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Association of Hypertensive Disorders of Pregnancy With Left Ventricular Remodeling Later in Life

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ABSTRACT

BACKGROUND Hypertensive disorders of pregnancy (HDP) are associated with short-term cardiac structure and function abnormalities, but later life changes are not well studied.

OBJECTIVES This study aimed to determine if HDP history is associated with echocardiographic differences 8 to 10 years after delivery, and if subgroups with placental maternal vascular malperfusion (MVM) lesions or current hypertension may be particularly affected.

METHODS Women with pregnancies delivered from 2008 to 2009 were selected from a clinical cohort with abstracted pregnancy and placental pathology data to undergo transthoracic echocardiography (2017 to 2020). Medical history, blood pressure, and weight were measured at the study visit.

RESULTS The authors enrolled 132 women (10 ± 1 years post-delivery, age 38 ± 6 years): 102 with normotensive pregnancies and 30 with HDP: pre-eclampsia (n = 21) or gestational hypertension (n = 9). Compared with women with normotensive pregnancies, those with HDP history were more likely to have current hypertension (63% vs. 26%; $p < 0.001$). After adjusting for age, race, MVM lesions, body mass index, current hypertension, and hemoglobin A1c, women with HDP history had higher interventricular septal thickness ($\beta = 0.08$; $p = 0.04$) and relative wall thickness ($\beta = 0.04$; $p = 0.04$). In subgroup analyses, those with both HDP history and current hypertension had a higher proportion of left ventricular remodeling (79.0%) compared with all other groups (only HDP [36.4%; $p = 0.01$], only current hypertension [46.2%; $p = 0.02$], and neither HDP nor hypertension [38.2%; $p < 0.001$]), and lower mitral inflow E/A and annular e′. Accounting for placental MVM lesions did not impact results.

CONCLUSIONS Women with both HDP history and current hypertension have pronounced differences in left ventricular structure and function a decade after pregnancy, warranting continued surveillance and targeted therapies for cardiovascular disease prevention. (J Am Coll Cardiol 2021;77:1057–68) © 2021 by the American College of Cardiology Foundation.

Hypertensive disorders of pregnancy (HDP), such as pre-eclampsia and gestational hypertension, have consistently been shown to be associated with an increased risk of later-life cardiovascular disease (CVD) (1–3). The pathophysiological mechanism linking these pregnancy complications to CVD decades later is poorly understood, thus constraining the development of approaches to prevent future CVD in these women.

Around the time of delivery, women with HDP are more likely to have structural cardiac changes compared with women who are normotensive during

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ABBREVIATIONS AND ACRONYMS

ASE = American Society of Echocardiography

BMI = body mass index

CVD = cardiovascular disease

GLS = global longitudinal strain

HDP = hypertensive disorders of pregnancy

IVS = interventricular septum

LV = left ventricle/ventricular

LVMI = left ventricular mass index

PW = posterior wall

RV = right ventricle/ventricular

RWT = relative wall thickness

pregnancy (4,5). On peripartum transthoracic echocardiogram, women with HDP have more prominent changes in diastolic function parameters, including an exaggerated reduction in E/A mitral inflow ratio and increased E/e′ ratio, as measured with spectral and tissue Doppler, respectively (6). They also have changes in left ventricular (LV) and right ventricular (RV) structure and function including increased LV wall thickness, LV mass index, estimated RV systolic pressure, and abnormalities in RV strain (7) that can persist up to 1 year postpartum (8).

A limited number of studies have reported inconsistent echocardiographic findings in later life for women with a history of HDP. Among women in their fifth decade of life, ranging 9 to 16 years after the index pregnancy, pre-eclampsia history was associated with a higher estimated left atrial pressure (mean E/e′ ratio), increased LV mass index and increased relative wall thickness (RWT) compared with those without HDP (9,10). More severe forms of pre-eclampsia were associated with higher proportion of LV concentric remodeling and lower LV global longitudinal strain (GLS) up to a few years after delivery (11). Other studies have shown an association of pre-eclampsia history with concentric LV remodeling and preclinical heart failure 4 to 10 years after delivery; however, these associations were attenuated after accounting for current blood pressure (12,13).

Although there has been some characterization of structural cardiac changes among women with a history of HDP, the underlying mechanisms for these changes are incompletely understood. The timing of postpartum echocardiograms in prior studies has varied widely from 1 to 16 years postpartum making their findings difficult to compare. Also, women with HDP have a higher likelihood of developing hypertension in the years after delivery (1), an important comorbidity that could contribute to the LV remodeling and diastolic changes (14). To date, however, echocardiographic studies performed in later life have not consistently accounted for the development of chronic hypertension after an HDP, such that its contribution to the structural cardiac changes in women with a history of HDP is not clearly understood.

Vascular changes in the placenta may provide additional insight to the mechanistic link between HDP and later-life cardiac structural changes and CVD. About 40% to 50% of women with HDP have placental maternal vascular malperfusion (MVM), a pathophysiological finding characterized by incomplete maternal vascular placental remodeling and vessel wall impairments (15–18). This decidual vasculopathy has features similar to those found in atherosclerosis (16,19,20), and include the placental response to hypoxia. Placental MVM lesions are thought to arise from an impaired maternal response to the vascular adaptations required to successfully perfuse the placenta, and thus, have been hypothesized to be a marker of CVD susceptibility and risk factors later in life (21–23). Although provocative, there are no studies linking placental vascular changes during pregnancy to adverse maternal cardiac remodeling in later life.

Based on the previously listed considerations, we hypothesized that women with a history of HDP are more likely to have ventricular remodeling and changes in systolic/diastolic LV function long-term, and that those with current hypertension or placental MVM lesions would be most affected. To test this hypothesis, we performed echocardiography 8 to 10 years after pregnancy in a unique cohort of women at our institution in whom placental pathology and complete clinical pregnancy data were available.

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METHODS

PARTICIPANTS. Eligible women were those with deliveries in 2008 to 2009 identified from the Magee Obstetric Maternal and Infant database at the University of Pittsburgh, Pittsburgh, Pennsylvania; this clinical cohort of women had detailed pregnancy data abstracted from medical records. About 45% of deliveries (n = 4,457) had placental pathology specimen collection at the time of delivery for clinical indications, and those with these data were the source population for the study (24). We recruited women from an ongoing study investigating placental vascular lesions, adverse pregnancy outcomes, and postpartum CVD (n = 498). We then randomly selected a subset to undergo 2-dimensional (2D) transthoracic B-mode, Doppler, and strain echocardiography (2017 to 2020) (Supplemental Figure 1). By design, one-half had placental MVM lesions (vasculopathy, placental infarct, accelerated villous maturation, and fibrin deposition; n = 65) (Supplemental Table 1) (21,25,26), and one-half did not have MVM lesions (n = 67). Placental features for enrolled women were re-evaluated by a study pathologist (W.T.P.), who was blinded to all clinical information except gestational age and there was substantial agreement between the blinded review and the clinical report (kappa = 0.78). We excluded from this study women who were currently pregnant; had a diagnosis of chronic hypertension prior to pregnancy; or had clinical CVD including congenital heart

disease, valvular heart disease, myocardial infarction, cardiomyopathy, heart failure, or stroke before the index pregnancy. Two of the women recruited had chronic hypertension predating pregnancy and were excluded from the analyses. One of these also had a history of inferior myocardial infarction, and thus had significant wall motion abnormalities.

