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POSTPARTUM CARDIOVASCULAR FUNCTION IN PATIENTS WITH HYPERTENSIVE DISORDERS OF PREGNANCY: A LONGITUDINAL STUDY

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TWEETABLE STATEMENT: A longitudinal cardiovascular assessment from the peripartum to the postpartum showed persistent maternal cardiovascular impairment, including chronic hypertension and myocardial dysfunction, in two-thirds of HDP patients.

SHORT TITLE: HDP and the postnatal cardiovascular course

AJOG AT A GLANCE:

A. Why was this study conducted?

- Patients with hypertensive disorders of pregnancy (HDP) are at increased risk of developing postpartum hypertension and other cardiovascular risk factors, however, there are no longitudinal data on changes in the maternal cardiovascular system from the peripartum into the postpartum.

B. What are the key findings?

- Cardiac changes in left ventricular geometry and function are more profound in the peripartum compared to the postpartum period.
- Women with pregnancies complicated by HDP have persistent postpartum hypertension and/or subclinical myocardial dysfunction in two-thirds of cases.

C. What does this study add to what is already known?

Postpartum care of women with HDP has received increasing attention because it appears to be important for prevention of subsequent maternal cardiovascular disease. This study shows how maternal cardiovascular function changes from the peripartum to the postpartum period after HDP. This data would help physicians in the management of HDP women in their “fourth trimester.

ABSTRACT

Background: Women with a history of hypertensive disorders of pregnancy (HDP) are at increased risk of cardiovascular diseases that are usually mediated by the development of cardiovascular risk factors, such as chronic hypertension, metabolic syndrome or subclinical myocardial dysfunction. Increasing evidence has been showing that little time elapses between the end of pregnancy and the development of these cardiovascular risk factors.

Objectives: To assess the persistence of hypertension and myocardial dysfunction at four months postpartum in a cohort of women with HDP and to compare the echocardiographic parameters between the peripartum and the postpartum period.

Study design: In a longitudinal prospective study, a cohort of women with preterm or term HDP and an unmatched group of women with term normotensive pregnancy were recruited. Women with pre-existing chronic hypertension (n=29) were included in the HDP cohort. All participants underwent two cardiovascular assessments: the first was conducted either before or within one week of delivery (V1: peripartum assessment), and the second was between three and 12 months following giving birth (V2: postpartum assessment). The cardiovascular evaluation included blood pressure profile, maternal transthoracic echocardiography (left ventricular mass index (LVMI), relative wall thickness (RWT), left atrial volume index (LAVI), E/A, E/e', peak velocity of tricuspid regurgitation (TR), ejection fraction (EF), and LV global longitudinal strain (GLS) and twist) and metabolic assessment (fasting glycemia, insulin, lipid profile and waist measurement). Echocardiographic data were compared between V1 and V2 using paired t-test or McNemar test in HDP and in the control groups.

Results: Among 260 patients with pregnancies complicated by HDP and 33 patients with normotensive pregnancies, 219 (84.2%) and 30 (90.9%) attended postpartum

follow-up, respectively. Patients were evaluated at a median (IQR) of 124 (103-145) days after delivery. Paired comparisons of echocardiographic findings demonstrated significant improvements in cardiac remodeling rates (left ventricular mass index (g/m2) 63.4±14.4 vs 78.9±16.2, p<0.0001; relative wall thickness 0.35±0.1 vs 0.42±0.1, p<0.0001), most diastolic indices (E/E' 6.3±1.6 vs 7.4±1.9, p<0.0001), ejection fraction (EF<55%: 9 (4.1%) vs 28 (13.0%), p<0.0001) and global longitudinal strain (-17.3±2.6% vs -16.2±2.4%, p<0.0001) in the postpartum period compared to the peripartum. The same improvements in cardiac indices were observed in the normotensive group. However, at the postnatal assessment, 153/219 (69.9%) had either hypertension (76/219, 34.7%) or an abnormal global longitudinal strain (125/219, 57.1%), 13/67 (19.4%) had metabolic syndrome and 18/67 (26.9%) exhibited insulin resistance.

Conclusions: Although persistent postpartum cardiovascular impairment was evident in a substantial proportion of these patients since more than two-thirds had either hypertension or myocardial dysfunction postpartum, cardiac modifications due to pregnancy-related overload and hypertension were significantly more pronounced in the peripartum than in the postpartum periods.

KEY WORDS: pre-eclampsia, gestational hypertension, echocardiography, pregnancy, hypertension, global longitudinal strain, cardiovascular diseases, cardiovascular risk, metabolic syndrome.

INTRODUCTION

Women with hypertensive disorders of pregnancies (HDP), including hypertension with and without end-organ involvement, exhibit maternal cardiovascular changes which diverge from those observed in normotensive pregnancy, irrespective of the gestational age at the onset of the disease. [1, 2] These findings indicate a maladaptation to increased cardiovascular demand during pregnancy when HDP develops, and this hypothesis is supported by a well-established link between HDP and the development of cardiovascular diseases (CVD) in the postpartum period.[3, 4] Therefore, hypertensive complications in pregnancy might be crucial to detect women destined to develop CVD, the leading cause of mortality in the female population. However, it is unknown how the postpartum cardiovascular impairment after HDP might be related to cardiovascular manifestations of HDP in the peripartum period.

