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Ultrasound Obstet Gynecol 2024; **64**: 308–313
Published online 4 August 2024 in Wiley Online Library (wileyonlinelibrary.com). **DOI:** 10.1002/uog.27632

Long-term cardiovascular assessment of women with previous pregnancy complicated by hypertensive disorder

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KEYWORDS: cardiovascular risk; echocardiography; hypertensive disorder of pregnancy; maternal cardiovascular assessment; ophthalmic artery Doppler; speckle tracking

CONTRIBUTION

What are the novel findings of this work?
In midgestation, women who subsequently developed a hypertensive disorder of pregnancy (HDP) had increased ophthalmic artery peak systolic velocity ratio, reflective of increased peripheral vascular resistance. At 2 years postpartum, women who experienced HDP, compared to those who did not, continued to have mild cardiovascular abnormalities with alteration in left ventricular systolic and diastolic functional indices. Longitudinal analysis demonstrated that the evolution of cardiovascular changes in the HDP and non-HDP groups was similar.

What are the clinical implications of this work?
Mild cardiac functional and morphological alterations precede the development of HDP and such changes persist for at least 2 years postpartum. The cardiac changes are likely to be the consequence of pre-existing maternal cardiovascular risk factors rather than an adverse consequence of HDP.

ABSTRACT

Objectives *Women with a hypertensive disorder of pregnancy (HDP) are at increased risk of developing hypertension and cardiovascular disease later in life. However, from previous studies, it is difficult to define whether this association reflects pre-existing maternal cardiovascular risk or a potentially causal relationship between HDP and later cardiovascular risk. In this study, we performed detailed cardiovascular assessment in women in midgestation, prior to development of HDP, and at 2 years postpartum, aiming to identify cardiovascular changes prior to development of HDP and to assess persistent cardiovascular alterations long after the HDP event.*

Methods *This was a prospective observational study in which we performed detailed cardiovascular assessment in midgestation and at a median of 2.3 (interquartile range, 2.1–2.4) years postpartum. We examined 112 women who developed HDP and 451 women whose pregnancy was not complicated by hypertension. We used conventional and more advanced (i.e. speckle tracking) echocardiographic techniques to determine accurately left ventricular systolic and diastolic function. We used M-mode measurements to determine left ventricular remodeling and estimate left ventricular mass. Maternal vascular status was assessed using ophthalmic artery Doppler and by calculating peak systolic velocity (PSV) ratio, as a marker of peripheral vascular resistance.*

Results *In midgestation, women who subsequently developed HDP had increased ophthalmic artery PSV ratio. These women also had mild cardiac functional and morphological alterations, which were accounted for mostly by maternal cardiovascular risk factors. At 2 years postpartum, women who had experienced HDP, compared to those who did not, had cardiovascular abnormalities with reduction in left ventricular systolic and diastolic function, which remained after multivariable analysis. Longitudinal analysis demonstrated that the evolution of cardiovascular changes in the HDP and non-HDP groups was similar.*

Conclusions *Mild cardiac functional and morphological alterations precede the development of HDP and such changes persist for at least 2 years postpartum. The cardiac*

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Accepted: 21 February 2024

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INTRODUCTION

Epidemiological studies have indicated that development of a hypertensive disorder of pregnancy (HDP), which includes gestational hypertension (GH) and pre-eclampsia (PE), increases the maternal cardiovascular risk during their lifetime[1]. For example, women who experienced a HDP, compared to those who did not, have double the risk of experiencing an adverse cardiovascular event in the first decade after the index pregnancy and four times higher risk of developing chronic hypertension[2–4]. However, from these studies, it is difficult to determine whether the findings reflect progressive cardiac dysfunction which starts prior to development of a HDP and continues thereafter, or whether HDPs are the sole culprits for these adverse consequences.