This study was approved by the University of Pittsburgh Institutional Review Board (STUDY19110278). All participants signed written informed consent.

STUDY PROCEDURES. Between 2017 and 2019 (8 to 10 years after their delivery) we enrolled women to attend a study visit where we measured height, weight, and blood pressure by standardized methods. Trained research personnel took 3 blood pressure measurements after participants had been sitting at rest for 5 min using an automated, validated device (Microlife A6 PC/BP 3GUI-8X, Microlife USA, Clearwater, Florida) and an appropriately sized cuff following measurement of arm circumference. Participants completed a survey that included questions about current medications and medical history. Diabetes was identified by self-report or if a participant had a hemoglobin A1c (HbA1c) ≥6.5%. We defined current hypertension according to the 2018 JNC-8 guidelines with average measured systolic blood pressure >130 mm Hg, average diastolic blood pressure >80 mm Hg, or self-reported antihypertensive medication use. We classified women with a history of HDP including those with gestational hypertension (elevated systolic blood pressure >140 mm Hg or diastolic >90 mm Hg diagnosed after 20 weeks gestation) or pre-eclampsia (elevated blood pressure plus proteinuria) by abstraction of the medical record data for their index pregnancy based on the American College of Obstetricians and Gynecologists definitions at the time of delivery (27). Development of pre-eclampsia in any pregnancy other than the index pregnancy was assessed by Magee Obstetric Maternal and Infant database abstraction of other deliveries recorded in this database. We defined pre-term birth as delivery at <37 weeks gestation.

TRANSTHORACIC ECHOCARDIOGRAM. At the study visit, participants underwent a standard transthoracic 2D echocardiogram performed by a dedicated research sonographer on a clinical ultrasound imaging system (IE33, Phillips Healthcare, Andover, Massachusetts). Two cardiologists (M.E.C., K.L.B.) certified by the National Board of Echocardiography independently interpreted the studies, and discrepancies were resolved by discussion and consensus agreement. Both cardiologists and the sonographer were blinded to the participant's obstetric history.

We used standard 2D echocardiographic methods to obtain measurements of LV interventricular septum (IVS) thickness, LV posterior wall (PW) thickness, and LV end-diastolic diameter according to American Society of Echocardiography (ASE) guidelines (28). We calculated left atrial volume index by summation of disks method and indexing to body surface area (28). We calculated ejection fraction by biplane method summation of discs (28). Measures of diastolic dysfunction were obtained by pulse-wave Doppler of the mitral inflow (E and A velocity) and pulse-wave tissue Doppler of the lateral and septal mitral annulus (e′ velocity). Diastolic dysfunction was defined by the 2016 ASE guidelines including indeterminant diastolic, which was defined by 2 of 4 positive criteria for diastolic dysfunction (29). RWT was calculated as: 2 • (LV PW thickness)/(LV end-diastolic diameter). Left ventricular mass index (LVMI) was calculated using formulas for chamber quantification by the ASE (28). LV remodeling was defined as a RWT of >0.42 and LV hypertrophy was defined as LVMI >95 g/m^2 (28).

Assessment of myocardial strain was performed by postprocessing acquired images using 2D speckle-tracking technique on 2D grayscale loops with commercially available software (2D Cardiac Performance Analysis version 4.3.2.5, TomTec, Munich, Germany). LV GLS was calculated by averaging the negative peak systolic longitudinal strain from 16 ventricular segments in the apical 4-, 3-, and 2-chamber views (30). The RV free wall strain was assessed by averaging the negative peak systolic longitudinal strain from the RV basal, mid, and apical free wall segments. Abnormal GLS was defined as >−20% (30). Two cardiologist readers (M.E.C., J.L.C.) adjudicated strain images for 20 participants.

Biplane LV ejection fraction could not be measured due to suboptimal image quality in 2 participants. LV GLS was unable to be measured in 17 participants (14%) and RV strain was unable to be measured in 35 participants (27%) due to suboptimal image quality or lack of dedicated RV images.

STATISTICAL METHODS. Comparison of continuous, normally distributed demographic variables between women with a history of HDP in the index pregnancy and women with normotensive pregnancies were analyzed using analysis of variance. Categorical variables were compared using chi-square or Fisher exact tests for groups with <5 participants. Echocardiographic outcome variables were chosen based on prior data showing potential influence of HDP, including variables for LV structure, diastolic function, and LV GLS (4). Linear and logistic regression

TABLE 1 Participant Demographic Characteristics

	Normotensive in Pregnancy (n = 102)	HDP History (n = 30)	p Value
Age, yrs	38.6 ± 6.1	38.3 ± 6.3	0.82
Follow-up, yrs	9.8 ± 0.7	9.5 ± 0.9	0.04
Black	39 (38.2)	12 (40.0)	0.63
Education			1.00
Less than high school	7 (6.9)	1 (3.3)	
High school graduate	33 (32.4)	10 (33.3)	
College+	61 (59.8)	19 (63.3)	
Smoking current	23 (23.0)	6 (20.0)	0.77
BMI, kg/m^2	31.2 ± 8.7	33.3 ± 6.5	0.24
Hypertension*	26 (25.5)	19 (63.3)	<0.0001
Any antihypertensive medication	3 (2.9)	9 (30.0)	<0.0001
ACE inhibitor	1 (33.3)	2 (22.2)	
Diuretic	1 (33.3)	1 (11.1)	
Calcium-channel blocker	0 (0.0)	2 (22.2)	
2 or more antihypertensive medications	0 (0.0)	4 (44.4)	
Other	1 (33.0)	0 (0.0)	
Diabetes†	7 (7.0)	6 (20.7)	0.03
Dyslipidemia‡	12 (11.9)	3 (10.7)	0.87
Systolic BP, mm Hg	113.7 ± 12.6	124.6 ± 11.8	<0.0001
Diastolic BP, mm Hg	74.2 ± 8.7	81.7 ± 9.6	<0.0001
Total number of pregnancies	3 (2-5)	3 (2-4)	0.55
Pre-eclampsia in nonindex pregnancy	3 (2.9)	3 (10.0)	0.13
Index pregnancy variables			
Pre-term birth	27 (26.5)	9 (30.0)	0.70
Gestational diabetes	10 (9.8)	2 (7.1)	0.67
Placental MVM lesions	46 (45.1)	19 (63.3)	0.08

Values are mean ± SD, n (%), or median (interquartile range). *Defined by systolic BP >130 mm Hg, diastolic BP >80 mm Hg, or being on antihypertensive medications. †Defined by self-report or HbA1c. ‡Defined by self-report.