The increased risk of CVD in women with a history of HDP is mediated by cardiovascular risk factors that develop shortly after pregnancy, particularly hypertension.[5] The risk of developing hypertension after HDP is six-fold higher compared to women after normotensive pregnancy within two years postpartum.[3] The short-term burden of preterm pre-eclampsia has been revealed by the fact that two-thirds of patients are still hypertensive at around six months postpartum.[6, 7] Similarly, the higher prevalence of asymptomatic left ventricular geometric anomalies in women with a history of HDP might explain the subsequent development of heart failure.[8]

Pregnancy and its "4th trimester" could offer a window of opportunity to prevent adverse outcomes in women with HDP. Pilot RCT studies, indeed, have demonstrated that interventions started in the early postpartum period after HDP and based on optimizing BP control could be promising strategies to improve patients' CVD prognosis in the long term.[9, 10] These interventions should be targeted to HDP women

at risk of developing postpartum hypertension. A recent study showed that a peripartum screening based on maternal factors, such as maternal age, body mass index (BMI) and blood pressure (BP), and echocardiographic data, evaluating LV geometry and function, could effectively identify women at risk of postpartum hypertension.[11]

However, there is a paucity of longitudinal data on the postnatal course and putative cardiovascular recovery assessed by maternal echocardiography from peripartum cardiovascular dysfunction in women with all types of HDP.[3, 6, 7] Therefore, the present study aimed to assess the persistence of hypertension and cardiac dysfunction at about four months postpartum in a heterogeneous cohort of HDP women and to compare longitudinally maternal echocardiographic findings between the peripartum and postpartum periods in hypertensive and normotensive pregnancies.

MATERIALS AND METHODS

Study design and population

This prospective longitudinal cohort study was conducted at St George's University Hospital NHS Foundation Trust between February 2019 and August 2021. The Local Ethics Committee (19/LO/0794) approved it, and all participants provided written informed consent. Women with a pregnancy complicated by HDP, including chronic hypertension, pre-eclampsia and gestational hypertension (n=263), were recruited consecutively from the Maternity Department. They underwent a first cardiovascular assessment in the peripartum period (V1), including before or within one week of delivery. We have previously demonstrated that the dramatic hemodynamic changes associated with the delivery do not affect cardiac geometry and function when

comparing echocardiography performed before delivery or within one week of delivery.[12] Afterwards, they underwent a second cardiovascular assessment (V2) that was performed at least three months (up to one year postpartum) since guidelines reported six weeks or three months as the point where normalization of BP after HDP should be expected.[13, 14] A group of consecutive normotensive and uncomplicated pregnancies (n=33) was recruited at term during a pre-operative assessment for an elective caesarean section because of breech presentation or maternal request. They were not directly compared to the HDP group, but a parallel comparison between V1 and V2 assessments was also carried out in this group. Pregnancies complicated by genetic syndromes or major fetal abnormalities and patients affected by known cardiac conditions were not included. Pregnancy data and outcomes were ascertained from the maternity databases (ViewPoint version 5.6.26.148, ViewPoint Bildverarbeitung GMBH, Wessling, Germany, EuroKing E3, Wellbeing software group, Surrey, UK), discharge letters and by direct patient enquiry. All study data were collected and managed using REDCap electronic data capture tools hosted at St George's University.

Definitions and outcomes

HDP was defined according to the criteria of the International Society for the Study of Hypertension in Pregnancy.[13] Pre-existing chronic hypertension was defined as systolic BP ≥140 mm Hg and/or diastolic BP ≥90 mm Hg before pregnancy (n=5) or before 20 weeks' gestation (n=24).[15] The primary outcome was to determine the rate of postpartum hypertension. The postpartum hypertension was classified according to the guidelines of the European Society of Cardiology, the European Society of Hypertension and the International Society of Hypertension, defining hypertension as

a systolic BP ≥140 mmHg and/or diastolic BP ≥90 mmHg and/or the use of anti-hypertensive medication.[16] The secondary outcomes were myocardial and metabolic dysfunction. Myocardial dysfunction was defined by an abnormal left ventricular global longitudinal strain (GLS) using the lowest expected values for age and female sex calculated as ± 1.96 standard deviations from the mean.[17] GLS is a more sensitive marker of LV dysfunction than ejection fraction (EF) and an impaired GLS has been associated with an increased risk of heart failure, acute myocardial infarction or cardiovascular death in high and low risk populations.[18] Metabolic dysfunction was defined by the presence of metabolic syndrome or by insulin resistance. Metabolic syndrome was defined as the presence of 3 or more of the following characteristics: waist circumference >88 cm, triglyceride levels ≥1.7 mmol/L, high-density lipoprotein cholesterol <1.3 mmol/L, BP ≥130/85 mmHg, and fasting glucose levels ≥5.6 mmol/L. Insulin resistance was estimated using the Homeostasis Model Assessment (HOMA-IR) by the formula: insulin(mUI/l)*glycemia(mg/dl)/405 and a value higher than 2.5 was defined as pathological.[19]

