.963)
Left atrial area delta†	−0.007 (−0.053 to 0.040)	0.0767 (−0.127 to 0.280)	0.029 (−0.107 to 0.166)	−0.064 (−0.569 to 0.440)
Left atrial volume MoM†	0.999 (0.990–1.008)	1.0165 (0.975–1.059)	1.003 (0.976–1.031)	0.978 (0.883–1.083)
Left ventricular systolic function				
Myocardial performance index MoM	0.999 (0.993–1.005)	1.020 (0.995–1.046)	1.028 (1.010–1.045)*	1.011 (0.952–1.075)
Global longitudinal systolic strain delta	−0.007 (−0.075 to 0.061)	0.446 (0.149–0.742)*	0.244 (0.043–0.446)*	0.319 (−0.404 to 1.042)
Ejection fraction delta	−0.027 (−0.227 to 0.173)	−0.524 (−1.396 to 0.348)	0.330 (−0.260 to 0.921)	1.877 (−0.236 to 3.989)
Mitral valve S′ delta	0.014 (−0.035 to 0.063)	−0.130 (−0.341 to 0.081)	−0.027 (−0.170 to 0.117)	−0.447 (−0.964 to 0.070)
Isovolumic contraction time delta	−0.061 (−0.393 to 0.271)	−0.188 (−1.625 to 1.250)	0.731 (−0.248 to 1.709)	−1.447 (−4.968 to 2.073)
Hemodynamic parameter				
Peripheral vascular resistance MoM	1.000 (0.994–1.006)	1.099 (1.070–1.128)*	1.023 (1.004–1.041)*	1.134 (1.062–1.210)*
Mean arterial pressure MoM	1.000 (0.998–1.002)	1.076 (1.065–1.087)*	1.009 (1.002–1.016)*	1.070 (1.045–1.096)*
Left ventricular cardiac output MoM	1.000 (0.993–1.006)	0.995 (0.968–1.023)	1.007 (0.988–1.026)	0.999 (0.934–1.067)
Left ventricular stroke volume delta†	0.096 (−0.143 to 0.335)	−0.899 (−1.926 to 0.146)	−0.273 (−0.978 to 0.432)	−1.961 (−4.493 to 0.571)
Structural marker				
Left ventricular mass delta†	−0.065 (−0.350 to 0.221)	0.603 (−0.643 to 1.849)	0.124 (−0.720 to 0.968)	2.093 (−0.926 to 5.11)

*Significantly different from unaffected pregnancies. †Indexed to body surface area. GDM, gestational diabetes mellitus; HDP, hypertensive disorders of pregnancy.

