

## OBSTETRICS

# Postpartum cardiovascular function in patients with hypertensive disorders of pregnancy: a longitudinal study

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**BACKGROUND:** Women with a history of hypertensive disorders of pregnancy are at increased risk of cardiovascular diseases, which 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.

**OBJECTIVE:** This study aimed to assess the persistence of hypertension and myocardial dysfunction at 4 months postpartum in a cohort of women with hypertensive disorders of pregnancy, 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 hypertensive disorders of pregnancy and an unmatched group of women with term normotensive pregnancy were recruited. Women with preexisting chronic hypertension ( $n=29$ ) were included in the hypertensive disorders of pregnancy cohort. All participants underwent 2 cardiovascular assessments: the first was conducted either before or within 1 week of delivery (V1: peripartum assessment), and the second between 3 and 12 months following delivery (V2: postpartum assessment). The cardiovascular evaluation included blood pressure profile, maternal transthoracic echocardiography (left ventricular mass index, relative wall thickness, left atrial volume index, E/A, E/e', peak velocity of tricuspid regurgitation, ejection fraction, and left ventricular global longitudinal strain 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 hypertensive disorders of pregnancy and in the control groups.

**RESULTS:** Among 260 patients with pregnancies complicated by hypertensive disorders of pregnancy and 33 patients with normotensive pregnancies, 219 (84.2%) and 30 (90.9%) attended postpartum follow-up, respectively. Patients were evaluated at a median of 124 days (interquartile range, 103–145) after delivery. Paired comparisons of echocardiographic findings demonstrated significant improvements in cardiac remodeling rates (left ventricular mass index [ $\text{g}/\text{m}^2$ ],  $63.4\pm 14.4$  vs  $78.9\pm 16.2$ ;  $P<.001$ ; relative wall thickness,  $0.35\pm 0.1$  vs  $0.42\pm 0.1$ ;  $P<.001$ ), most diastolic indices (E/e',  $6.3\pm 1.6$  vs  $7.4\pm 1.9$ ;  $P<.001$ ), ejection fraction (ejection fraction  $<55\%$ , 9 [4.1%] vs 28 [13.0%];  $P<.001$ ), and global longitudinal strain ( $-17.3\pm 2.6\%$  vs  $-16.2\pm 2.4\%$ ;  $P<.001$ ) in the postpartum period compared with the peripartum. The same improvements in cardiac indices were observed in the normotensive group. However, at the postnatal assessment, 153 of 219 (69.9%) had either hypertension (76/219; 34.7%) or an abnormal global longitudinal strain (125/219; 57.1%), 13 of 67 (19.4%) had metabolic syndrome, and 18 of 67 (26.9%) exhibited insulin resistance.

**CONCLUSION:** Although persistent postpartum cardiovascular impairment was evident in a substantial proportion of patients given that more than two-thirds had either hypertension or myocardial dysfunction postpartum, cardiac modifications because of pregnancy-related overload and hypertension were more pronounced in the peripartum than in the postpartum period.

**Key words:** cardiovascular diseases, cardiovascular risk, echocardiography, gestational hypertension, global longitudinal strain, hypertension, metabolic syndrome, preeclampsia, pregnancy

## Introduction

Women with hypertensive disorders of pregnancy (HDP), including hypertension with and without end-organ involvement, exhibit maternal cardio-

vascular changes that diverge from those observed in normotensive pregnancy, irrespective of the gestational age at the onset of the disease.<sup>1,2</sup> These findings indicate a maladaptation to increased cardiovascular demand during pregnancy when HDP develop, and this hypothesis is supported by a well-established link between HDP and the development of cardiovascular diseases (CVD) in the postpartum period.<sup>3,4</sup> 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.<sup>5</sup> The risk of developing hypertension after HDP is 6-fold higher compared with women after normotensive pregnancy within 2 years postpartum.<sup>3</sup> The short-term burden of preterm preeclampsia has been revealed by findings that two-thirds of patients are still hypertensive at approximately 6 months postpartum.<sup>6,7</sup> Similarly, the higher prevalence of asymptomatic left

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## AJOG at a Glance

**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.

**Key findings**

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

**What does this add to what is known?**

Postpartum care of women with HDP has received increasing attention because it seems 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. These data could help physicians in the management of HDP women in their “fourth trimester.”

ventricular geometric anomalies in women with a history of HDP might explain the subsequent development of heart failure.<sup>8</sup>

Pregnancy and its “fourth trimester” could offer a window of opportunity to prevent adverse outcomes in women with HDP. Indeed, pilot randomized controlled trials have demonstrated that interventions started in the early postpartum period after HDP and based on optimizing blood pressure (BP) control could be promising strategies to improve patients’ CVD prognosis in the long term.<sup>9,10</sup> These interventions should be targeted to women with HDP 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 BP) and echocardiographic data, evaluating left ventricular geometry and function, could effectively identify women at risk of postpartum hypertension.<sup>11</sup>

However, there is a paucity of longitudinal data on the postnatal course and putative cardiovascular recovery from peripartum cardiovascular dysfunction assessed by maternal echocardiography in women with all types of HDP.<sup>3,6,7</sup> Therefore, the present study aimed to assess the persistence of hypertension

and cardiac dysfunction at approximately 4 months postpartum in a heterogeneous cohort of women with HDP, 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 Hospitals NHS Foundation Trust between February 2019 and August 2021. The local ethics committee (19/LO/0794) approved the study, and all participants provided written informed consent. Women with a pregnancy complicated by HDP, including chronic hypertension, preeclampsia, 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 1 week of delivery. We have previously demonstrated that the dramatic hemodynamic changes associated with delivery do not affect cardiac geometry and function when comparing echocardiograms obtained before and within 1 week of delivery.<sup>12</sup> Afterward,

participants underwent a second cardiovascular assessment (V2) that was performed at 3 months up to 1 year postpartum because guidelines reported 6 weeks or 3 months as the point at which normalization of BP after HDP should be expected.<sup>13,14</sup> A group of patients with consecutive normotensive and uncomplicated pregnancies (n=33) was recruited at term during a preoperative assessment for an elective cesarean delivery for breech presentation or maternal request. They were not directly compared with the HDP group, but a parallel comparison between V1 and V2 assessments was also conducted 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, Well-being Software Group, Surrey, United Kingdom), discharge letters, and by direct patient inquiry. All study data were collected and managed using REDCap (Vanderbilt University, Nashville, TN), an electronic data capture tool hosted at St George’s University of London.