Cardiovascular Assessment

Measurements at both peripartum and postpartum visits were performed in a standardized environment according to a predetermined protocol, including anthropometric measurements, BP profile, and maternal transthoracic echocardiography. BMI (kg/m^2) was calculated by dividing body weight (kg) by the squared height in meters (m^2), and body surface area (BSA, m^2) was measured using the following equation: $0.007184*\text{height(cm)}^{0.725}*\text{weight(kg)}^{0.425}$. A BP profile with at least three measurements with one min between them was obtained by an upper arm automatic BP monitor (Microlife®, Microlife AG Swiss Corporation, Widnau,

Switzerland) with the woman in a sitting position with a cuff size appropriate for arm circumference, as per guideline recommendations.[20] The average of the last two measurements was used to diagnose hypertension.[16] Mean arterial pressure (MAP) was calculated as (2*diastolic BP+systolic BP)/3. Moreover, women with elevated BP but not already on hypertensive medication at the postpartum assessment (V2) were provided with a BP monitor (Microlife®, Microlife AG Swiss Corporation, Widnau, Switzerland), and they were instructed to check their BP at home once a day and to communicate their readings after one week. If BP at home was less than 135/85mmHg, a diagnosis of white coat hypertension was made.[21]

Women with pre-eclampsia with severe features (i.e, preterm delivery, hemolysis, elevated liver enzymes and low platelets (HELLP) syndrome, eclampsia, severe fetal growth restriction and stillbirth) were eligible for a postpartum metabolic assessment in addition to the cardiovascular evaluation. The metabolic assessment included fasting glucose, insulin, total cholesterol, HDL, LDL, triglyceride levels, creatinine and protein: creatinine ratio. Metabolic syndrome was diagnosed according to the National Cholesterol Education Program Adult Treatment Panel III.[19, 22]

Transthoracic echocardiography was performed at rest in the left lateral decubitus position using GE Vivid E95 with a M5Sc-D probe (GE Healthcare, Horten, Norway), and the analysis was performed using EchoPAC version 203 (GE Healthcare, Horten, Norway). Two-dimensional, Doppler and Speckle tracking echocardiography was performed following international guidelines.[23-27] For each image acquisition, three cardiac cycles of non-compressed data were stored in cine-loop format and analyzed off-line by one investigator on a dedicated workstation who was blinded to participant order and condition. Echocardiographic measurements used to assess left ventricular geometry, diastolic, systolic function and maternal hemodynamics are summarized in

Table 1. Left ventricular systolic dysfunction was defined as the presence of reduced ejection fraction (<55%).[23, 24] The primary diastolic parameters were: early (e') diastolic mitral annulus velocity (≤7 cm/s for septal E' and ≤10 cm/s for lateral E'), ratio between E and average e' (E/e'≥9), left atrial volume index (>34 ml/m^2), and peak velocity of tricuspid regurgitation (>2.8 m/s).[28] The cut-off for E/e', septal e' and lateral e' were derived from gender- and age-specific normal range in women 20-40 years of age using mean ± 2SD reference.[29, 30] A diagnosis of diastolic dysfunction requires more than half of these variables to meet the cut-off values, i.e. at least 3 of 4 or 2 of 3 if one variable is missing. Diastolic dysfunction was graded using E/A and the three main diastolic parameters (E/e'≥9, left atrial volume index >34 ml/m^2, peak velocity of tricuspid regurgitation >2.8 m/s) in women with diastolic dysfunction and in women with abnormal GLS that represents a better method than EF to identify co-existent systolic dysfunction in hypertrophic ventricles.[28] All images were examined to validate quality for speckle-tracking analysis, and those that did not meet the required level were excluded. The standardisation digital images were selected with a frame rate of 60-90 frames/second. A full-thickness myocardial region of interest was selected, and the observer readjusted the endocardial trace line and/or region-of-interest width to ensure an acceptable tracking score. Left ventricular GLS (%) values from the apical 2-, 3-, and 4-chamber views were calculated. Radial and circumferential strain were obtained from parasternal short axis views obtained from the left ventricular base at the level of the mitral valve and the LV apex. These measurements were used to calculate left ventricular twist (deg) which is the relative rotation of the apex around the long axis of the left ventricle with respect to the base during the cardiac cycle. Twisting and untwisting rate (deg/s) were calculated as the time derivative of twist.[31]

Statistical Analysis

The sample size was 250 HDP pregnancies, and this was calculated considering the hospital birth rate (5000 births per year), the reported incidence of HDP (~4%), a recruitment rate of 50% over a total study period of 2.5 years and 20% loss to follow-up. The proportion of the population with postnatal chronic hypertension (primary outcome) was estimated at around 30%. Therefore, 156 HDP women at the postnatal follow-up were necessary to have a confidence level of 95% with a margin of error of 5%.