ACE = angiotensin-converting enzyme; BMI = body mass index; BP = blood pressure; HDP = hypertensive disorder of pregnancy; MVM = maternal vascular malperfusion.

models were used to adjust for covariates. We adjusted first for nonmodifiable factors that may influence echocardiographic measures (age, race) (28), then added factors that may be on the causal pathway for the development of CVD by first including placental MVM lesions, then body mass index (BMI), current hypertension, and HbA1c. Interaction terms then guided further subgroup analysis of variance to investigate differential influence of current hypertension and HDP on echocardiographic outcomes. Similarly, we explored the interaction between placental MVM lesions and HDP on echocardiographic outcomes. Between-group pairwise comparisons were conducted using Bonferroni methods for continuous variables and pairwise comparison for categorical variables. A p value <0.05 was considered significant (2-tailed). The p values and 95% confidence intervals presented in this report have not been adjusted for multiplicity, and therefore, inferences drawn from these statistics may not be reproducible. Given our modest numbers in each group, an interaction p value <0.10 was determined to indicate possible interaction and thus warranted stratified analyses. Statistical analyses were conducted using Stata version 15.1 (StataCorp LLC, College Station, Texas).

RESULTS

STUDY POPULATION. We enrolled 132 women (mean 10 ± 1 years post-delivery; age 39 ± 6 years): 102 had normotensive pregnancies and 30 had HDP history in their index pregnancy including pre-eclampsia (n = 21) or gestational hypertension (n = 9) (Supplemental Figure 1, **Table 1**). Women recruited for echocardiograms differed only by BMI (31.4 ± 8.3 kg/m^2 vs. 29.7 ± 7.8 kg/m^2; p = 0.04) compared with those from the parent study not selected for echocardiograms (Supplemental Table 2). Of the women with pre-eclampsia, 6 (29%) had severe pre-eclampsia and 7 (33%) had pre-term delivery. In total, 3 women (3%) in the normotensive group and 3 (10%) in the HDP group had a pregnancy other than the index complicated by pre-eclampsia (p = 0.13). Compared with women without HDP, those with HDP during the index pregnancy were more likely to have current hypertension 8 to 10 years after delivery by study visit blood pressure or antihypertensive medication use (63.3% vs. 25.5%; p < 0.0001), current diabetes (20.7% vs. 7.0%; p = 0.03), higher systolic blood pressure (125 ± 12 mm Hg vs. 114 ± 13 mm Hg; p < 0.0001), higher diastolic blood pressure (82 ± 10 mm Hg vs. 74 ± 9 mm Hg; p < 0.0001), and a trend toward higher proportion of placental MVM lesions during pregnancy (63.3% vs. 45.1%; p = 0.08) (**Table 1**).

HDP HISTORY AND ECHOCARDIOGRAPHIC OUTCOMES. In a linear regression model adjusting for age and race, women with HDP history had higher LV wall thickness, higher biplane LV ejection fraction, lower mitral inflow E/A ratio, and higher RWT compared with women without HDP (**Table 2**) (unadjusted results provided in Supplemental Table 3). In a model additionally adjusting for placental MVM lesions, results were unchanged. In a model further adjusting for BMI, current hypertension, and HbA1c, HDP history was still associated with higher LV IVS thickness (β = 0.08; p = 0.04), higher RWT (β = 0.04; p = 0.04), and higher biplane LV ejection fraction (β = 3.8; p = 0.004). Subgroup analyses for women with only pre-eclampsia history (rather than combined HDP variable with both pre-eclampsia and gestational HTN) compared with those who were normotensive during

TABLE 2 Adjusted Echocardiographic Parameters in Participants With Hypertensive Disorders of Pregnancy History Versus Those Without Hypertensive Disorders of Pregnancy

	Model 1 β (95% CI)*	p Value	Model 2 β (95% CI)†	p Value	Model 3 β (95% CI)‡	p Value
2D echo measures						
Biplane EF, %	2.9 (0.59 to 5.20)	0.01	2.8 (0.48 to 5.10)	0.02	3.8 (1.2 to 6.4)	0.004
LVEDd, cm	−0.13 (−0.34 to 0.07)	0.20	−0.13 (−0.33 to 0.08)	0.22	−0.15 (−0.37 to 0.06)	0.17
IVS thickness, cm	0.12 (0.05 to 0.19)	0.001	0.11 (0.04 to 0.18)	0.002	0.08 (0.004 to 0.150)	0.04
PW thickness, cm	0.09 (0.03 to 0.15)	0.004	0.09 (0.02 to 0.15)	0.007	0.06 (−0.008 to 0.120)	0.09
LAVI, ml/m^2	−1.8 (−5.1 to 1.5)	0.28	−1.8 (−5.1 to 1.5)	0.28	−0.51 (−4.1 to 3.1)	0.78
LVMI, g/m^2	3.4 (−3.7 to 10.6)	0.35	3.3 (−4.0 to 10.5)	0.38	1.54 (−6.5 to 9.6)	0.71
LV remodeling						
RWT	0.06 (0.02 to 0.09)	0.002	0.05 (0.02 to 0.09)	0.003	0.04 (0.003 to 0.080)	0.04
Diastolic function						
E/A	−0.22 (−0.36 to −0.08)	0.002	−0.21 (−0.36 to −0.07)	0.003	−0.11 (−0.27 to 0.04)	0.14
Septal e', cm/s	−0.37 (−1.50 to 0.73)	0.51	−0.46 (−1.60 to 0.64)	0.41	0.16 (−1.0 to 1.3)	0.80
Lateral e', cm/s	−0.83 (−2.20 to 0.51)	0.22	−0.90 (−2.30 to 0.46)	0.19	−0.25 (−1.8 to 1.2)	0.74
E/e'	0.45 (−0.23 to 1.10)	0.19	0.53 (−0.16 to 1.20)	0.33	0.33 (−0.39 to 1.10)	0.37
TR velocity, m/s	0.08 (−0.08 to 0.25)	0.31	0.11 (−0.06 to 0.28)	0.22	0.10 (−0.10 to 0.29)	0.33
Strain						
LV GLS, %	0.49 (−0.88 to 1.80)	0.48	0.48 (−0.91 to 1.90)	0.50	−0.32 (−1.8 to 1.1)	0.66
RV strain, %	0.86 (−1.6 to 3.4)	0.50	1.1 (−1.5 to 3.7)	0.40	−0.41 (−3.1 to 2.3)	0.76
Logistic regression						
Odds of LV remodeling, RWT >0.42	3.4 (1.3 to 8.8)	0.01	3.2 (1.2 to 8.5)	0.02	2.5 (0.84 to 7.70)	0.10

*Adjusted for age and race. †Adjusted for age, race, and placental MVM lesion. ‡Adjusted for age, race, placental MVM lesion, BMI, current hypertension, hemoglobin A1c.
CI = confidence interval; EF = ejection fraction; GLS = global longitudinal strain; HDP = hypertensive disorder of pregnancy; HTN = hypertension; IVS = interventricular septum; LAVI = left atrial volume index; LV = left ventricle; LVEDd = left ventricular end diastolic diameter; LVMI = left ventricular mass index; PW = posterior wall; RV = right ventricle; RWT = relative wall thickness; TR = tricuspid regurgitation.

pregnancy yielded similar results (Supplemental Table 4). Sensitivity analyses removing the 3 women in the normotensive group reporting a nonindex pregnancy complicated by pre-eclampsia did not affect our results.