**Definitions and outcomes**

HDP were defined according to the criteria of the International Society for the Study of Hypertension in Pregnancy.<sup>13</sup> Preexisting chronic hypertension was defined as systolic BP  $\geq 140$  mm Hg and/or diastolic BP  $\geq 90$  mm Hg before pregnancy (n=5) or before 20 weeks’ gestation (n=24).<sup>15</sup> The primary outcome was the rate of postpartum hypertension, which 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  $\geq 140$  mm Hg and/or diastolic BP  $\geq 90$  mm Hg and/or the use of antihypertensive medication.<sup>16</sup> The secondary outcomes were myocardial and metabolic dysfunction. Myocardial dysfunction was defined by an abnormal left ventricular global

TABLE 1

## Echocardiographic measurements for the evaluation of left ventricular morphology and function and maternal hemodynamics

Views	Measurements	Calculations
LV geometry		
Parasternal long-axis view (end-diastole)	<ul style="list-style-type: none"> <li>• IVS (mm)</li> <li>• LVEDd (mm)</li> <li>• PWT (mm)</li> </ul>	LVM (g): $0.8 \times (1.04 \times [LVEDd + PWT + IVS]^3 - LVEDd^3) + 0.6$ LVMI (g/m <sup>2</sup> ): LVM/BSA RWT: $2 \times PWT/LVEDd$
LV diastolic function		
Apical 4-chamber view	Pulsed wave Doppler of mitral valve:	E/A ratio: E wave velocity/A wave velocity
	<ul style="list-style-type: none"> <li>• E wave velocity (m/s)</li> <li>• A wave velocity (m/s)</li> <li>• Deceleration time (ms)</li> </ul>	
	Pulsed-wave tissue Doppler imaging at the lateral and septal mitral annulus:	E/e' ratio: E wave velocity/mean e' velocity MPI: (isovolumic contraction time)+(isovolumic relaxation time)/ejection time
	<ul style="list-style-type: none"> <li>• Lateral e' velocity (cm/s)</li> <li>• Septal e' velocity (cm/s)</li> </ul>	
	<ul style="list-style-type: none"> <li>• LAV (mL)</li> </ul>	LAVI (mL/m <sup>2</sup> ): LAV/BSA
	Continuous wave Doppler of tricuspid valve:	
	<ul style="list-style-type: none"> <li>• Peak velocity of TR (m/s)</li> </ul>	
LV systolic function		
Apical 4-chamber and 2-chamber views (end-diastole and end-systole)	<ul style="list-style-type: none"> <li>• EDV (mL)</li> <li>• ESV (mL)</li> </ul>	EF (%) calculated by biplane Simpson method of disks
Maternal hemodynamics		
Apical 5-chamber view	<ul style="list-style-type: none"> <li>• LVOT (mm): measured 7 to 10 mm from the aortic valve</li> <li>• VTI (cm) measured by pulsed wave Doppler at LVOT</li> </ul>	SV (mL): $VTI \times 3.14 \times (LVOT/2)^2$ SVI (mL/m <sup>2</sup> ): SV/BSA CO (L/min): SV × HR CI (L/min/m <sup>2</sup> ): CO/BSA SVRI (dynes*sec/cm <sup>5</sup> *m <sup>2</sup> ): $MAP \times 80/CI$

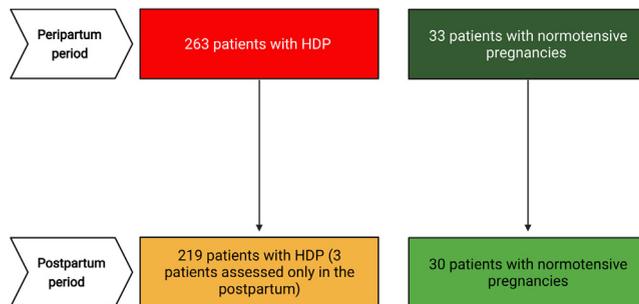
BSA, body surface area; CI, cardiac index; CO, cardiac output; EDV, end-diastolic volume; EF, ejection fraction; ESV, end-systolic volume; HR, heart rate; IVS, interventricular septum; LAV, left atrial volume; LAVI, left atrial volume index; LV, left ventricular; LVEDd, left ventricular end-diastolic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

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longitudinal strain (GLS) using the lowest expected values for age and female sex calculated as  $\pm 1.96$  standard deviations from the mean.<sup>17</sup> GLS is a more sensitive marker of left ventricular dysfunction than ejection fraction (EF), and an impaired GLS has been associated with increased risk of heart failure, acute myocardial

infarction, or cardiovascular death in high- and low-risk populations.<sup>18</sup> Metabolic dysfunction was defined by the presence of metabolic syndrome or by insulin resistance. Metabolic syndrome was defined as the presence of  $\geq 3$  of the following characteristics: waist circumference  $> 88$  cm, triglyceride levels  $\geq 1.7$  mmol/L, high-density

lipoprotein cholesterol  $< 1.3$  mmol/L, BP  $\geq 130/85$  mm Hg, and fasting glucose levels  $\geq 5.6$  mmol/L. Insulin resistance was estimated using the homeostasis model assessment for insulin resistance (HOMA-IR) by the formula:  $\text{insulin (mUI/l)} \times \text{glycemia (mg/dL)} / 405$ ; a value  $> 2.5$  was defined as pathologic.<sup>19</sup>

**FIGURE 1**  
**Participant flowchart**

HDP, hypertensive disorders of pregnancy. Figure 1 was created on Biorender.com.