Variables were assessed for normality by the Shapiro-Wilk test and by visualizing their histograms. Continuous variables were expressed as mean±SD or as median, interquartile range (IQR) according to the data distribution. Echocardiographic data were compared between V1 and V2 using paired t-test or McNemar test in HDP patients and controls. A sub-analysis was performed after excluding women with chronic hypertension. Statistical significance was deemed a priori as $p<0.05$. The p values have not been adjusted for multiplicity, so inferences drawn from these statistics may not be reproducible. Inter- and intra-observer reproducibility analyses for the main echocardiographic measurements were assessed in 24 randomly selected subjects (Table S1).

The analysis was performed using the statistical software package SPSS 27.0 (SPSS Inc., Chicago, IL, USA).

RESULTS

Two hundred and sixty women with pregnancies complicated by HDP were recruited during the study period. Among them, 216 women with HDP attended the follow-up appointment in the postpartum period, and three women were only assessed in the postpartum period because they were referred to the unit after delivery. During the same period, 33 patients with uncomplicated pregnancies at term were included and 30 out 33 attended the postpartum cardiovascular assessment appointment (Figure 1). The characteristics of the HDP participants who attended the postpartum follow-up are shown in Table 1. Five (2.3%) participants were on antihypertensive medications before the index pregnancy, and 18 (8.2%) women had a recorded BP ≥140/90 mmHg in early pregnancy. The cohort included 135 (61.6%) women with a diagnosis of pre-eclampsia and 72 (32.9%) delivered preterm (Table 1). High dependence unit admission was required in 53 (24.2%) women, 81 (37.0%) neonates showed a birthweight below the 10th centile and 61 (27.9%) were admitted to the neonatal intensive care unit.

Postpartum cardiovascular and metabolic findings in HDP

Patients with HDP were evaluated at a median (IQR) of 124 (103-145) days after delivery (Table S2). At the postnatal cardiovascular assessment, 76 (34.7%) women were still hypertensive (n=43) or needed anti-hypertensive medications (n=33) (Table 2). Among the 43 women who were not on anti-hypertensive medication, six (14.0%) were subsequently diagnosed with white-coat syndrome.

Postpartum echocardiographic investigations showed an abnormal GLS in 125 (57.1%) women. A total of 153 (69.9%) women had either hypertension or impaired myocardial function that persisted into the postpartum period after HDP. Diastolic

dysfunction was diagnosed in two cases (0.9%). Abnormal diastolic parameters in postpartum included lateral e' ≤10 cm/s (9.1%), septal e' ≤7 cm/s (6.8%), E/e'≥9 (8.2%), left atrial volume index >34 ml (2.7%) and peak velocity of tricuspid regurgitation >2.8 m/s (0.5%). In women with diastolic dysfunction and/or abnormal GLS, diastolic dysfunction was graded as grade I in 93/106 (87.7%) cases, grade II 4/106 (3.8%) cases, and grade III in one case (0.9%).

There was no difference in the rate of postnatal hypertension (31.9% vs 39.3%, p=0.261) and abnormal GLS (58.5% vs 55.4%, p=0.653) between preeclamptic and non-preeclamptic patients.

Out of the 67 women who were assessed, 13 (19.4%) and 18 (26.9%) fulfilled the criteria for metabolic syndrome and showed insulin resistance, respectively. Eight (11.9%) women presented with both conditions and 23 (34.3%) had either metabolic syndrome or insulin resistance.

TTE comparison between peripartum and postpartum in HDP and controls

There were significant reductions in left ventricular mass index and cardiac remodeling rates in the postpartum assessment compared with the peripartum in women with HDP (Table 3). Left ventricular chamber dimensions were reduced, and all diastolic indices improved significantly during this period. EF and GLS were increased whilst twist, twist rate and untwist rate were reduced when assessed at least three months after delivery compared to the peripartum period (Figure 2). Hemodynamic changes are shown in Table 3. Similar results were similar when women with pre-existing chronic hypertension (n=29) were excluded (Table S3). In women with uncomplicated pregnancies, all cardiovascular geometric and functional parameters demonstrated significant improvement in the postpartum period (Table S4). A comparison between

left ventricular geometry in women with normotensive and hypertensive pregnancies is illustrated in Figure 3. In normotensive patients, there were 18 (60%) patients with abnormal GLS in the peripartum period, and persistent abnormal GLS was evident in 6 (20%) women in the postpartum assessment.

COMMENT

Principal findings

The findings of the current study demonstrated that at around four months postpartum, one-third of patients with HDP showed persistent hypertension and that two-thirds of them have either hypertension or myocardial dysfunction. The postnatal cardiovascular impairment in HDP group did not differ between preeclamptic and non-preeclamptic patients. The longitudinal echocardiographic evaluation of these women showed that the most severe cardiac changes were observed in the peripartum, although the postpartum persistence of myocardial impairment was evident in a substantial proportion of HDP women. These findings support cardiovascular screening for all women with HDP in the peripartum period to identify women at risk of postpartum hypertension and asymptomatic myocardial dysfunction.[11] This stratification could guide a targeted cardiovascular prevention strategy and improve maternal cardiovascular health.