In a logistic regression model adjusting for age, race, and placental MVM lesions, HDP was an independent predictor for LV remodeling defined as RWT >0.42, with an adjusted OR of 3.2 (confidence interval: 1.2 to 8.5; p = 0.02); results were attenuated after further adjustment for BMI, current hypertension, and HbA1c (2.5 [confidence interval: 0.84 to 7.7]; p = 0.10) (Table 2).

ECHOCARDIOGRAPHY OUTCOMES STRATIFIED BY HDP AND CURRENT HYPERTENSION. There was evidence that the echocardiographic differences according to HDP varied among those who had progressed to current hypertension (p = 0.08 for interaction for E/A ratio). Across the 4 groups stratified by a history of HDP and current hypertension, women with both HDP and current hypertension had higher interventricular septal thickness (p = 0.001), LV posterior wall thickness (p = 0.006), and RWT (p = 0.005); a higher proportion of LV remodeling defined as RWT >0.42 (p = 0.01); lower LV GLS (p = 0.007); and a higher proportion of abnormal RV strain (p = 0.02) (Table 3). There were also differences in diastolic function measures, including lower E/A ratio (p < 0.001) and lower septal (p < 0.001) and lateral e′ (p = 0.007). Between-group post hoc pairwise comparisons showed significant differences between the group with both HDP history and current hypertension versus the group without HDP history or hypertension, with higher IVS thickness (p = 0.001), LV PW thickness (p = 0.004), and RWT (p = 0.002); lower E/A ratio (p < 0.001); and lower septal e′ (p = 0.02) and lateral e' (p = 0.04) (Table 3, Figure 1, Central Illustration). Those with both HDP history and current hypertension also had lower E/A and septal e′ compared with those with only HDP history. Pairwise comparisons showed that a higher proportion of women with both HDP history and current hypertension had LV remodeling (79.0%) compared with only HDP history (36.4%; p = 0.01), only current hypertension (46.2%; p = 0.02), and no HDP history or current hypertension (38.2%; p < 0.001). There were no between-group differences among women with only HDP history compared with those without HDP and without hypertension.

ECHOCARDIOGRAPHIC OUTCOMES STRATIFIED BY HDP AND PLACENTAL MVM LESIONS. Associations between HDP and echocardiography results did not

TABLE 3 Echocardiographic Parameters Among Participants Stratified by Hypertensive Disorders of Pregnancy History and Current Hypertension

	No HTN/No HDP (n = 76)	No HTN/+HDP (n = 11)	+HTN/No HDP (n = 26)	+HTN/+HDP (n = 19)	p Value
2D echo measures					
Biplane EF, %	63.4 ± 5.3	65.2 ± 6.1	61.6 ± 5.1	65.2 ± 6.4	0.12
LVEDd, cm	4.5 ± 0.5	4.5 ± 0.4	4.6 ± 0.5	4.3 ± 0.4	0.15
IVS thickness, cm	0.92 ± 0.15	0.97 ± 0.22	0.99 ± 0.15	1.1 ± 0.21*	0.001
PW thickness, cm	0.91 ± 0.14	0.95 ± 0.22	0.97 ± 0.14	1.0 ± 0.14*	0.006
LAVI, ml/m^2	24.3 ± 6.7	23.1 ± 6.2	25.6 ± 8.0	23.4 ± 9.5	0.72
LVMI, g/m^2	71.9 ± 15.7	74.7 ± 19.1	80.9 ± 17.0	78.1 ± 19.6	0.10
LV remodeling					
RWT	0.41 ± 0.08	0.43 ± 0.13	0.42 ± 0.08	0.49 ± 0.08*	0.005
LV remodeling, RWT >0.42	29 (38.2)	4 (36.4)	12 (46.2)	15 (79.0)*†‡	0.01
LV hypertrophy					0.08
No hypertrophy (LVMI ≤95 g/m^2, RWT <0.42)	44 (57.9)	6 (54.6)	12 (46.2)	4 (21.2)	
Concentric remodeling (LVMI ≤95 g/m^2, RWT >0.42)	26 (34.2)	4 (36.4)	10 (38.5)	12 (63.2)	
Eccentric hypertrophy (LVMI >95 g/m^2, RWT ≤0.42)	3 (4.0)	1 (9.1)	2 (7.7)	0 (0)	
Concentric hypertrophy (LVMI >95 g/m^2, RWT >0.42)	3 (4.0)	0 (0)	2 (7.7)	3 (15.8)	
RV function					
TAPSE	2.3 ± 0.33	2.4 ± 0.35	2.3 ± 0.42	2.3 ± 0.31	0.53
S′	13.3 ± 2.5	12.8 ± 2.8	13.6 ± 2.1	13.7 ± 2.3	0.74
Diastolic function					
E/A	1.42 ± 0.36	1.41 ± 0.26	1.30 ± 0.39	1.01 ± 0.28*†‡	<0.001
Septal e′, cm/s	10.1 ± 2.7	11.5 ± 2.9	8.7 ± 1.7‡	8.2± 2.4*†	<0.001
Lateral e′, cm/s	13.5 ± 3.3	13.7 ± 3.1	11.7 ± 2.7	11.2 ± 3.1*	0.007
Septal e′ <7 or Lateral e′ <11	10 (13.2)	0 (0)	7 (26.9)	6 (31.6)	0.049
E/e′	7.1 ± 1.9	7.4 ± 1.3	7.9 ± 1.9	7.6 ± 2.9	0.43
Peak TR velocity, m/s	1.9 ± 0.31	2.0 ± 0.33	2.0 ± 0.35	2.0 ± 0.20	0.87
Indeterminant diastolic function	3 (4.0)	0 (0)	2 (7.7)	2 (12.5)	0.37
Strain					
LV GLS, %	−23.8 ± 3.2	−22.9 ± 2.6	−21.3 ± 1.9*	−22.4 ± 2.3	0.003
LV GLS >−20%	8 (12.1)	1 (10.0)	8 (33.3)	4 (25.0)	0.09
RV free wall strain	−24.8 ± 4.6	−24.9 ± 5.6	−22.2 ± 4.1	−21.7 ± 5.3	0.06
RV free wall strain >−20%	4 (7.0)	2 (22.2)	5 (23.8)*	4 (33.3)*	0.02

Values are mean ± SD or n (%). *Pairwise comparison with no HTN/no HDP group significant for p value <0.05. †Pairwise comparison with HDP-only group significant for p value <0.05. ‡Pairwise comparison with HTN-only group significant for p value <0.05.

Abbreviations as in Table 2.