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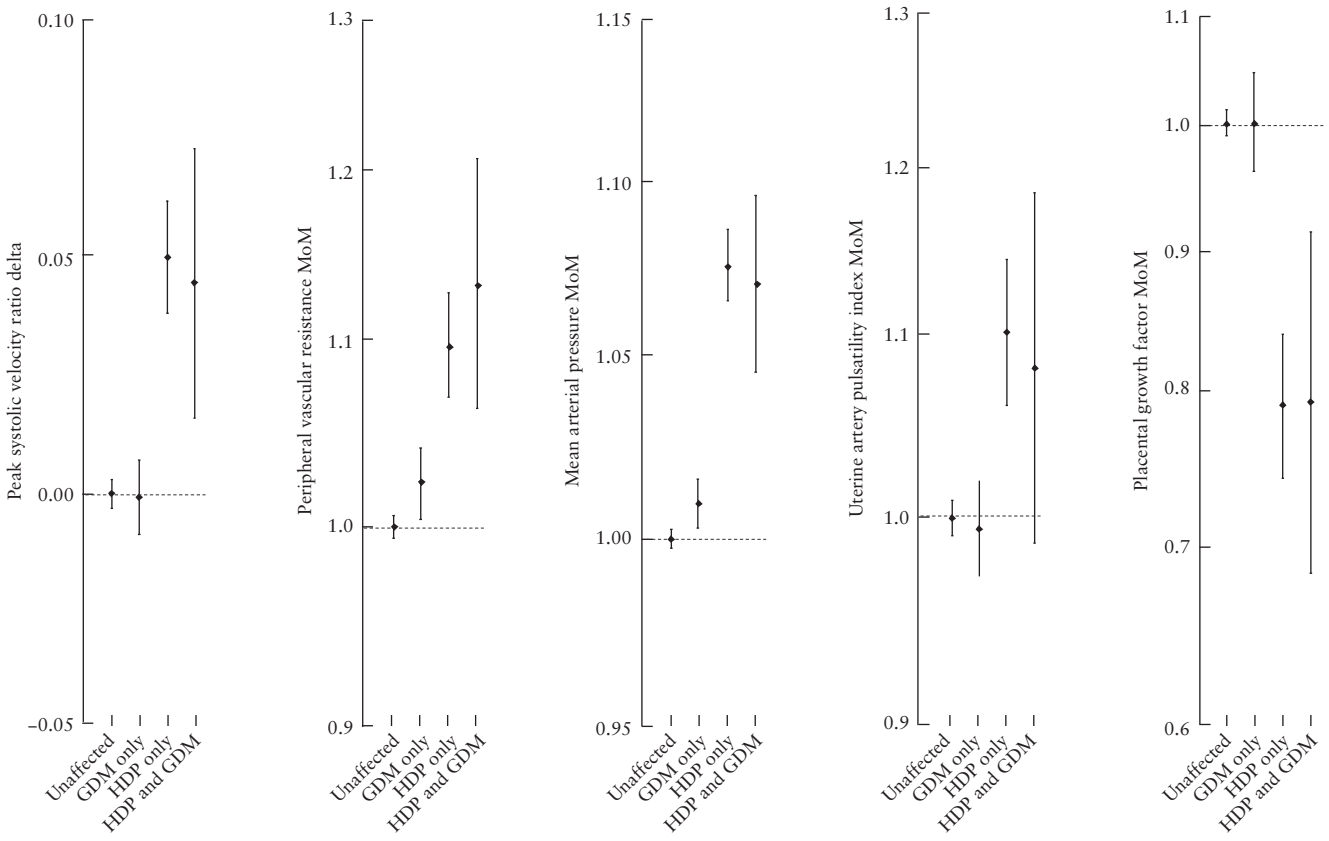

Figure 1 Mean with 95% CI of ophthalmic artery peak systolic velocity ratio delta, peripheral vascular resistance multiples of the median (MoM), mean arterial pressure MoM, uterine artery pulsatility index MoM and placental growth factor MoM in pregnancies with gestational diabetes mellitus (GDM) only, hypertensive disorders of pregnancy (HDP) only or both GDM and HDP, and in pregnancies unaffected by HDP or GDM.

peripheral vascular resistance and MAP were increased but to a lesser degree than in the HDP group. In the HDP group, there was an increase in global longitudinal systolic strain and isovolumic relaxation time, while in the GDM group, there was an increase in mitral valve E/e′, myocardial performance index and global longitudinal systolic strain.

DISCUSSION

Principal findings of this study

In this prospective screening study of an unselected population of singleton pregnancies at 19–23 weeks' gestation, we assessed maternal ophthalmic artery Doppler and cardiovascular function. There were three main findings: first, in the presence of HDP, with or without GDM, there was evidence of impaired placentation, with a decrease in PlGF, and increased impedance to peripheral blood flow, as demonstrated by an increase in MAP, ophthalmic artery PSV ratio and echocardiographic estimation of peripheral vascular resistance. Second, in the GDM group without HDP, there was no evidence of altered placental perfusion or function and ophthalmic artery PSV ratio was not significantly different from that in the unaffected group; peripheral vascular resistance and MAP were increased but to a lesser degree than in the HDP groups. Third, in both HDP and GDM groups, there was mild subclinical reduction in left myocardial deformation and left ventricular diastolic function.