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### 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 ( $\text{kg}/\text{m}^2$ ) was calculated by dividing body weight (kg) by the squared height in meters ( $\text{m}^2$ ), and body surface area ( $\text{m}^2$ ) was measured using the following equation:  $0.007184 \times \text{height}(\text{cm})^{0.725} \times \text{weight}(\text{kg})^{0.425}$ . A BP profile with at least 3 measurements with 1 minute between them was obtained by an upper-arm automatic BP monitor (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.<sup>20</sup> The average of the last 2 measurements was used to diagnose hypertension.<sup>16</sup> Mean arterial pressure was calculated as  $(2 \times \text{diastolic BP} + \text{systolic BP})/3$ . Moreover, women with elevated BP but not already on hypertensive medication at the postpartum assessment (V2) were provided with a BP monitor (Microlife AG Swiss Corporation), and they were instructed to check their BP at home once a day and to communicate their readings after 1 week. If BP at home was  $<135/85$  mm Hg, a diagnosis of white-coat hypertension was made.<sup>21</sup>

Women with preeclampsia with severe features (ie, preterm delivery, HELLP

[hemolysis, elevated liver enzymes, and low platelets] 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, high-density lipoprotein, low-density lipoprotein, triglyceride levels, creatinine, and protein-to-creatinine ratio. Metabolic syndrome was diagnosed according to the National Cholesterol Education Program Adult Treatment Panel III.<sup>19,22</sup>

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). Two-dimensional Doppler and speckle-tracking echocardiography was performed following international guidelines.<sup>23–27</sup> For each image acquisition, 3 cardiac cycles of noncompressed data were stored in cine-loop format and analyzed offline by one investigator on a dedicated workstation who was blinded to participant order and condition. Echocardiographic measurements used to assess left ventricular geometry, diastolic and systolic function, and maternal hemodynamics are summarized in Table 1. Left ventricular systolic dysfunction was defined as the presence of reduced EF ( $<55\%$ ).<sup>23,24</sup> The primary diastolic parameters were:

early ( $e'$ ) diastolic mitral annulus velocity ( $\leq 7$  cm/s for septal  $E'$  and  $\leq 10$  cm/s for lateral  $E'$ ), ratio between  $E$  and average  $e'$  ( $E/e' \geq 9$ ), left atrial volume index ( $>34$  mL/ $\text{m}^2$ ), and peak velocity of tricuspid regurgitation ( $>2.8$  m/s).<sup>28</sup> The cutoffs for  $E/e'$ , septal  $e'$ , and lateral  $e'$  were derived from gender- and age-specific normal range in women aged 20 to 40 years using mean  $\pm 2$  SD reference.<sup>29,30</sup> A diagnosis of diastolic dysfunction requires more than half of these variables to meet the cutoff values, that is, at least 3 of 4 or 2 of 3 if 1 variable is missing. Diastolic dysfunction was graded using  $E/A$  and the 3 main diastolic parameters ( $E/e' \geq 9$ , left atrial volume index  $>34$  mL/ $\text{m}^2$ , peak velocity of tricuspid regurgitation  $>2.8$  m/s) in women with diastolic dysfunction and in women with abnormal GLS, which represents a better method than EF to identify coexistent systolic dysfunction in hypertrophic ventricles.<sup>28</sup> All images were examined to validate quality for speckle-tracking analysis, and those that did not meet the required level were excluded. The standardization digital images were selected with a frame rate of 60 to 90 frames per 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 left ventricular apex. These measurements were used to calculate left ventricular twist (degrees [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.<sup>31</sup>

### 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 approximately 30%. Therefore, 156 women with HDP 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 subanalysis was performed after excluding women with chronic hypertension. Statistical significance was deemed a priori as *P*<.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 participants (Supplemental Table 1).

The analysis was performed using the statistical software package SPSS Statistics, version 27.0 (IBM Corp, Armonk, NY).

## Results

A total of 260 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 3 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 of 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 2. Five (2.3%) participants were on antihypertensive medications before the index pregnancy, and 24 (11.0%) women had a recorded BP ≥140/90 mm Hg in

**TABLE 2**

**Baseline prepregnancy characteristics of the 219 women in the hypertensive disorders of pregnancy cohort assessed in the postpartum period**

Demographics		Total
Maternal age (y)		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	White	148 (67.6%)
	Afro-Caribbean	32 (14.6%)
	Asian	27 (12.3%)
	Mixed/Other	12 (5.5%)
Smoker	In pregnancy	3 (1.4%)
	Preconceptional	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%)
Preexisting chronic hypertension		29 (13.2%)
Diabetes mellitus type 1 or 2		5 (2.3%)
<b>First trimester data</b>		
BMI (kg/m <sup>2</sup> )		26.93 (23.11–31.25)
MAP (mm Hg)		94.67 (90.00–99.33)
High risk for preterm preeclampsia		54/166 (32.5%)
<b>Second and third trimester data</b>		
BMI (kg/m <sup>2</sup> ) <sup>a</sup>		27.82 (24.22–31.96)
MAP (mm Hg) <sup>a</sup>		97.33 (91.33–104.00)
Diagnosis of preeclampsia		135 (61.6%)
Early-onset preeclampsia (<34 wk)		47 (36.2%)
Gestational age at delivery (wk)		38.00 (35.86–39.43)
Mode of delivery	Vaginal delivery	90 (41.10%)
	Cesarean delivery	129 (58.90%)
HELLP syndrome		6 (2.7%)
Eclampsia or neurologic 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 edema n=1, DIC n=1, placental abruption n=3)		6 (2.7%)

Data are expressed as median (interquartile range) and number (percentage).