Our group and others have shown that women at increased risk for HDP have evidence of increased peripheral vascular resistance and subclinical cardiac maladaptation long before the clinical onset of the HDP[5–7]. We have also shown that some of the reported cardiac functional changes persist in the peripartum and early postpartum periods and are attributed mostly to changes in maternal risk-factor profile[8,9]. Recently, our group also demonstrated, in a large cohort of 26 000 women, that shared underlying risk factors drive the association between HDP and risk of future hypertension; and that use of a prediction model which includes maternal demographic characteristics and blood pressure measurement from the first trimester can help in early identification of women who are at high risk for future chronic hypertension[10]. However, it remains unknown whether occurrence of HDP can accelerate or modify the trajectory of maternal cardiovascular adaptation in the long term. To address this issue, in the current study, we monitored women longitudinally, in midgestation and at around 2 years postpartum, with the aims of identifying maternal cardiovascular alterations prior to the development of HDP and assessing persistent cardiovascular alterations long after the HDP event.

METHODS

Study population

This was a prospective observational and non-interventional study of 112 women who experienced HDP (GH, $n = 54$; PE, $n = 58$) and 451 normotensive women who delivered in the same period at King's College Hospital, London, UK. The follow-up study was performed between June 2022 and March 2023. All women had detailed assessment of cardiac function in midgestation, as part of the Advanced Cardiovascular Imaging Study (REC No, 18/NI/0013, 2018; IRAS ID, 237936). Eligible women were recruited at the time of their delivery and were asked to attend the Harris Birthright Research Centre for cardiovascular assessment at 2 years postpartum. We did not undertake postnatal management of the participants. When necessary, women were managed by their general practitioners according to standard care in the UK.

Inclusion criteria were singleton pregnancy and delivery of a non-malformed liveborn or stillborn neonate. We excluded pregnancies with aneuploidy or major fetal abnormality. Mothers who had breast implants were also excluded from the study as these obstruct the echocardiographic windows.

We recorded information on maternal demographic characteristics, such as age, weight, height and self-reported ethnic origin (white, black, South Asian, East Asian, mixed), and previous obstetric and medical histories. Weight and body mass index were obtained at both clinical visits. Data on pregnancy outcome were collected from the hospital maternity records or the women's general medical practitioners. The obstetric records of all women were examined to determine the diagnosis of PE or GH. Diagnosis of PE and GH was made according to the definitions of the American College of Obstetricians and Gynecologists[11]. All women provided written informed consent to participate in the study.

Maternal cardiovascular assessment

Cardiovascular assessment was performed using two-dimensional and Doppler transthoracic echocardiography. Measurements were performed in the parasternal and apical views using a Canon Aplio i900 scanner (Canon Medical Systems Europe BV, Zoetermeer, The Netherlands) as per the American Society of Echocardiography and European Association of Cardiovascular Imaging recommendations[12].

Left ventricular systolic function was assessed using M-mode in the parasternal long-axis view to calculate fractional shortening and ejection fraction. Tissue Doppler mitral valve systolic (s′) mean velocity was also calculated, as the average of the lateral and septal myocardial walls. Speckle-tracking analysis was performed in the four-chamber, two-chamber and three-chamber views to calculate left ventricular global longitudinal systolic function. Increased negative values denote increased deformation and improved myocardial strain. Left ventricular diastolic function was assessed using pulsed Doppler in the four-chamber view at the level of the mitral valve. Early (E) and late (A) mitral inflow were measured and E/A ratio was calculated[13]. Tissue Doppler was assessed at the left ventricular septal and lateral walls and mean values were calculated. Diastolic filling pressure was estimated by using the E/e′ index. Left atrial volume and area were measured and global myocardial contractility was assessed by calculating myocardial performance index. Structural left ventricular parameters which were calculated included relative wall thickness (RWT) and left ventricular mass (LVM). RWT was estimated using the formula (2 × posterior wall thickness)/left ventricular internal diameter at end-diastole. LVM was categorized as either

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concentric (RWT > 0.42) or eccentric (RWT ≤ 0.42) hypertrophy and was indexed to body surface area[13]. Hemodynamic measurements included assessment of cardiac output and peripheral vascular resistance. Vascular assessment was performed using ophthalmic artery Doppler. This involved recording of flow velocity waveforms from the left and right maternal ophthalmic arteries twice, and calculating the average of the four measurements of the first and second peak systolic velocity (PSV) and recording the ratio of the second to the first PSV[7].