Results in the Context of What is Known

Chronic hypertension in the postpartum period could be either new-onset or persistent after a pregnancy complicated by HDP.[32, 33] Although the concept of a 'dose effect' with more severe pregnancy-associated hypertensive disorders carries a greater risk of future hypertension, this risk increases considerably and quickly in the years following delivery in women who developed both gestational hypertension and pre-eclampsia.[34, 35] A meta-analysis that focused on the risk of hypertension after HDP in the first two years following delivery showed, consistent with our data, that almost one third (28.4%) of patients with HDP were still hypertensive and the OR (95% CI) for hypertension was 5.42 (3.12-9.41) up to one year postpartum.[3] More recently, in a

large multicenter prospective study, a higher incidence (71%) of postpartum hypertension at 6 months was reported and found not to be explained by factors other than exposure to preterm pre-eclampsia.[6] Therefore, the clinically significant effects of HDP persist after birth, and this should be borne in mind when considering their discharge from obstetrical care.

Chronic hypertension is one of the significant risk factors for developing cardiovascular disease.[5, 36] To facilitate cardiovascular screening in women with a history of HDP, identifying enduring cardiac impairment might be essential for their subsequent cardiovascular management. Pre-eclampsia and other HDPs have been associated with an increased risk of heart failure soon after delivery, such as peripartum cardiomyopathy with reduced EF and acute peripartum heart failure with preserved EF.[37] Altered left ventricular morphology and asymptomatic systolic-diastolic dysfunction are common findings in women after a pregnancy complicated by HDP.[8, 38] Women with HDP and persistent hypertension have the most pronounced echocardiographic changes, including left ventricular remodeling and abnormal diastolic and systolic function parameters compared to controls and women with a history of HDP or hypertension.[38, 39] In the current study cohort, which includes HDP at all gestations, the findings of systolic dysfunction in 4.1% and diastolic dysfunction in 0.9% of women are consistent with data from McCarthy *et al.,* where 10% of women with preterm pre-eclampsia had systolic dysfunction, and 2% had diastolic dysfunction.[6] Notably, 57.1% of women from our HDP cohort also presented with persistent myocardial dysfunction measured by GLS. Abnormal cardiac findings after hypertensive pregnancies might explain why HDP is a strong and independent risk factor for heart failure in women.[40]

Our echocardiographic data show that cardiac indices related to left ventricular morphology and function were more impaired in the peripartum compared to the postpartum in hypertensive and normotensive patients and this might be related to the cardiovascular overload caused by the pregnant state. Other studies had shown a recovery of cardiac abnormalities caused by pregnancy and hypertension when assessed from one year to several years after delivery.[38, 41] Our data also corroborate myocardial impairment caused by pregnancy, showing opposing trends for GLS and twist parameters, where GLS was increased and twist/twist rate reduced in the postpartum period compared to at the time HDP was diagnosed (Figure 2). We hypothesize that this paradoxical finding might be related to early subendocardial dysfunction leading to a reduction in longitudinal left ventricular mechanics seen in HDP.[42] Since epicardial fibers remain spared, circumferential strain and twist mechanics of the LV show normal or even increased values, compensating for the longitudinal mechanical dysfunction and thus preserving stroke volume and EF.[43] These findings suggest that peripartum cardiac morphological and functional assessment may offer the best opportunity to screen for women at risk of CVD. Indeed, a recent study from the same HDP cohort on the peripartum screening for the prediction of postnatal hypertension showed that prediction models based on a combination of maternal age, BMI, BP and echocardiographic parameters measured during the peripartum period showed excellent discrimination (AUC from 0.80 to 0.86).[11] Therefore, a clinical and cardiovascular evaluation during the peripartum admission for delivery in women with HDP could detect those who are at increased risk of postpartum hypertension, and, who could benefit from targeted preventive strategies for CVD.

Clinical Implications

First, all healthcare professionals dealing with women in pregnancy and postpartum should be aware that delivery of the placenta can stop acute end-organ damage caused by HDP but does not prevent the enduring postpartum cardiovascular legacy of HDP. And, consequently, women with any HDP must be counselled regarding their risk of CVD before hospital discharge. Another important aspect is that most women usually have a single medical assessment, with or without BP measurement, at 6-8 weeks postpartum after a pregnancy complicated by hypertension, and this should not be the case today[14] Current data strongly support the need to have at least regular BP checks in the community during the first year following delivery complicated by HDP. And, a diagnosis of hypertension in these women at increased risk of CVD should be promptly referred to physicians for behavioral and/or pharmacological treatments.

Research implications

Despite the conflict between different guidelines on how and when to start primary prevention for CVD, the endeavor to reduce the burden of preventable CVD, which represent the leading cause of mortality in the female population, must be continued.[44] Lifestyle and dietary advice can help promote cardiovascular and metabolic health and should be offered to all women after HDP. Optimal postpartum control of BP in this population is highly desirable, as this is one of the few available strategies to prevent heart failure and other CVD.[45] Home blood pressure monitoring could be a valuable technique, given that it is convenient for the new mother and has shown long-term benefits for postpartum control of BP.[10] In terms of anti-hypertensive medication, although the 6-month use of ACE-inhibitors after pre-eclampsia demonstrated

advantageous effects on maternal cardiac remodeling,[9] it is unknown which is the best anti-hypertensive regime to use in the postpartum period. More specific pharmacological interventions, such as lipid-lowering therapy or aspirin for primary cardiovascular prevention, might be tailored to those women with a history of HDP who are at increased risk of persistent cardiovascular impairment.[9, 46] And, a peripartum cardiovascular screening in women with HDP could help stratify maternal cardiovascular risk by identifying women with persistent postpartum hypertension who might most benefit from these more aggressive cardiovascular interventions.[11]