BMI, body mass index; CVD, cardiovascular disease; DIC, disseminated intravascular coagulation; HDP, hypertensive disorders of pregnancy; HELLP, hemolysis, elevated liver enzymes, and low platelets; ICSI, intracytoplasmic fertilization; IUI, intrauterine insemination; IVF, in vitro fertilization; MAP, mean arterial pressure.

<sup>a</sup> Measured at peripartum assessment (V1).

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TABLE 3

**Clinical and cardiovascular findings of the 219 women in the hypertensive disorders of pregnancy cohort at postpartum follow-up**

Postpartum clinical findings	
SBP $\geq$ 140 or DBP $\geq$ 90 or medication	76 (34.7%)
On antihypertensive medication	33 (15.1%)
SBP $\geq$ 140 or DBP $\geq$ 90 (not on medication)	43 (19.6%)
Metabolic syndrome ( $\geq$ 3 criteria)	13/67 (19.4%)
Fasting glycemia $\geq$ 5.6 mmol/L or treatment	3
Fasting HDL $<$ 1.3 mmol/L or treatment	19
Fasting triglycerides $\geq$ 1.7 mmol/L or treatment	8
Waist $\geq$ 88 cm (80 cm in Asian patients)	30
BP $\geq$ 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 $\geq$ 140 or DBP $\geq$ 90 or medication	153 (69.9%)
Markers of diastolic dysfunction	
Lateral e' $\leq$ 10 cm/s or septal e' $\leq$ 7 cm/s	24 (11.0%)
E/e' $\geq$ 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 1	93/106 (87.7%)
Grade 2	4/106 (3.8%)
Grade 3	1/106 (0.9%)
Not determined	8/106 (7.5%)

Data are expressed as number (percentage).

BMI, body mass index; BP, blood pressure; DBP, diastolic blood pressure; EF, ejection fraction; GLS, global longitudinal strain; HDL, high-density lipoprotein; HOMA-IR, homeostatic model assessment for insulin resistance; LAVI, left atrial volume index; SBP, systolic blood pressure; TR, tricuspid regurgitation.

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early pregnancy. The cohort included 135 (61.6%) women with a diagnosis of preeclampsia, and 72 (32.9%) delivered preterm (Table 2). High-dependency unit admission was required in 53 (24.2%) women; 81 (37.0%) neonates had a birthweight  $<$ 10th centile, and 61 (27.9%) were admitted to the neonatal intensive care unit.

### Postpartum cardiovascular and metabolic findings in hypertensive disorders of pregnancy

Patients with HDP were evaluated at a median of 124 days (IQR, 103–145) after delivery (Supplemental Table 2). At the postnatal cardiovascular assessment, 76 (34.7%) women were still hypertensive (n=43) or needed antihypertensive

medications (n=33) (Table 3). Among the 43 women who were not on antihypertensive medication, 6 (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 2 cases (0.9%). Abnormal postpartum diastolic parameters included lateral e'  $\leq$ 10 cm/s (9.1%), septal e'  $\leq$ 7 cm/s (6.8%), E/e'  $\geq$ 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 1 in 93 of 106 (87.7%) cases, grade 2 in 4 of 106 (3.8%) cases, and grade 3 in 1 case (0.9%) (Table 3).