Statistical analysis

Continuous variables were presented as mean ± SD and categorical variables as *n* (%). Comparison of cardiac measurements between the HDP group and controls was carried out using the *t*-test for normally distributed variables and Mann–Whitney *U*-test for non-normally distributed data. For categorical variables, the chi-square test was used.

We fitted mixed-effects linear models to account for the longitudinal structure of the data. Specifically, we developed random-intercept models assuming that fixed intercepts and coefficients are the same across different levels, whereas random intercepts were allowed to vary across different levels. The mixed-effects approach primarily models the correlated errors observed in repeat measurements, describing the biological variability of the variable, at the same time. Repeat measurements for each pregnancy and individual measurements were the different levels of our modeling.

Maternal echocardiographic variables measured in our cohort during pregnancy and at 2 years postpartum were the dependent variables. We explored the distributional properties of each echocardiographic index to define the need for transformation, to achieve homogeneity of variance and approximate Gaussian distribution. We aimed to examine the association between HDP and a range of echocardiographic variables adjusting for a prespecified set of confounders, including maternal age, weight and height, method of conception, gestational diabetes or diabetes mellitus, aspirin administration, systemic lupus erythematosus/antiphospholipid syndrome, chronic hypertension, previous gestational diabetes, parity, gestational age at delivery in previous pregnancy, previous birth weight, interpregnancy interval, history of HDP, family history of PE or diabetes mellitus, thyroid dysfunction, heart rate, mean arterial pressure, smoking status, birth-weight *Z*-score for gestational age at delivery, estimated fetal weight by ultrasound *Z*-score for gestational age at assessment and ethnicity. The confounders were inserted as fixed parameters in the model.

Backward elimination was used for variable selection. The model selection process and comparisons of intermediate models were carried out using Akaike information criterion (AIC) and log-likelihood. We checked for significant interactions and the final models were chosen on the basis of parsimony. Residual diagnostics were used to examine model fitting and refine the parameter's inferences. A likelihood ratio test was applied to assess the significance of the random part. We also quantified the individual variability and the necessity for random effects by the intraclass correlation coefficient (ICC), computed as the ratio between the individual variance and the total variance.

Statistical analysis was performed using the STATA package, version 17.0 (StataCorp, College Station, TX, USA) and the statistical software package R[14].

RESULTS

Maternal characteristics

In the group with pregnancy affected by HDP, compared to those who had a normotensive pregnancy, there was a similar distribution of ethnic background, but higher incidence of conception by *in-vitro* fertilization (Table 1). Gestational age at delivery was approximately 1 week earlier in women who had experienced HDP, compared to those who had had a normotensive pregnancy, and birth weight was also lower in the HDP group. Women from the HDP group, compared to the normotensive

Table 1 Population characteristics at 2 years postpartum following pregnancy that had been normotensive or affected by hypertensive disorder (HDP)