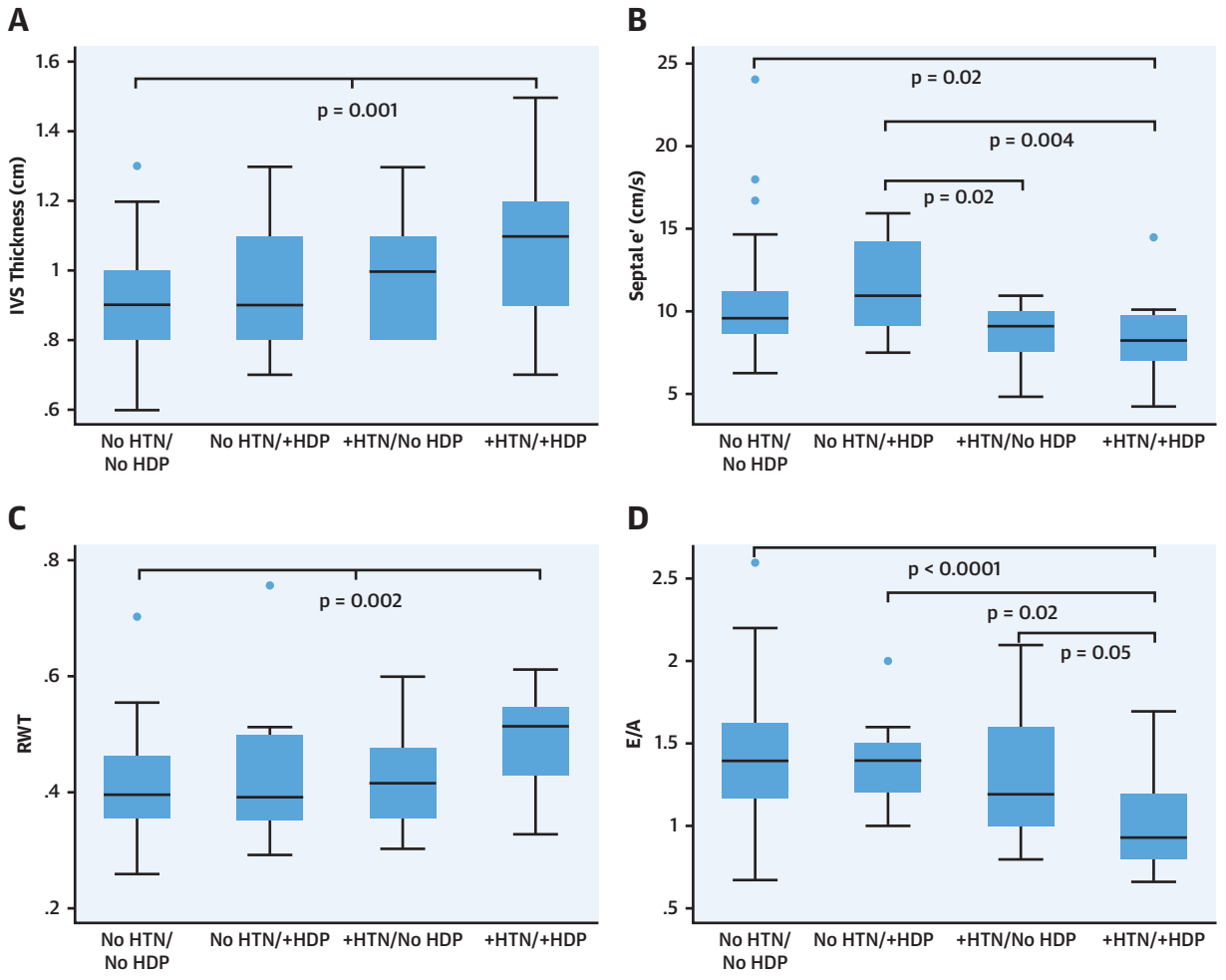
vary according to presence of placental MVM lesions (p for interaction for RWT = 0.33; p for interaction for E/A = 0.90). Subgroup analyses of women stratified by presence of placental MVM lesions (n = 65) with and without HDP history showed differences in interventricular septal thickness, RWT, and E/A ratio that were primarily driven by HDP history, not presence of MVM lesions (Supplemental Table 5).

DISCUSSION

The main finding of this study was that women with HDP history have increased LV wall thickness compared with women who did not have HDP when evaluated nearly 1 decade after delivery. Furthermore, our stratified analyses reveal that women with both HDP history and current hypertension are the highest-risk group, as they have the most pronounced echocardiographic differences, with almost 80% having LV remodeling, which could in turn account for differences we observed in diastolic function parameters and GLS. Of note, this group had higher rates of LV remodeling compared with women with only current hypertension or only HDP history. Contrary to our hypothesis, the presence of placental MVM lesions did not appear to further predict higher risk of adverse echocardiographic findings.

Prior studies have shown similar, although not consistent, imaging findings at various time points after delivery among women with a history of HDP. Similar to the findings in our study, a study by Bokslag et al. (9) included 131 women with a history of early-onset pre-eclampsia and looked at longer-term echocardiographic findings, 9 to 16 years after index pregnancy, compared with women with uncomplicated pregnancies. They found that a history of early-

FIGURE 1 Selected Echocardiographic Parameters Stratified by HDP History and Current Hypertension

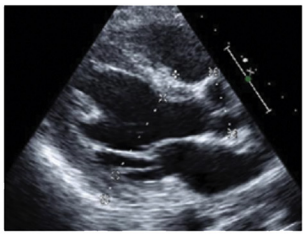


Between group post hoc pairwise comparisons of selected echocardiographic parameters, demonstrated as box plots of mean ± SD for those with or without HDP history and with or without current hypertension. **(A)** Between-group comparison of left ventricular interventricular septal wall thickness. **(B)** Between-group comparison of septal e′ mitral annular velocity. **(C)** Between-group comparison of relative wall thickness. **(D)** Between-group comparison of mitral inflow E/A ratio. HDP = hypertensive disorders of pregnancy; HTN = hypertension; IVS = interventricular septum; RWT = relative wall thickness.

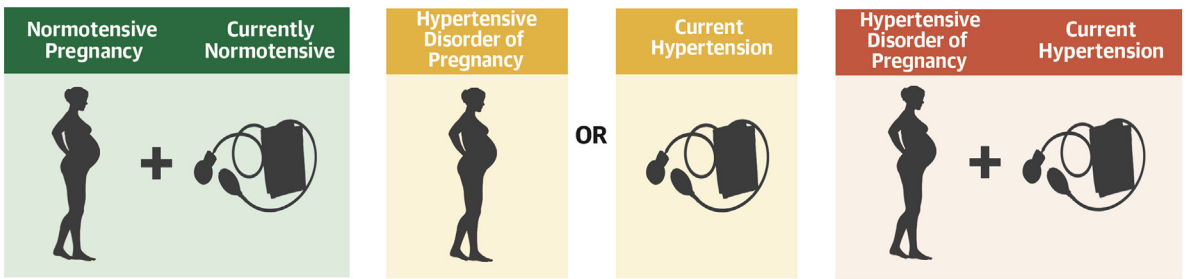
onset pre-eclampsia was associated with thicker LV walls and increased LVMI in unadjusted analyses, and with changes in measures of diastolic dysfunction such as lower e′ and increased E/e’ ratio in fully adjusted analyses (9). Another recent study showed that women with HDP history had increased LV mass and left atrial size measured by cardiac magnetic resonance imaging in adjusted analyses measured 5 to 10 years after pregnancy (31). Other studies have shown an association of pre-eclampsia history with concentric LV remodeling and preclinical heart failure (12,13) 4 to 10 years after delivery; however, these associations were attenuated after adjusting for age, BMI, and current hypertension. In contrast to these studies, which included mostly women in their fifth decade of life, our study evaluated rather younger women (mean age of 39 years), some of them already with adverse cardiac changes occurring early in their lifetime, and with the potential of these early findings to carry a longer exposure risk.