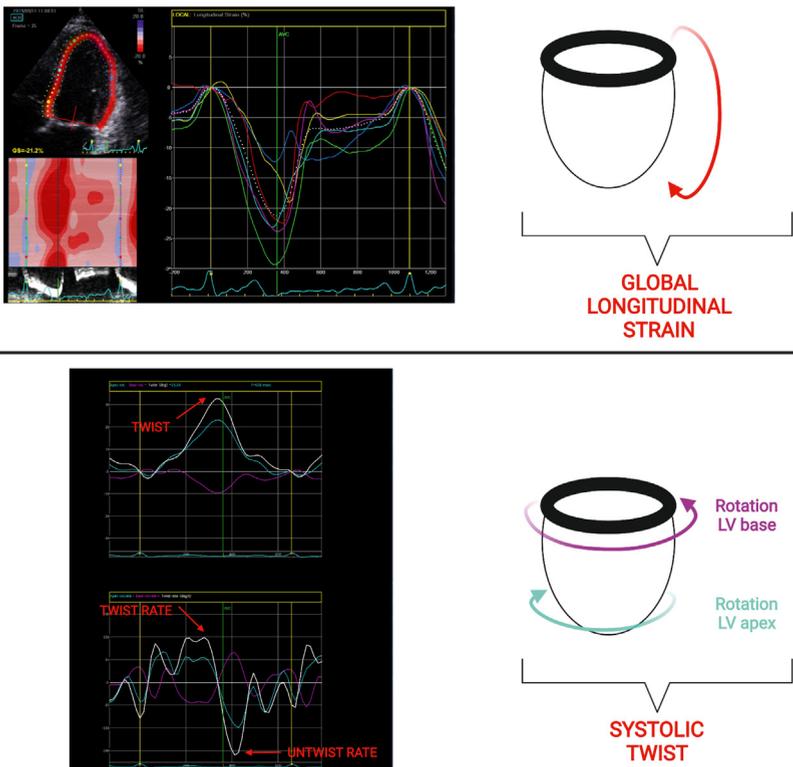
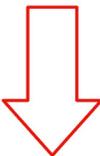
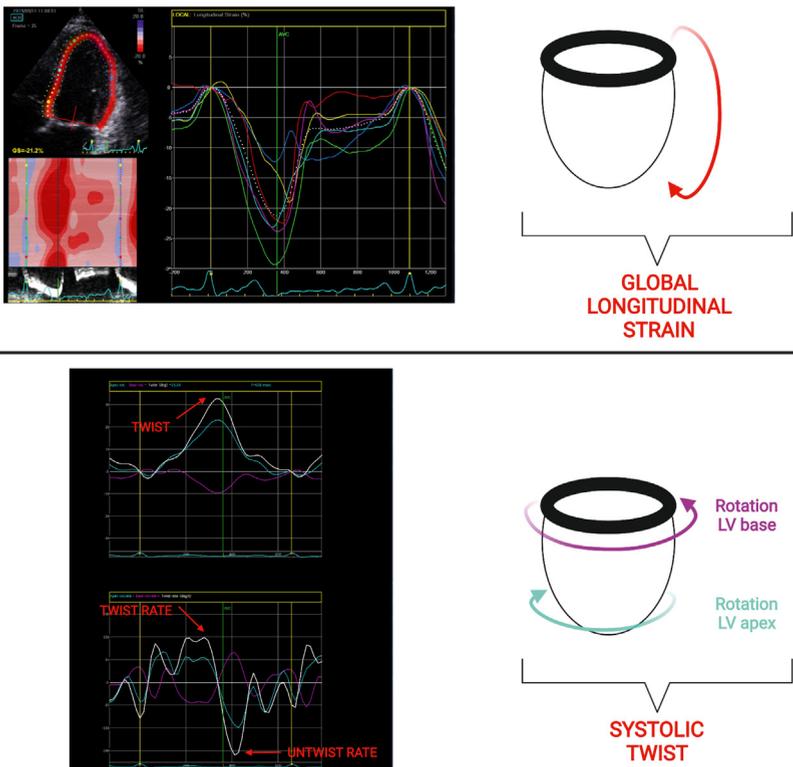
There was no difference in the rate of postnatal hypertension (31.9% vs 39.3%;  $P=.261$ ) or abnormal GLS (58.5% vs 55.4%;  $P=.653$ ) between patients with and without preeclampsia.

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 (Table 3).

### Comparison between peripartum and postpartum transthoracic echocardiograms of participants with hypertensive disorders of pregnancy 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 4). Left ventricular chamber dimensions were reduced, and all diastolic indices improved significantly during this period. EF and GLS were increased, whereas twist, twist rate, and untwist rate were reduced when assessed at least 3 months after delivery compared with the peripartum period (Figure 2).

**FIGURE 2**  
Left ventricular mechanics in HDP patients

Left ventricular mechanics	Peripartum	Postpartum
 <p>The upper part of the table shows echocardiographic images and a graph of GLOBAL LONGITUDINAL STRAIN (GLS) over time. The lower part shows a graph of SYSTOLIC TWIST with sub-graphs for TWIST, TWIST RATE, and UNTWIST RATE. Diagrams illustrate the mechanics: GLOBAL LONGITUDINAL STRAIN (red arrow) and SYSTOLIC TWIST (purple and green arrows) at the LV base and apex.</p>		
 <p>The upper part of the table shows echocardiographic images and a graph of GLOBAL LONGITUDINAL STRAIN (GLS) over time. The lower part shows a graph of SYSTOLIC TWIST with sub-graphs for TWIST, TWIST RATE, and UNTWIST RATE. Diagrams illustrate the mechanics: GLOBAL LONGITUDINAL STRAIN (red arrow) and SYSTOLIC TWIST (purple and green arrows) at the LV base and apex.</p>		

The upper part of the table shows the left ventricular global longitudinal strain that is lower (arrow down) in the peripartum compared with the postpartum (arrow up). The lower part of the table shows systolic twist that is higher (arrow up) in the peripartum compared with the postpartum (arrow down). Figure 2 was created on Biorender.com.

HDP, hypertensive disorders of pregnancy.

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Hemodynamic changes are shown in Table 4. The results were similar when women with preexisting chronic hypertension (n=29) were excluded (Supplemental Table 3). In women with uncomplicated pregnancies, all cardiovascular geometric and functional parameters demonstrated significant improvement in the postpartum period (Supplemental Table 4). A comparison of left ventricular geometry between women with normotensive and hypertensive pregnancies is illustrated in Figure 3. Among 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.

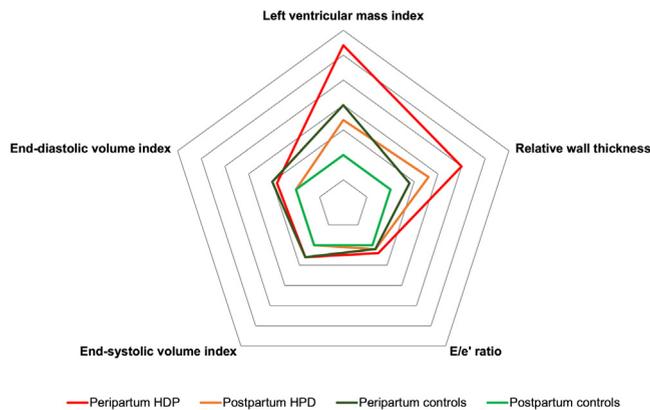
### Comment

#### Principal findings

The findings of this study demonstrated that at approximately 4 months postpartum, one-third of patients with HDP showed persistent hypertension, and two-thirds of them had either hypertension or myocardial dysfunction. The postnatal cardiovascular impairment in the HDP group did not differ between patients with and without preeclampsia. 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.<sup>11</sup> This stratification could guide a targeted cardiovascular prevention strategy and improve maternal cardiovascular health.