Characteristic	*Normotensive (n = 451)*	*HDP (n = 112)*	P
Age (years)	34.1 ± 4.9	34.1 ± 5.9	0.929
Weight (kg)	71.2 ± 16.6	76.1 ± 16.3	0.006
Height (cm)	165.9 ± 6.4	165.5 ± 6.9	0.434
Systolic blood pressure (mmHg)	120.3 ± 11.7	130.3 ± 14.2	< 0.001
Diastolic blood pressure (mmHg)	73.3 ± 9.8	80.6 ± 11.0	< 0.001
Mean arterial pressure (mmHg)	88.9 ± 9.1	96.7 ± 9.1	< 0.001
Ethnicity			0.634
Black	56 (12.4)	23 (20.5)	
East Asian	16 (3.6)	4 (3.5)	
South Asian	22 (4.9)	6 (5.4)	
Mixed	18 (4.0)	4 (3.5)	
White	339 (75.2)	75 (67.0)	
Conception			0.001
In-vitro fertilization	21 (4.7)	15 (13.4)	
Use of ovulation drugs	2 (0.4)	1 (0.9)	
Natural	428 (94.9)	96 (85.7)	
Medical history			
Chronic hypertension	15 (3.3)	5 (4.5)	0.538
DM Type I or II	1 (0.2)	4 (3.6)	<0.001
Hypothyroidism	16 (3.5)	3 (2.7)	0.794
SLE/APS	1 (0.2)	1 (0.9)	0.255
Gestational DM	54 (12)	17 (15.2)	0.392
GA at delivery (weeks)	39.5 ± 1.9	38.7 ± 2.4	< 0.001
Birth weight (g)	3374 ± 559	3173 ± 699	0.001
Birth weight < 10th percentile	54 (12)	25 (22.3)	0.005

Data are given as mean ± SD or *n* (%). APS, antiphospholipid syndrome; DM, diabetes mellitus; GA, gestational age; SLE, systemic lupus erythematosus.

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group, at 2 years post-delivery, had increased weight and higher systolic and diastolic blood pressures.

Maternal cardiovascular assessment in midgestation

In midgestation, women who later in pregnancy developed HDP, compared to those who did not, had increased systolic and diastolic blood pressures and higher ophthalmic artery PSV ratio (Table 2). Left ventricular systolic function, as assessed by global longitudinal strain, was mildly reduced and left ventricular diastolic index E/e′ was increased, denoting reduced diastolic function. Global myocardial function, as assessed by myocardial performance index, was also marginally reduced in women with HDP (Table 2). From structural cardiac indices, left ventricular RWT was increased in the HDP group, whereas LVM was comparable between the groups.

After multivariable analysis, there was no significant difference in E/e′ between the groups (coefficient, 0.2; 95% CI, −0.2 to 0.6). Similarly, no significant difference was found in left ventricular global longitudinal strain (coefficient, −0.02; 95% CI, −0.6 to 0.5) or RWT (coefficient, 0.01; 95% CI, −0.00 to 0.03), whereas the difference in the ophthalmic artery PSV ratio remained significant (coefficient, 0.1; 95% CI, 0.02–0.7; $P < 0.001$).

Cardiovascular assessment at 2 years postpartum

Cardiovascular assessment was performed at a median of 2.3 (interquartile range, 2.1–2.4) years after delivery. Hemodynamic parameters in the HDP and non-HDP groups are shown in Table 2. The ophthalmic artery PSV ratio in the HDP group was increased and this association remained after multivariable analysis (coefficient, 0.02; 95% CI, 0.01–0.05; $P = 0.015$).

Left ventricular systolic functional index (mitral valve s′) was lower in the HDP compared to the non-HDP group ($P = 0.004$). Left ventricular diastolic parameters, E/e′ and E/A, were higher in the HDP group (Table 2). These differences remained following multivariable analysis (E/A ratio: coefficient, 0.3; 95% CI, 0.1–0.4; $P = 0.001$; E/e′: coefficient, 0.4; 95% CI, 0.1–0.8; $P = 0.012$; and mitral valve s′: coefficient, −0.7; 95% CI, −1.1 to −0.14; $P = 0.014$). LVM indexed to body surface area was higher in the HDP group compared to the non-HDP group ($P = 0.049$) and RWT was also greater in the HDP group ($P < 0.001$). After multivariable analysis, the difference between groups remained significant only for RWT (coefficient, 0.10; 95% CI, 0.04–0.13; $P < 0.001$).