Strengths and limitations

The main strengths of this study are its prospective design and the inclusion of all women with HDP, irrespective of severity or gestational age. Moreover, in our echocardiographic protocol, more advanced techniques, such as speckle tracking echocardiography, were included to explore the myocardial function/damage. On the other hand, study limitations had (by intention) a relatively short cardiovascular follow-up. The inability to offer home blood pressure monitoring to all participants may have led to the underdiagnosis of masked hypertension.[47] Although the inclusion of women with chronic hypertension could have overestimated the rate of persistent chronic hypertension and/or cardiovascular impairment in the postpartum, their inclusion made our population more representative of patients encountered in clinical practice.

Conclusions

One-third of women remain hypertensive, and half show persistent myocardial dysfunction in the first months following a pregnancy complicated by HDP. All healthcare providers should be aware of the enduring cardiovascular legacy of HDP,

and women need to be screened regularly for CVD risk and the need for effective primary cardiovascular prevention.

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Figure 1 and Figure 2 were created with Biorender.com.

AUTHOR CONTRIBUTIONS

VG: Data curation; Formal analysis; Investigation; Methodology; Roles/Writing - original draft. AK: Funding acquisition; Writing - review & editing. JO: Investigation; Methodology; Writing - review & editing. BT: Conceptualization; Supervision; Writing - review & editing.

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615 **TABLES**

616 **Table 1. Echocardiographic measurements for the evaluation of left ventricular**
617 **morphology and function and maternal hemodynamics.**
618

VIEWS	MEASUREMENTS	CALCULATIONS
LV geometry		
Parasternal long axis view (end-diastole)	• Interventricular septum (IVS, mm) • Left ventricular end-diastolic diameter (LVEDd, mm) • Posterior wall thickness (PWT, mm)	Left ventricular mass (LVM, g): $0.8*(1.04*(LVEDd+PWT+IVS)^3-LVEDd^3)+0.6$ Left ventricular mass index (LVMI, g/m^2): *LVM/BSA* Relative Wall Thickness (RWT): *2*PWT/LVEDd*
LV Diastolic function		
Apical 4-chamber view	Pulsed wave Doppler of mitral valve: • E wave velocity (m/s) • A wave velocity (m/s) • Deceleration time (ms)	E/A ratio: *E wave velocity/A wave velocity*
	Pulsed-wave tissue Doppler imaging at the lateral and septal mitral annulus: • Lateral e′ velocity (cm/s) • Septal e′ velocity (cm/s)	E/e' ratio: *E wave velocity/mean e′ velocity* Myocardial performance index (MPI): *(isovolumic contraction time)+(isovolumic relaxation time)/ejection time*
	• Left atrial volume (LAV, ml)	Left atrial volume index (LAVI, ml/m^2): *LAV/BSA*
	Continuous wave Doppler of tricuspid valve: • Peak velocity of tricuspid regurgitation (TR) (m/s)	
LV systolic function		

Apical 4-Chamber and 2-Chamber views (end-diastole and end-systole)	• End-diastolic volume (EDV, ml) • End-systolic volumes (ESV, ml)	Ejection Fraction (EF, %) calculated by *biplane Simpson's method of discs*
Maternal hemodynamics		
Apical 5-Chamber View	• Left Ventricular Outflow Tract (LVOT, mm): measured 7 to 10 mm from the aortic valve • Velocity Time Integral (VTI, cm) measured by Pulsed wave Doppler at LVOT	Stroke Volume (SV, ml): *VTI*3.14*(LVOT/2)^2* Stroke Index (SVI, ml/m^2): *SV/BSA* Cardiac Output (CO, L/min): *SV*Heart Rate (HR)* Cardiac Index (L/m^2): *CO/BSA* Systemic vascular resistance index (SVRI, dynes*sec/cm^5/m^2): *Mean arterial pressure (MAP)*80/CI*

LV: left ventricular, BSA: body surface area, IVS: interventricular septum, LVEDd: left ventricular end-diastolic diameter, PWT: posterior wall thickness, LVM: left ventricular mass, LVMI: left ventricular mass index, RWT: relative wall thickness, EDV: end-diastole volume, ESV: end-systole volume, EDVI: end-diastole volume index, ESVI: end-systole volume index, LAV: left atrial volume, LAVI: left atrial volume index, MPI: myocardial performance index, TR: tricuspid regurgitation, EF: ejection fraction, HR: heart rate, LVOT: left ventricular outflow Tract, VTI: velocity time integral, SVI: stroke volume index, CI: cardiac index, SVRI: systemic vascular resistance index, MAP: mean arterial pressure.

Table 2. Baseline pre-pregnancy characteristics of the 219 women in the HDP cohort assessed in the postpartum period.