Interpretation of results and comparison with findings of previous studies

Women with GDM are at increased risk of developing HDP[25]. In our study, the incidence of HDP in women with GDM was 7.5% (41/550), whereas the incidence of HDP without GDM in the total population was 4.5% (235/5214). The mechanisms that underpin this relationship, however, remain unclear. For instance, cohort studies initiated in early or mid-pregnancy suggest that both GDM and pre-eclampsia may be more prevalent in women with greater insulin resistance[26,27]. It is also plausible that the association between GDM and hypertension reflects pre-existing common risk factors for the two conditions[25]. Women with GDM and HDP in our cohort had higher MAP, weight and body mass index compared to women with unaffected pregnancy. Additionally, it is possible that pre-existing latent cardiovascular disease in the mother can contribute to the development of these complications.

Consistent with our previous observations in a subgroup of the same cohort, we showed that, in women at risk of GDM, there is a mild subclinical

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derangement of systolic and diastolic left ventricular function, which persists after accounting for maternal characteristics[12]. In this expanded series, we found increased global longitudinal left ventricular systolic strain and myocardial performance index, suggesting mild reduction in myocardial contractility and ventricular function. The sensitive marker of diastolic function E/e′ was also increased, indicating an increase in left ventricular filling pressure. Similarly, there were cardiac alterations in women at risk of HDP; left myocardial deformation was reduced, whereas among left ventricular diastolic indices, only isovolumic relaxation time was mildly increased. Although pregnancy has been thought to act as a natural stress test which can unmask latent cardiovascular disease, the noted cardiac changes were mild and unlikely to be of clinical relevance. In addition, we have reported previously that these cardiac changes do not assist in the prediction of development of these pregnancy complications[6,12]. However, we cannot exclude the possibility that, with the clinical onset of HDP and GDM, the cardiac changes can be accentuated and contribute to the maternal long-term cardiovascular risk.

In the GDM group, the peripheral vascular markers, including MAP and peripheral vascular resistance assessed by echocardiography, were only mildly increased and ophthalmic artery PSV ratio did not differ from that in unaffected pregnancies. Development of GDM predicts later manifestation of the metabolic syndrome, including Type-II diabetes[28,29], and both these entities have been associated with vascular dysfunction and atherogenesis. However, our findings do not indicate significant vascular disease in women prior to GDM development and suggest that increased impedance to peripheral blood flow is predominantly a feature of women at risk of HDP, as these had consistently increased ophthalmic artery PSV ratio both in the presence and absence of GDM.

The contribution of placental dysfunction to the increased impedance to peripheral blood flow in the maternal circulation has not been explored extensively. In our cohort, women at risk of HDP had increased UtA-PI and reduced PlGF, whereas in women with GDM, these markers were unaffected. These findings suggest that low PlGF is indicative of pronounced endothelial dysfunction and possibly vascular disease, and might be predominantly a feature of women at risk of HDP[30]. This hypothesis would be consistent with findings from a recent large cohort study, in which women with low midgestation PlGF concentrations, compared to women with high PlGF, had higher blood pressure 6 and 9 years after pregnancy[31].

Strengths and limitations

The main strengths of the study are, first, prospective examination of a large, unselected population of pregnant women attending for a routine ultrasound examination in midgestation, second, use of standardized techniques for maternal ophthalmic artery and cardiovascular assessment by appropriately trained research fellows and, third, adjustment of measured indices for maternal characteristics and elements from the medical history. The main limitation of the study is that we did not assess metabolic parameters and, therefore, we can only speculate about the pathophysiology of mild reduction in cardiac function seen in women at risk of GDM.

Conclusions

Our study suggests that assessment of ophthalmic artery PSV ratio in pregnancy can provide useful information about peripheral vascular status and that this marker seems to be primarily affected in women at risk of HDP. Women at risk of GDM show subclinical reduction in cardiac function, whereas impedance to peripheral blood flow is largely unaffected.

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