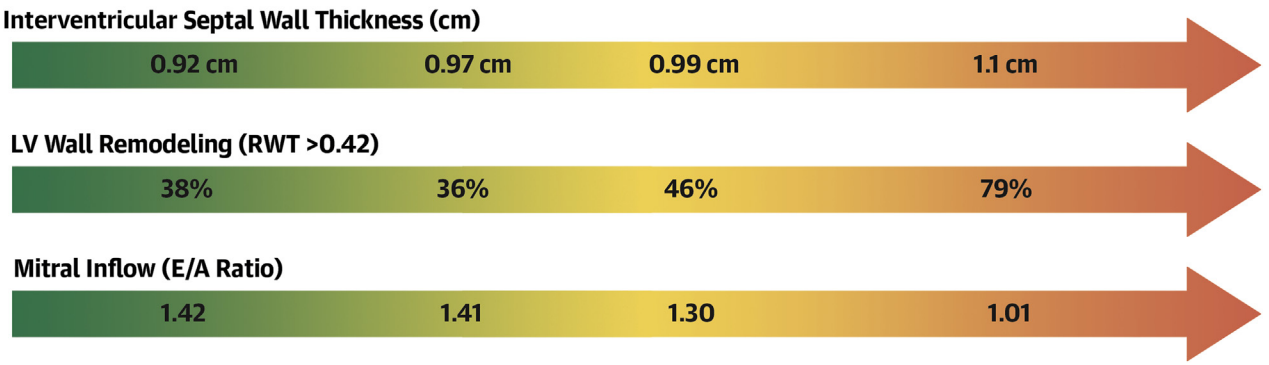
Another unique feature of our study is that we paid particular attention to adjusted and subgroup analyses to further clarify the distinct impact of HDP versus other traditional CVD risk factors on echocardiographic measurements of ventricular structural remodeling and function. Women with HDP during

CENTRAL ILLUSTRATION **Echocardiographic Differences Among Women With Both Hypertensive Disorder of Pregnancy History and Current Hypertension 8 to 10 Years After Delivery**



Echocardiogram 8-10 Years After Delivery





Countouris, M.E. et al. J Am Coll Cardiol. 2021;77(8):1057–68.

Women with and without a history of a hypertensive disorder of pregnancy and with and without current hypertension underwent transthoracic echocardiogram 8 to 10 years after index pregnancy delivery (n = 132). Women with both hypertensive disorder of pregnancy history and current hypertension (n = 19) had the most adverse echocardiogram findings, including increased interventricular septal wall thickness, higher percentage of LV remodeling (RWT >0.42), and adverse diastolic function parameters including a decreased mitral inflow E/A ratio (all p values <0.05 compared with those without a prior hypertensive disorder of pregnancy and without current hypertension). This suggests a "double-hit" phenomenon; women with prior hypertensive disorder of pregnancy and current hypertension are a high-risk group that warrants closer surveillance and targeted therapies for cardiovascular disease prevention. LV = left ventricular; RWT = relative wall thickness.

the index pregnancy had increased interventricular septal wall thickness and RWT compared with women without HDP in index pregnancy, even after adjustment for known cardiovascular (CV) risk factors such as BMI, current hypertension, and HbA1c. These results support the hypothesis that the occurrence of HDP may in itself independently mediate the initiation of LV hypertrophy and remodeling and, hence, progression to CVD in later life. Although definitive mechanisms for LV remodeling among women with HDP have not been established, one explanation may relate to changes in the renin-angiotensin-aldosterone system, which is known to be dysregulated with pre-eclampsia (32,33). Circulating renin, aldosterone, and angiotensin II levels are suppressed in pre-eclampsia as the maternal system strives to maintain homeostasis in response to the physiological changes with pre-eclampsia (33,34). Interestingly, this dysregulation may persist postpartum, and 1 study found augmented vasoconstrictor sensitivity

to angiotensin II among women with recent pre-eclampsia (35), which could contribute to development of hypertension and adverse LV remodeling. Alternatively, alterations in antiangiogenic proteins such as sFLT-1 and soluble endoglin have been associated with peripartum LV dysfunction among women with HDP, including lower LV GLS and increasing LV mass index (36), and thus could also play a mechanistic role, as could inflammation (9). More work is needed to identify the pathway implicated to guide intervention trials to prevent or reverse cardiac remodeling in women with HDP.

Known modifiable risk factors may also affect the structural cardiac changes seen in this population, although prior studies have not fully accounted for these. Our subgroup analyses demonstrated that those with both HDP history and current hypertension had the most adverse changes compared with those who were normotensive in pregnancy and at follow-up. Women with a history of HDP are at increased risk to develop hypertension in the years after delivery (1), as we also found in our study. Elevated blood pressure can have a significant pathological impact on LV wall thickness, remodeling, and hypertrophy (14,37), and thus may be a part of the pathway for remodeling among women with a history of HDP. Prior longitudinal cohort studies (38) have suggested that hypertension partially, but incompletely, accounts for HDP's association with coronary artery disease and heart failure. Additionally, we did not see significant structural cardiac changes among women with only hypertension in our study, suggesting that HDP history adds an adverse pathological mechanism beyond the adverse effects of hypertension alone (i.e., a "double-hit phenomenon"). Intriguingly, prior data suggest that changes such as increased LV mass index and LV GLS may even pre-date the development of hypertension in preeclamptic women early postpartum (39), and this warrants additional study.

LV remodeling and hypertrophy have major clinical implications as they have been shown to be associated with increased CV risk, including the development of ischemic heart disease, heart failure, arrhythmia, and mortality (40–42). Even potentially earlier in the remodeling pathway, increases in RWT have been associated with LV systolic and diastolic dysfunction and resulting clinical heart failure, as well as increased morbidity and mortality (43,44). Importantly, by identifying higher risk subgroups of women with a history of HDP who have developed subclinical CV changes, such as increased RWT or remodeling, we can potentially target these groups for aggressive therapies that might mitigate the evolution of adverse ventricular remodeling. Medications that target the renin-angiotensin-aldosterone system, such as angiotensin receptor blockers, aldosterone antagonists, and angiotensin receptor neprilysin inhibitors, have been shown to reverse LV remodeling with hypertension-related LV changes (45,46), but have not yet been studied in HDP-affected women. Treating or preventing known risk factors, such as hypertension, obesity, diabetes, and dyslipidemia, may also change the risk trajectory for these women (47). By the 2017 ACC/AHA hypertension guidelines (48), those at high risk for CVD should receive antihypertensive medication treatment of stage 1 hypertension. In our cohort, 42% of women with HDP history and stage 1 hypertension were not on antihypertensive therapy, supporting that these women may warrant inclusion as a higher-risk group for more aggressive treatment. Lifestyle interventions may also be an important strategy to reduce the burden of CVD development in this population (49–51). Our data support the need for further research to understand optimal therapeutic approaches in women with HDP history, particularly approaches to prevent or manage chronic hypertension and to target reversal of LV remodeling.