**FIGURE 3**  
**Left ventricular geometric and diastolic alterations in HDP and normotensive patients**



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 green, respectively).

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### 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.<sup>32,33</sup> Although the concept of a “dose effect” with more severe pregnancy-associated hypertensive disorders implies a greater risk of future hypertension, this risk increases considerably and quickly in the years following delivery in women who develop both gestational hypertension and preeclampsia.<sup>34,35</sup> A meta-analysis that focused on the risk of hypertension after HDP in the first 2 years following delivery showed, consistent with our data, that almost one-third (28.4%) of patients with HDP were still hypertensive, and the odds ratio (95% confidence interval) for hypertension was 5.42 (3.12–9.41) up to 1 year postpartum.<sup>3</sup> 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 preeclampsia.<sup>6</sup> Therefore, the clinically considerable

effects of HDP persist after birth, and this should be taken into account when considering patient discharge from obstetrical care.

Chronic hypertension is one of the most important risk factors for developing CVD.<sup>5,36</sup> To facilitate cardiovascular screening in women with a history of HDP, identifying enduring cardiac impairment might be essential for their subsequent cardiovascular management. Preeclampsia 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.<sup>37</sup> Altered left ventricular morphology and asymptomatic systolic-diastolic dysfunction are common findings in women after a pregnancy complicated by HDP.<sup>8,38</sup> Women with HDP and persistent hypertension have the most pronounced echocardiographic changes, including left ventricular remodeling and abnormal diastolic and systolic function parameters compared with controls and women with a history of HDP or hypertension.<sup>38,39</sup> 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,<sup>6</sup> who found that 10% of women with preterm preeclampsia had systolic dysfunction, and 2% had diastolic dysfunction. 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.<sup>40</sup>

Our echocardiographic data show that cardiac indices related to left ventricular morphology and function were more impaired in the peripartum compared with the postpartum in hypertensive and normotensive patients, and this might be related to the cardiovascular overload caused by the pregnant state. Other studies have shown a recovery of cardiac abnormalities caused by pregnancy and hypertension when assessed from 1 year to several years after delivery.<sup>38,41</sup> Our data also corroborate myocardial impairment caused by pregnancy, showing opposing trends for GLS and twist parameters: GLS was increased and twist/twist rate reduced in the postpartum period compared with the time at which HDP was diagnosed (Figure 2). We hypothesize that this paradoxical finding might be related to early sub-endocardial dysfunction leading to a reduction in longitudinal left ventricular mechanics observed in HDP.<sup>42</sup> Because epicardial fibers remain spared, circumferential strain and twist mechanics of the left ventricle show normal or even increased values, compensating for the longitudinal mechanical dysfunction and thus preserving stroke volume and EF.<sup>43</sup> These findings suggest that peripartum cardiac morphologic 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

TABLE 4

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

Echocardiographic parameters	Peripartum	Postpartum	P value
<b>LV geometry</b>			
LVMI (g/m <sup>2</sup> )	78.92±16.16	63.39±14.43	<.001
RWT	0.42±0.09	0.35±0.08	<.001
LV remodeling	Concentric remodeling	82 (38.0%)	33 (15.1%)
	Concentric hypertrophy	25 (11.6%)	4 (1.8%)
	Eccentric hypertrophy	8 (3.7%)	2 (0.9%)
LV ESVI (mL/m <sup>2</sup> )	25.79±6.51	24.29±5.27	<.001
LV EDVI (mL/m <sup>2</sup> )	61.92±12.27	58.81±10.91	<.001
<b>LV diastolic function</b>			
LAVI (mL/m <sup>2</sup> )	27.42±6.17	23.40±5.53	<.001
E/A	1.22±0.27	1.37±0.29	<.001
Lateral e' (cm/s)	13±3	15±3	<.001
Septal e' (cm/s)	10±3	11±2	<.001
MPI	0.50±0.10	0.48±0.08	<.001
E/e'	7.4±1.91	6.3±1.61	<.001
Peak TR velocity (m/s)	2.09±0.36	2.05±0.32	.002
<b>LV systolic function</b>			
EF <55%	28 (13.0%)	9 (4.1%)	<.001
<b>LV mechanics</b>			
GLS (%)	-16.24±2.44	-17.26±2.25	<.001
Twist (deg)	15.51±5.10	15.34±6.11	.019
Twist rate (deg/s)	111.53±35.78	107.11±34.53	<.001
Untwist rate (deg/s)	-122.61±44.61	-114.60±45.73	.020
<b>Maternal hemodynamic changes</b>			
HR (bpm)	81.47±12.89	71.66±11.11	<.001
VTI (cm)	23.77±4.10	22.90±3.51	.001
SVI (mL/m <sup>2</sup> )	37.54±7.71	37.97±7.50	.420
CI (L/min/m <sup>2</sup> )	3.04±0.71	2.70±0.60	<.001
SVRI (dynes*sec/cm <sup>5</sup> *m <sup>2</sup> )	2896.42±702.19	3052.63±728.80	.010

Data are expressed as mean ± standard deviation and number (percentage).

CI, cardiac index; EDVI, end-diastolic volume index; EF, ejection fraction; ESVI, end-systolic volume index; GLS, global longitudinal strain; HR, heart rate; LAVI, left atrial volume index; LV, left ventricular; LVMI, left ventricular mass index; MPI, myocardial performance index; RWT, relative wall thickness; SVI, stroke volume index; SVRI, systemic vascular resistance index; TR, tricuspid regurgitation; VTI, velocity time integral.