Demographics		**Total**
Maternal age (years)		33.84 (30.67-37.40)
Nulliparity		147 (67.1%)
Assisted conception (IUI, IVF/ICSI, egg donation)		16 (7.3%)
Twin pregnancy		7 (3.2%)
Ethnicity	Caucasian	148 (67.6%)
	Afro-Caribbean	32 (14.6%)
	Asian	27 (12.3%)
	Mixed/Other	12 (5.5%)
Smoker	In pregnancy	3 (1.4%)
	Pre-conceptional	21 (9.6%)
Higher education (after secondary)		152 (69.4%)
Family history of CVD		31 (14.2%)
Previous pregnancy complicated by HDP		35/72 (48.6%)
Pre-existing chronic hypertension		29 (13.2%)
Diabetes mellitus type 1 or 2		5 (2.3%)
First trimester data		
BMI (kg/m^2)		26.93 (23.11-31.25)
MAP (mmHg)		94.67 (90.00-99.33)
High risk for preterm pre-eclampsia		54/166 (32.5%)
Second and third trimester data		
BMI (kg/m^2)*		27.82 (24.22-31.96)
MAP (mmHg)*		97.33 (91.33-104.00)
Diagnosis of pre-eclampsia		135 (61.6%)
Early-onset pre-eclampsia (<34 weeks)		47 (36.2%)
Gestational age at delivery (weeks)		38.00 (35.86-39.43)
Mode of delivery	Vaginal delivery	90 (41.10%)
	Caesarean section	129 (58.90%)
HELLP syndrome		6 (2.7%)
Eclampsia or neurological symptoms		7 (3.2%)
Acute kidney injury		20 (9.1%)
Raised liver enzymes		30 (13.7%)
Low platelets		15 (6.8%)
Composite adverse maternal outcomes (stroke n=1, pulmonary oedema n=1, DIC n=1, placental abruption n=3)		6 (2.7%)

632 Data are expressed as median (IQR) and n (%). BMI: body mass index, MAP: mean
633 arterial pressure, IUI: intrauterine insemination, IVF: in vitro fertilization, ICSI: Intra-
634 cytoplasm fertilisation, CVD: cardiovascular diseases, CHT: chronic hypertension,
635 HDP: hypertensive disorders of pregnancy, HELLP: Hemolysis, Elevated Liver
636 enzymes and Low Platelets, DIC: Disseminated intravascular coagulation * measured
637 at peripartum assessment (V1).
638
639

Table 3. Clinical and cardiovascular findings of the 219 women in the HDP cohort at postpartum follow-up.

POSTPARTUM CLINICAL FINDINGS	
SBP≥140 or DBP≥90 or medication	76 (34.7%)
On anti-hypertensive medication	33 (15.1%)
SBP≥140 or DBP≥90 (not on medication)	43 (19.6%)
Metabolic syndrome (≥ 3 criteria)	13/67 (19.4%)
Fasting glycaemia ≥5.6 mmol/l or treatment	3
Fasting HDL <1.3 mmol/l or treatment	19
Fasting triglycerides ≥ 1.7 mmol/l or treatment	8
Waist ≥88 cm (80 cm in Asian patients)	30
BP ≥130/85 or treatment	35
HOMA-IR > 2.5	18/67 (26.9%)
POSTPARTUM ECHOCARDIOGRAPHIC FINDINGS	
Abnormal EF (<55%)	9 (4.1%)
Abnormal GLS	125 (57.1%)
Abnormal GLS or SBP ≥140 or DBP ≥90 or medication	153 (69.9%)
Markers of diastolic dysfunction	
Lateral E' ≤10 cm/s or septal E' ≤7 cm/s	24 (11.0%)
E/E'≥9	18 (8.2%)
LAVI >34 ml	6 (2.7%)
Peak TR velocity >2.8 m/s	1 (0.5%)
Borderline diastolic dysfunction (2 markers)	11 (5.0%)
Diastolic dysfunction (3 or 4 markers)	2 (0.9%)
Diastolic dysfunction grading	
Grade I	93/106 (87.7%)
Grade II	4/106 (3.8%)
Grade III	1/106 (0.9%)
Not determined	8/106 (7.5%)

Data are expressed as n (%). BMI: body mass index, BP: blood pressure, SBP: systolic blood pressure, DBP: diastolic blood pressure, EF: ejection fraction, GLS: global longitudinal strain, LAVI: left atrial volume index, TR: tricuspid regurgitation.

Table 4. Comparison between peripartum and postpartum echocardiographic left ventricle findings in 216 women with hypertensive disorders of pregnancy.