Leveraging our validated placental pathology data, we uniquely investigated potential associations between placental MVM lesions and structural cardiac findings on echocardiogram; however, these subgroup analyses did not further risk-stratify our patients. One possible reason may be that our pathological characterization of the placenta is not specific enough. Decidual vasculopathy, a placental MVM lesion most akin to atherosclerotic lesions elsewhere in the body, may have the highest specificity for CVD (21), but in our cohort there were only 13 cases with this placental lesion. Alternatively, placental MVM lesions may not predict the later-life abnormalities in cardiac structure found among patients with HDP, but rather may be more associated with other vascular abnormalities such as coronary microvascular dysfunction. It is possible that women have a predisposition to placental malperfusion that is partially predicted by lack of the physiological early pregnancy drop in diastolic blood pressure (52). Placental MVM lesions are not present in all patients with HDP; thus, there may be a separate, chronic pathway that leads to LV remodeling. Future studies looking more closely at specific placental lesions and coronary vascular function may help elucidate potential connections between placental MVM and future CVD risk.

STUDY LIMITATIONS. Although it is one of the larger studies to date investigating later-life echocardiographic findings among women with a history of HDP,

it is still a relatively small sample size from a single center. Future, larger multicenter studies are needed to confirm these findings and may provide the ability to further stratify groups based on severity of HDP and pre-term delivery. HDP diagnosis was obtained by chart abstraction for the index pregnancy and 60% of subsequent births, and thus we were not able to precisely account for all HDP occurrences in pregnancies other than the index. Because HDP during index pregnancy was defined by definitions at the time of delivery, participants may have been reclassified based on newer definitions of HDP. However, this reclassification would likely have increased the number of participants with HDP and potentially strengthened our results. In the normotensive pregnancy group, 3 women developed pre-eclampsia in a nonindex pregnancy. Removal of these women from our analyses did not change our results. The group with recurrent HDP (n = 3) was too small to evaluate. It is also worth noting that at the time of delivery, women in our study had a clinical indication for placental pathological evaluation, and thus, our control group may not have had entirely normal pregnancies or deliveries. We might have seen more pronounced differences had our comparison group consisted of participants with entirely normal pregnancies. Finally, our RV strain data analysis was limited by suboptimal image quality in almost 30% of participants. Dedicated RV strain software was not available for these analyses but could help optimize images in the future.

CONCLUSIONS

Women with HDP are more likely to have evidence of increased LV wall thickness in the decade after pregnancy compared with women (with or without current hypertension) who had normotensive pregnancies. Those with both HDP history and current hypertension have the most pronounced differences in cardiac structure and function, including the highest proportion of LV remodeling and abnormal diastolic function parameters. This suggests a "double-hit" phenomenon of HDP history and current hypertension warranting closer surveillance and early and targeted therapies for CVD prevention in this higher-risk group.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: HDP are associated with increased LV wall thickness and relative wall thickness 8 to 10 years after delivery. Women with both a history of hypertension during pregnancy and current hypertension exhibit the most pronounced structural cardiac abnormalities, including LV remodeling, potentially warranting more aggressive preventive strategies.

TRANSLATIONAL OUTLOOK: Further investigations are needed to understand the mechanisms linking HDP with later hypertrophic ventricular remodeling and to develop therapeutic interventions that prevent adverse outcomes.

REFERENCES

1. Bellamy L, Casas JP, Hingorani AD, Williams DJ. Pre-eclampsia and risk of cardiovascular disease and cancer in later life: systematic review and meta-analysis. BMJ 2007;335:974.

2. Ray JG, Vermeulen MJ, Schull MJ, Redelmeier DA. Cardiovascular health after maternal placental syndromes (CHAMPS): population-based retrospective cohort study. Lancet 2005;366:1797–803.

3. Wu P, Haththotuwa R, Kwok CS, et al. Preeclampsia and future cardiovascular health: a systematic review and meta-analysis. Circ Cardiovasc Qual Outcomes 2017;10:e003497.

4. Castleman JS, Ganapathy R, Taki F, Lip GY, Steeds RP, Kotecha D. Echocardiographic structure and function in hypertensive disorders of pregnancy: a systematic review. Circ Cardiovasc Imaging 2016;9:e004888.

5. Melchiorre K, Sharma R, Thilaganathan B. Cardiovascular implications in preeclampsia: an overview. Circulation 2014;130:703–14.

6. Rafik Hamad R, Larsson A, Pernow J, Bremme K, Eriksson MJ. Assessment of left ventricular structure and function in preeclampsia by echocardiography and cardiovascular biomarkers. J Hypertens 2009;27:2257–64.

7. Vaught AJ, Kovell LC, Szymanski LM, et al. Acute cardiac effects of severe pre-eclampsia. J Am Coll Cardiol 2018;72:1–11.

8. Melchiorre K, Sutherland GR, Liberati M, Thilaganathan B. Preeclampsia is associated with

persistent postpartum cardiovascular impairment. Hypertension 2011;58:709–15.

9. Bokslag A, Franssen C, Alma LJ, et al. Early-onset preeclampsia predisposes to preclinical diastolic left ventricular dysfunction in the fifth decade of life: an observational study. PLoS One 2018;13:e0198908.

10. AbdelWahab MA, Farrag HM, Saied CE. 24-hour blood pressure variability as a predictor of short-term echocardiographic changes in normotensive women with past history of preeclampsia/eclampsia. Pregnancy Hypertens 2018;13:72–8.

11. Orabona R, Vizzardi E, Sciatti E, et al. Maternal cardiac function after HELLP syndrome: an echocardiography study. Ultrasound Obstet Gynecol 2017;50:507–13.

12. Ghossein-Doha C, van Neer J, Wissink B, et al. Pre-eclampsia: an important risk factor for asymptomatic heart failure. Ultrasound Obstet Gynecol 2017;49:143–9.

13. Breetveld NM, Ghossein-Doha C, van Neer J, et al. Decreased endothelial function and increased subclinical heart failure in women several years after pre-eclampsia. Ultrasound Obstet Gynecol 2018;52:196–204.

14. Drazner MH. The progression of hypertensive heart disease. Circulation 2011;123:327–34.

15. Veerbeek JH, Nikkels PG, Torrance HL, et al. Placental pathology in early intrauterine growth restriction associated with maternal hypertension. Placenta 2014;35:696–701.

16. Kim YM, Bujold E, Chaiworapongsa T, et al. Failure of physiologic transformation of the spiral arteries in patients with preterm labor and intact membranes. Am J Obstet Gynecol 2003;189:1063–9.

17. Morgan TK. Role of the placenta in preterm birth: a review. Am J Perinatol 2016;33:258–66.

18. Bustamante Helfrich B, Chilukuri N, He H, et al. Maternal vascular malperfusion of the placental bed associated with hypertensive disorders in the Boston Birth Cohort. Placenta 2017;52:106–13.

19. Powers RW, Catov JM, Bodnar LM, Gallaher MJ, Lain KY, Roberts JM. Evidence of endothelial dysfunction in preeclampsia and risk of adverse pregnancy outcome. Reprod Sci 2008;15:374–81.