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echocardiographic parameters measured during the peripartum period showed excellent discrimination (area under the curve, 0.80–0.86).<sup>11</sup> Therefore, a clinical and cardiovascular evaluation during the peripartum admission for delivery in women with HDP could detect those at

increased risk of postpartum hypertension, and who could benefit from targeted preventive strategies for CVD.

### Clinical implications

First, all healthcare professionals providing care to women in the

pregnancy and postpartum periods 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. Consequently, women with any HDP must be

counseled regarding their risk of CVD before hospital discharge. Another important consideration is that most women usually have a single medical assessment, with or without BP measurement, at 6 to 8 weeks postpartum after a pregnancy complicated by hypertension, and this should not be the case today.<sup>14</sup> 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. Furthermore, a diagnosis of hypertension in women at increased risk of CVD should be followed by prompt referral to physicians for behavioral and/or pharmacologic 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 represents the leading cause of mortality in the female population, must be continued.<sup>44</sup> 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 because this is one of the few available strategies to prevent heart failure and other CVD.<sup>45</sup> Home BP 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.<sup>10</sup> In terms of antihypertensive medication, although 6-month use of angiotensin-converting-enzyme inhibitors after preeclampsia demonstrated advantageous effects on maternal cardiac remodeling,<sup>9</sup> it is unknown which is the best antihypertensive regimen to use in the postpartum period. More specific pharmacologic interventions, such as lipid-lowering therapy or aspirin for primary cardiovascular prevention, might be tailored to women with a history of HDP who are at increased risk of persistent cardiovascular impairment.<sup>9,46</sup> Furthermore, 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.<sup>11</sup>

### 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. Conversely, study limitations included (by intention) a relatively short cardiovascular follow-up. The inability to offer home BP monitoring to all participants may have led to the underdiagnosis of masked hypertension.<sup>47</sup> 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 of the need for cardiovascular screening that could be the first step for an effective primary cardiovascular prevention (Video files 1 and 2). ■

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SUPPLEMENTAL TABLE 1

## Inter- and intraobservation reproducibility

Echocardiographic parameters	ICC (95% confidence interval)	
	Interobservation	Intraobservation
IVS (cm)	0.977 (0.945–0.990)	0.963 (0.915–0.984)
LVIDd (cm)	0.977 (0.946–0.990)	0.971 (0.934–0.988)
PWT (cm)	0.943 (0.869–0.975)	0.918 (0.812–0.964)
LA size	0.911 (0.794–0.961)	0.932 (0.843–0.970)
MV E (m/s)	0.990 (0.975–0.996)	0.992 (0.980–0.997)
MV A (m/s)	0.935 (0.827–0.974)	0.982 (0.958–0.992)
Deceleration time (ms)	0.850 (0.589–0.939)	0.973 (0.936–0.988)
Lateral E' (m/s)	0.994 (0.986–0.997)	0.982 (0.957–0.992)
Lateral A' (m/s)	0.977 (0.946–0.990)	0.958 (0.904–0.982)
Lateral S' (m/s)	0.964 (0.918–0.984)	0.964 (0.918–0.984)
Septal E' (m/s)	0.987 (0.970–0.994)	0.996 (0.991–0.998)
Septal A' (m/s)	0.965 (0.918–0.985)	0.923 (0.819–0.967)
Septal S' (m/s)	0.908 (0.788–0.960)	0.969 (0.928–0.986)
4C EF (%)	0.878 (0.718–0.947)	0.927 (0.832–0.969)
4C LV EDV (mL)	0.968 (0.926–0.986)	0.980 (0.955–0.992)
4C LV ESV (mL)	0.943 (0.869–0.975)	0.973 (0.938–0.988)
2C EF (%)	0.830 (0.582–0.929)	0.828 (0.590–0.927)
2C LV EDV	0.945 (0.872–0.977)	0.976 (0.944–0.990)
2C LV ESV	0.970 (0.928–0.987)	0.968 (0.925–0.986)
4C GLS (%)	0.925 (0.827–0.968)	0.911 (0.796–0.961)
2C GLS (%)	0.899 (0.752–0.959)	0.958 (0.897–0.983)
3C GLS (%)	0.888 (0.723–0.955)	0.952 (0.879–0.981)

EDV, end-diastolic volume; EF, ejection fraction; ESV, end-systolic volume; GLS, global longitudinal strain; ICC, intraclass correlation coefficient; IVS, interventricular septum; LA, left atrial; LV, left ventricular; LVIDd, left ventricular internal dimension at end-diastole; MV, mitral valve; PWT, posterior wall thickness; 2C, 2-chamber view; 3C, 3-chamber view; 4C, 4-chamber view.

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## SUPPLEMENTAL TABLE 2

## Postpartum characteristics of the 219 women with hypertensive disorders of pregnancy at postpartum follow-up

Postpartum characteristics	HDP patients	
Time of postpartum assessment (d)	124.00 (103.00–145.00)	
Time of postpartum assessment	3–6 mo	194 (88.6%)
	7–12 mo	25 (11.4%)
Postpartum BMI (kg/m <sup>2</sup> )	27.82 (24.22–31.96)	
Postpartum MAP (mm Hg)	97.33 (91.22–104.00)	
Breastfeeding	139 (63.5%)	
Oral contraceptive	14 (6.4%)	
Regular physical activity (3 times/wk)	61 (27.9%)	
Postpartum HBPM	69 (31.5%)	
Readmission for hypertension	14 (6.4%)	
Antihypertensive medication prescribed at discharge	151 (68.9%)	
	Labetalol	69 (31.5%)
	Nifedipine	99 (45.2%)
	Amlodipine	9 (4.1%)
	ACE inhibitors	17 (7.8%)
Antihypertensive medication stopped at:	<6 wk	61 (52.1%)
	6–12 wk	49 (41.9%)
	>12 wk	7 (6.0%)

Data are expressed as median (interquartile range) and number (percentage).