		Peripartum	Postpartum	p value
LV geometry				
LVMI (g/m^2)		78.92 ±16.16	63.39 ±14.43	<0.001
RWT		0.42±0.09	0.35±0.08	<0.001
LV Remodelling	Concentric remodelling	82 (38.0%)	33 (15.1%)	<0.001
	Concentric hypertrophy	25 (11.6%)	4 (1.8%)	<0.001
	Eccentric hypertrophy	8 (3.7%)	2 (0.9%)	0.070
LV ESVI (ml/m^2)		25.79±6.51	24.29±5.27	<0.001
LV EDVI (ml/m^2)		61.92±12.27	58.81±10.91	<0.001
LV diastolic function				
LAVI (ml/m^2)		27.42±6.17	23.40±5.53	<0.001
E/A		1.22±0.27	1.37±0.29	<0.001
Lateral e' (cm/s)		13±3	15±3	<0.001
Septal e' (cm/s)		10±3	11±2	<0.001
MPI		0.50±0.10	0.48±0.08	<0.001
E/e'		7.4±1.91	6.3±1.61	<0.001
Peak TR velocity (m/s)		2.09±0.36	2.05±0.32	0.002
LV systolic function				
EF<55%		28 (13.0%)	9 (4.1%)	<0.001
LV mechanics				
GLS (%)		-16.24±2.44	-17.26±2.25	<0.001
Twist (deg)		15.51±5.10	15.34±6.11	0.019
Twist rate (deg/s)		111.53±35.78	107.11± 34.53	<0.001
Untwist rate (deg/s)		-122.61±44.61	-114.60±45.73	0.020
Maternal hemodynamic changes				
HR (bpm)		81.47±12.89	71.66±11.11	<0.001
VTI (cm)		23.77±4.10	22.90±3.51	0.001
SVI (ml/m^2)		37.54±7.71	37.97±7.50	0.420
CI (l/m/m^2)		3.04±0.71	2.70±0.60	<0.001
SVRI (dynes*sec/cm^5/m^2)		2896.42±702.19	3052.63±728.80	0.010

Data are expressed as mean±SD and n (%). LV: left ventricular, LVMI: left ventricular mass index, RWT: relative wall thickness, EDVI: end-diastole volume index, ESVI: end-systole volume index, LAVI: left atrial volume index, MPI: myocardial performance index, TR: tricuspid regurgitation, EF: ejection fraction, GLS: global longitudinal strain,

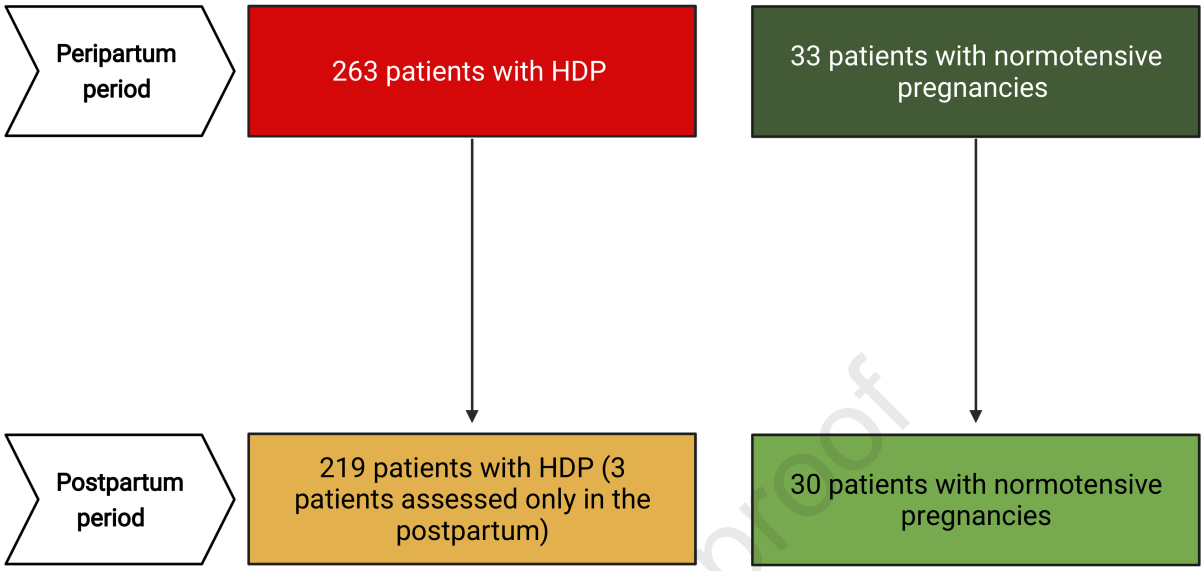
654 HR: heart rate, VTI: velocity time integral, SVI: stroke volume index, CI: cardiac index,
655 SVRI: systemic vascular resistance index.

FIGURE LEGENDS

Figure 1. Participant flow-chart. HDP: hypertensive disorders of pregnancy.

Figure 2. Left ventricular mechanics in HDP patients in the peripartum and the postpartum by speckle tracking echocardiography. The upper part of the table shows the left ventricular global longitudinal strain that is lower (arrow down) in the peripartum compared to the postpartum (arrow up). The lower part of the table shows systolic twist that is higher (arrow up) in the peripartum compared to the postpartum (arrow down).

Figure 3. Spiderweb plot summarizing cardiac geometric and diastolic alterations in hypertensive and normotensive pregnancies in the peripartum and postpartum. The cardiac changes of left ventricular mass index, relative wall thickness, E/e' ratio, end-diastolic volume index and end-systolic volume index between peripartum and postpartum are illustrated for the HDP group (red and orange, respectively) and for the control group (dark and light greed respectively).



Left ventricular mechanics	Peripartum	Postpartum