20. Savvidou MD, Hingorani AD, Tsikas D, Frolich JC, Vallance P, Nicolaides KH. Endothelial dysfunction and raised plasma concentrations of asymmetric dimethylarginine in pregnant women who subsequently develop pre-eclampsia. Lancet 2003;361:1511–7.

21. Catov JM, Muldoon MF, Reis SE, et al. Preterm birth with placental evidence of malperfusion is associated with cardiovascular risk factors after pregnancy: a prospective cohort study. BJOG 2018;125:1009–17.

22. Staff AC, Dechend R, Redman CW. Review: preeclampsia, acute atherosis of the spiral arteries and future cardiovascular disease: two new hypotheses. Placenta 2013;34 Suppl:S73–8.

23. Parks WT, Catov JM. The placenta as a window to maternal vascular health. Obstet Gynecol Clin North Am 2020;47:17–28.

24. Catov JM, Peng Y, Scifres CM, Parks WT. Placental pathology measures: can they be rapidly and reliably integrated into large-scale perinatal studies? Placenta 2015;36:687–92.

25. Langston C, Kaplan C, Macpherson T, et al. Practice guideline for examination of the placenta: developed by the Placental Pathology Practice Guideline Development Task Force of the College of American Pathologists. Arch Pathol Lab Med 1997;121:449–76.

26. Assibey-Mensah V, Parks WT, Gernand AD, Catov JM. Race and risk of maternal vascular malperfusion lesions in the placenta. Placenta 2018;69:102–8.

27. ACOG Committee on Practice Bulletins—Obstetrics. ACOG practice bulletin. Diagnosis and management of preeclampsia and eclampsia. Number 33, January 2002. Obstet Gynecol 2002;99:159–67.

28. Lang RM, Badano LP, Mor-Avi V, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. J Am Soc Echocardiogr 2015;28:1–39.e14.

29. Nagueh SF, Smiseth OA, Appleton CP, et al. Recommendations for the evaluation of left ventricular diastolic function by echocardiography: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. J Am Soc Echocardiogr 2016;29:277–314.

30. Voigt JU, Pedrizzetti G, Lysyansky P, et al. Definitions for a common standard for 2D speckle tracking echocardiography: consensus document of the EACVI/ASE/Industry Task Force to Standardize Deformation Imaging. J Am Soc Echocardiogr 2015;28:183–93.

31. Boardman H, Lamata P, Lazdam M, et al. Variations in cardiovascular structure, function, and geometry in midlife associated with a history of hypertensive pregnancy. Hypertension 2020;75:1542–50.

32. Malha L, Sison CP, Helseth G, Sealey JE, August P. Renin-angiotensin-aldosterone profiles in pregnant women with chronic hypertension. Hypertension 2018;72:417–24.

33. Brown MA, Wang J, Whitworth JA. The renin-angiotensin-aldosterone system in pre-eclampsia. Clin Exp Hypertens 1997;19:713–26.

34. Zitouni H, Raguema N, Gannoun MBA, et al. Impact of obesity on the association of active renin and plasma aldosterone concentrations, and aldosterone-to-renin ratio with preeclampsia. Pregnancy Hypertens 2018;14:139–44.

35. Stanhewicz AE, Jandu S, Santhanam L, Alexander LM. Increased angiotensin II sensitivity contributes to microvascular dysfunction in women who have had preeclampsia. Hypertension 2017;70:382–9.

36. Shahul S, Medvedofsky D, Wenger JB, et al. Circulating antiangiogenic factors and myocardial dysfunction in hypertensive disorders of pregnancy. Hypertension 2016;67:1273–80.

37. Chirinos JA, Segers P, De Buyzere ML, et al. Left ventricular mass: allometric scaling, normative values, effect of obesity, and prognostic performance. Hypertension 2010;56:91–8.

38. Honigberg MC, Zekavat SM, Aragam K, et al. Long-term cardiovascular risk in women with hypertension during pregnancy. J Am Coll Cardiol 2019;74:2743–54.

39. Ghossein-Doha C, Peeters L, van Heijster S, et al. Hypertension after preeclampsia is preceded by changes in cardiac structure and function. Hypertension 2013;62:382–90.

40. Vakili BA, Okin PM, Devereux RB. Prognostic implications of left ventricular hypertrophy. Am Heart J 2001;141:334–41.

41. Fabiani I, Pugliese NR, La Carrubba S, et al. Incremental prognostic value of a complex left ventricular remodeling classification in asymptomatic for heart failure hypertensive patients. J Am Soc Hypertens 2017;11:412–9.

42. Konstam MA, Kramer DG, Patel AR, Maron MS, Udelson JE. Left ventricular remodeling in heart failure: current concepts in clinical significance and assessment. J Am Coll Cardiol Img 2011;4:98–108.

43. Li L, Shigematsu Y, Hamada M, Hiwada K. Relative wall thickness is an independent predictor of left ventricular systolic and diastolic dysfunctions in essential hypertension. Hypertens Res 2001;24:493–9.

44. Koren MJ, Devereux RB, Casale PN, Savage DD, Laragh JH. Relation of left ventricular mass and geometry to morbidity and mortality in uncomplicated essential hypertension. Ann Intern Med 1991;114:345–52.

45. Schmieder RE, Wagner F, Mayr M, et al. The effect of sacubitril/valsartan compared to olmesartan on cardiovascular remodelling in subjects with essential hypertension: the results of a randomized, double-blind, active-controlled study. Eur Heart J 2017;38:3308–17.

46. Hadi NR, Abdulzahra MS, Al-Huseini LM, Al-Aubaidy HA. A comparison study of the echocardiographic changes in hypertensive patients treated with telmisartan vs. enalapril. Int J Cardiol 2017;230:269–74.

47. Hauspurg A, Countouris ME, Catov JM. Hypertensive disorders of pregnancy and future maternal health: how can the evidence guide postpartum management? Curr Hypertens Rep 2019;21:96.

48. Whelton PK, Carey RM, Aronow WS, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. J Am Coll Cardiol 2018;71:e127–248.

49. Berks D, Hoedjes M, Raat H, Duvekot JJ, Steegers EA, Habbema JD. Risk of cardiovascular disease after pre-eclampsia and the effect of lifestyle interventions: a literature-based study. BJOG 2013;120:924–31.

50. Rich-Edwards JW, Stuart JJ, Skurnik G, et al. Randomized trial to reduce cardiovascular risk in women with recent preeclampsia. J Womens Health (Larchmt) 2019;28:1493–504.

51. Chomistek AK, Chiuve SE, Eliassen AH, Mukamal KJ, Willett WC, Rimm EB. Healthy lifestyle in the primordial prevention of cardiovascular disease among young women. J Am Coll Cardiol 2015;65:43–51.

52. Atlass J, Menke M, Parks WT, Catov JM. Preconception blood pressure and evidence of placental malperfusion. BMC Pregnancy Childbirth 2020;20:25.

KEY WORDS echocardiogram, hypertension, left ventricular remodeling, pre-eclampsia, pregnancy

APPENDIX For supplemental tables and a figure, please see the online version of this paper.