Longitudinal evolution of maternal echocardiographic indices from pregnancy to postnatal period

Overall, maternal echocardiographic indices changed significantly from midgestation to the postnatal period (Tables S1–S3, Figure 1). There was improvement in diastolic functional indices in both the HDP and non-HDP groups and mild deterioration in left ventricular systolic indices (i.e. reduction in mitral valve s′ and global longitudinal strain). Several echocardiographic indices manifested substantial variation between different

Table 2 Maternal cardiovascular measurements at midgestation and 2 years postpartum following pregnancy that had been normotensive or affected by hypertensive disorder (HDP)

	Midgestation			*2 years postpartum*		
Variable	*Normotensive (n = 451)*	*HDP (n = 112)*	P	*Normotensive (n = 451)*	*HDP (n = 112)*	P
Hemodynamic parameters						
Heart rate (bpm)	73.6 ± 10.8	77.7 ± 11.4	< 0.001	69.8 ± 11.1	70.6 ± 11.8	0.493
Cardiac output (L/min)	5.8 ± 1.2	5.9 ± 1.3	0.216	5.7 ± 1.4	6.0 ± 1.5	0.155
Systolic blood pressure (mmHg)	117.4 ± 10.3	126.4 ± 8.7	< 0.001	120.3 ± 11.7	130.3 ± 14.2	< 0.001
Diastolic blood pressure (mmHg)	69.8 ± 7.5	75.5 ± 6.8	< 0.001	73.3 ± 9.8	80.6 ± 11.0	< 0.001
Systolic functional indices						
Ejection fraction (%)	64.0 ± 6.6	63.9 ± 7.2	0.953	64.7 ± 6.5	64.3 ± 7.0	0.608
Global longitudinal systolic strain (%)	−23.8 ± 2.7	−23.2 ± 2.7	0.031	−21.4 ± 2.7	−20.9 ± 2.9	0.101
Isovolumic contraction time (ms)	51.9 ± 11.8	50.8 ± 11.4	0.396	58.7 ± 13.8	57.1 ± 12.9	0.278
Mitral valve s′ (cm/s)	10.4 ± 1.5	10.3 ± 1.9	0.316	8.5 ± 1.8	8.0 ± 1.5	0.004
Diastolic functional indices						
Mitral valve E (cm/s)	92.8 ± 18.4	95.2 ± 19.2	0.228	75.7 ± 15.6	77.5 ± 16.7	0.268
Mitral valve A (cm/s)	42.5 ± 13.8	46.1 ± 15.8	0.018	40.6 ± 12.8	38.7 ± 12.5	0.149
Mitral valve E/A	2.4 ± 0.9	2.4 ± 1.2	0.838	2.0 ± 0.7	2.2 ± 0.8	0.015
Mitral valve E/e′	6.4 ± 1.6	7.0 ± 1.7	0.002	6.0 ± 1.6	6.7 ± 1.8	< 0.001
Isovolumic relaxation time (ms)	58.2 ± 13.1	60.5 ± 14.3	0.100	65.2 ± 13.9	64.9 ± 14.4	0.833
Left atrial area (cm^2)	14.1 ± 3.3	14.5 ± 3.1	0.254	11.7 ± 2.0	11.9 ± 2.1	0.354
Left atrial volume (mL)	38.5 ± 13.2	40.5 ± 12.9	0.153	28.8 ± 7.4	29.5 ± 7.6	0.377
Myocardial performance index	0.38 ± 0.1	0.40 ± 0.1	0.043	0.4 ± 0.1	0.4 ± 0.1	0.636
Structural parameters						
Relative wall thickness	0.36 ± 0.1	0.40 ± 0.1	< 0.001	0.6 ± 0.2	0.7 ± 0.3	< 0.001
LVM indexed to body surface area (g/m^2)	59.5 ± 9.3	61.0 ± 10.7	0.189	76.8 ± 18.1	80.6 ± 20.3	0.049
Ophthalmic artery PSV ratio	0.6 ± 0.1	0.7 ± 0.1	< 0.001	0.7 ± 0.1	0.8 ± 0.1	< 0.001

Data are given as mean ± SD. LVM, left ventricular mass; PSV, peak systolic velocity.