ACE, angiotensin-converting enzyme; BMI, body mass index; HBPM, home blood pressure monitoring; HDP, hypertensive disorders of pregnancy; MAP, mean arterial pressure. Giorgione. HDP and the postpartum cardiovascular course. *Am J Obstet Gynecol* 2023.

## SUPPLEMENTAL TABLE 3

## Comparison between peripartum and postpartum echocardiographic left ventricle findings in women with hypertensive disorders of pregnancy after excluding women with chronic hypertension (n = 29)

Echocardiographic parameters	Peripartum	Postpartum	P value
LV geometry			
LVMI (g/m <sup>2</sup> )	78.97 ± 15.83	61.98 ± 12.91	<.001
RWT	0.42 ± 0.09	0.34 ± 0.08	<.001
LV diastolic function			
LAVI (mL/m <sup>2</sup> )	27.65 ± 6.36	23.11 ± 5.18	<.001
E/A	1.23 ± 0.27	1.39 ± 0.30	<.001
Lateral e' (cm/s)	12.82 ± 3.0	14.83 ± 2.8	<.001
Septal e' (cm/s)	10.00 ± 2.5	11.17 ± 2.2	<.001
MPI	0.50 ± 0.09	0.47 ± 0.08	<.001
E/e'	7.3 ± 1.9	6.1 ± 1.3	<.001
Peak TR velocity (m/s)	2.1 ± 0.4	2.0 ± 0.3	.002
LV systolic function			
EF%	58.47 ± 4.29	58.76 ± 3.28	<.001
LV mechanics			
GLS (%)	-16.24 ± 2.39	-17.24 ± 2.28	<.001
Twist (deg)	14.71 ± 5.44	15.00 ± 6.05	.297
Maternal hemodynamic changes			
HR (bpm)	81.00 ± 12.90	71.45 ± 11.46	<.001
SVI (mL/m <sup>2</sup> )	37.84 ± 7.81	37.90 ± 7.53	<.001
CI (L/min/m <sup>2</sup> )	3.04 ± 0.72	2.68 ± 0.58	<.001
SVRI (dynes*sec/cm <sup>5</sup> *m <sup>2</sup> )	2887.97 ± 706.53	3045.58 ± 741.36	<.001

Data are expressed as mean ± standard deviation.

CI, cardiac index; EF, ejection fraction; GLS, global longitudinal strain; HR, heart rate; LAVI, left atrial volume index; LV, left ventricular; LVMI, left ventricular mass index; MPI, myocardial performance index; RWT, relative wall thickness; SVI, stroke volume index; SVRI, systemic vascular resistance index; TR, tricuspid regurgitation.

Giorgione. HDP and the postpartum cardiovascular course. *Am J Obstet Gynecol* 2023.

## SUPPLEMENTAL TABLE 4

## Comparison between peripartum and postpartum echocardiography in women with normotensive pregnancies (n = 30)

Echocardiographic parameters	Peripartum	Postpartum	P value
LV geometry			
LVMI (g/m <sup>2</sup> )	66.45 ± 12.37	56.36 ± 9.70	<.001
RWT	0.31 ± 0.06	0.27 ± 0.06	.005
LV ESVI (mL/m <sup>2</sup> )	26.02 ± 5.25	23.61 ± 5.22	.036
LV EDVI (mL/m <sup>2</sup> )	63.88 ± 10.16	58.70 ± 10.05	.017
Diastolic function			
LAVI (mL/m <sup>2</sup> )	25.06 ± 4.43	22.14 ± 5.04	.001
E/A	1.26 ± 0.24	1.43 ± 0.29	.001
Lateral E' (m/s)	0.15 ± 0.03	0.16 ± 0.02	.326
Septal E' (m/s)	0.11 ± 0.02	0.12 ± 0.01	.024
MPI	0.46 ± 0.08	0.43 ± 0.04	.011
E/E'	5.92 ± 1.39	5.41 ± 0.82	.082
Peak TR velocity (m/s)	2.06 ± 0.34	2.12 ± 0.19	.352
LV systolic function			
EF (%)	59.47 ± 4.18	60.00 ± 3.55	.496
LV mechanics			
GLS (%)	-17.13 ± 2.17	-18.49 ± 1.67	.001
Twist (deg)	15.51 ± 5.07	13.30 ± 5.28	.043
Twist rate (deg/s)	98.38 ± 25.64	96.22 ± 30.85	.707
Untwist rate (deg/s)	-118.85 ± 38.57	-108.59 ± 34.27	.172
Hemodynamic changes			
HR (bpm)	77.47 ± 12.88	68.30 ± 11.55	.004
VTI (cm)	23.62 ± 3.62	22.86 ± 3.54	.263
SVI (mL/m <sup>2</sup> )	37.13 ± 7.90	37.88 ± 6.97	.585
CI (L/min/m <sup>2</sup> )	2.85 ± 0.66	2.57 ± 0.54	.027
SVRI (dynes*sec/cm <sup>5</sup> *m <sup>2</sup> )	2659.34 ± 629.07	2809.32 ± 732.29	.274

Data are expressed as mean ± standard deviation.

CI, cardiac index; EDVI, end-diastolic volume index; EF, ejection fraction; ESVI, end-systolic volume index; GLS, global longitudinal strain; HR, heart rate; LAVI, left atrial volume index; LV, left ventricular; LVMI, left ventricular mass index; MPI, myocardial performance index; RWT, relative wall thickness; SVI, stroke volume index; SVRI, systemic vascular resistance index; TR, tricuspid regurgitation; VTI, velocity time integral.

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