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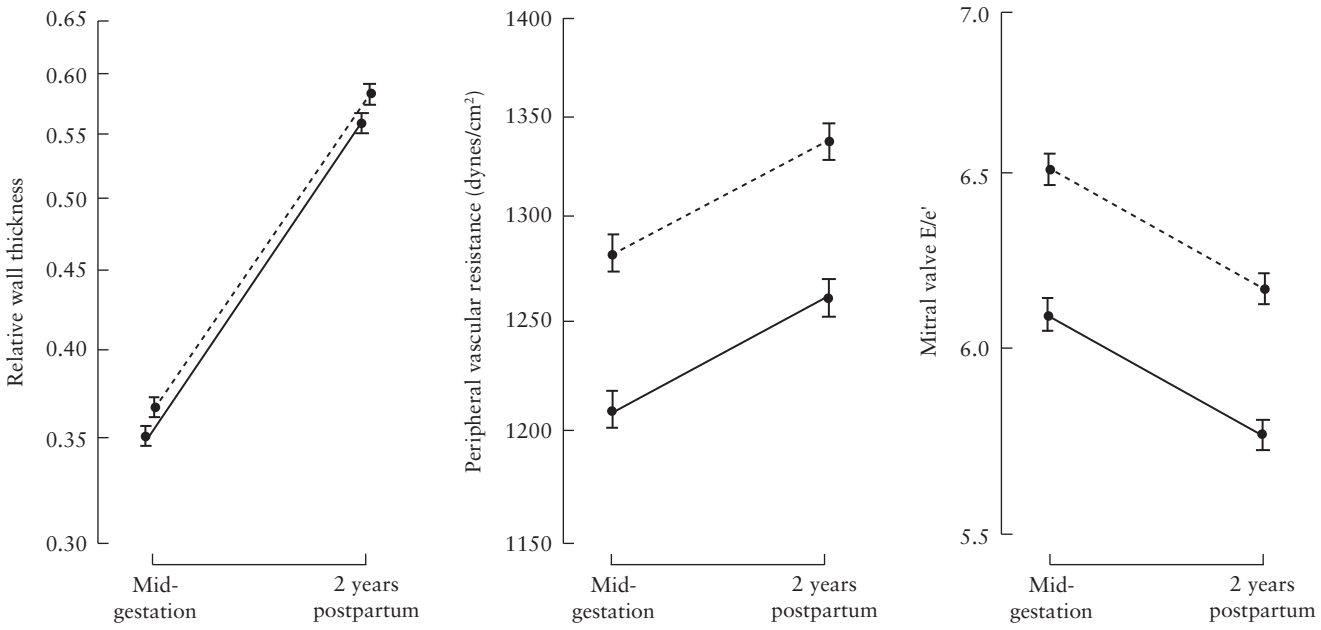

Figure 1 Longitudinal changes in mean (95% CI) relative wall thickness, peripheral vascular resistance and mitral valve E/e′ in women with hypertensive disorder of pregnancy (----) and in normotensive women (——) from midgestation to 2 years postpartum. Graphs apply to white, nulliparous women with a weight of 73 kg and age of 34 years, without gestational diabetes or chronic hypertension, and with a mean arterial pressure of 87 mmHg and heart rate of 74 bpm.

individuals. Women with HDP had higher RWT, peripheral vascular resistance, mitral valve E/A and E/e′, and lower mitral valve s′, compared to women without HDP (Tables S1–S3).

In the initial stages of our analysis, we examined separately PE and GH as fixed factors. The overall effects were quite similar to those when these were grouped together as HDP. However, for both mitral valve s′ and E/e′, GH was significant and PE was not (Tables S4–S6). The pattern of evolution of cardiovascular changes was similar in the HDP and non-HDP groups (Figure 1).

DISCUSSION

Main findings

There are three main findings of this study. First, in midgestation, women who subsequently developed HDP had increased ophthalmic artery PSV ratio, reflective of increased peripheral vascular resistance, and mild cardiac functional and morphological alterations. Second, at 2 years postpartum, women who had experienced HDP, compared to those who had not, continued to demonstrate mild cardiovascular abnormalities, with reduction in their left ventricular systolic and diastolic function. Third, the evolution of cardiovascular adaptations was similar in the HDP and non-HDP groups. These findings suggest that pre-existing maternal risk factors drive the development of both HDP and future maternal cardiovascular risk.

Interpretation of results and comparison with findings of previous studies

Several studies have compared cardiac function in women with and those without HDP, using conventional echocardiographic modalities, and reported that HDP is associated with mild reduction in left ventricular systolic and diastolic function and increase in LVM, suggesting that HDPs are causally related to cardiac functional changes[15–20]. We have demonstrated previously that, in midgestation prior to the development of HDP, women have increased peripheral vascular resistance and mild cardiac functional alterations which are driven mostly by maternal characteristics and risk-factor profile[6]. In the current study, we confirmed that women at increased risk for HDP in midgestation have an adverse risk factor profile and mild cardiovascular dysfunction.

We showed that, at around 2 years postpartum, women with HDP have an adverse cardiovascular phenotype, with increased systolic and diastolic blood pressure, increase in peripheral vascular resistance and subclinical reduction in left ventricular systolic and diastolic function, suggesting progression of cardiovascular ageing. Our longitudinal analysis demonstrated that the evolution of cardiovascular adaptations follows the same pattern in women with HDP and those without HDP, thus arguing against a particular detrimental effect of HDP on maternal cardiovascular function. Previous studies in the early postpartum period have reported that some women who had HDP showed persistent cardiac remodeling and left ventricular functional alterations[19,20]. In contrast, studies at 1 year following delivery reported that, in women who had HDP, there was recovery of cardiac indices[16,18]. Although these results may reflect differences in power as well as in maternal characteristics between studies, they clearly highlight that maternal cardiovascular risk factor profile remains the main driver of maternal cardiovascular risk. This is consistent with results of a recent study that demonstrated that use of a model that includes maternal

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demographic characteristics and blood pressure can identify women at high risk of developing future chronic hypertension from the first trimester of pregnancy[10].

Strengths and limitations

Our study has several strengths. We performed detailed cardiac phenotyping in a homogeneous group of women in midgestation attending for routine pregnancy care and aimed to investigate the long-term cardiac consequences of women who were at increased risk for HDP. We used as controls women who delivered at the same period as mothers with HDP, had a normotensive uncomplicated pregnancy and had similar ethnic background to those with HDP. In this well-characterized group of women, we demonstrated that, in the HDP group compared to non-HDP group, there was increased peripheral vascular resistance and mild alterations in systolic and diastolic left ventricular functional indices both in midgestation and at 2 years postpartum. From various cardiac indices, sensitive markers of systolic and diastolic function were able to better capture the differences between groups. We also had the opportunity to assess the evolution of cardiovascular changes using longitudinal analysis. We confirmed that the evolution of cardiovascular adaptations was similar in the HDP and non-HDP groups. A limitation of our study is that no serial measurements were performed during pregnancy or postpartum.

Conclusions

Mild cardiac functional and morphological alterations precede the development of HDP and such changes persist for at least 2 years postpartum. The cardiac changes are likely to be the consequence of pre-existing maternal cardiovascular risk factors rather than an adverse consequence of HDP.

ACKNOWLEDGMENTS

This study was funded by a grant from the Fetal Medicine Foundation (Charity No: 1037116). The ultrasound machines for echocardiography and software for speckle-tracking analysis were provided free of charge by Canon Medical. These bodies had no involvement in the study design, in the collection, analysis and interpretation of data, or in the writing of the report.

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SUPPORTING INFORMATION ON THE INTERNET

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

Tables S1–S6 Linear mixed models for prenatal to postnatal evolution of longitudinal measurements of maternal echocardiographic variables: structural and hemodynamic parameters (Tables S1 and S4), diastolic indices (Tables S2 and S5) and systolic indices (Tables S3 and S6), adjusting for time of assessment, maternal factors and hypertensive disorder of pregnancy (Tables S1–S3) and for time of assessment, pre-eclampsia and gestational hypertension (Tables S4–S6)

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