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This is the author accepted manuscript of the article published as:

Veronica Giorgione, Asma Khalil, Jamie O'Driscoll, Basky Thilaganathan,

Peripartum Screening for Postpartum Hypertension in Women With Hypertensive Disorders of Pregnancy,

Journal of the American College of Cardiology,

Volume 80, Issue 15,

2022,

Pages 1465-1476,

ISSN 0735-1097,

https://doi.org/10.1016/j.jacc.2022.07.028.

(https://www.sciencedirect.com/science/article/pii/S0735109722065329)

PERIPARTUM SCREENING FOR POSTPARTUM HYPERTENSION IN WOMEN WITH HYPERTENSIVE DISORDERS OF PREGNANCY

BRIEF TITLE: Risk Assessment after Hypertensive Pregnancy

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TOTAL WORD COUNT: 5269

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FUNDING: Veronica Giorgione received funding from the European Union's Horizon 2020 research and innovation programme under the Marie Skłodowska-Curie grant agreement No 765274 (iPLACENTA project). Graphical abstract was created with Biorender.com.

DISCLOSURE: Authors have no conflicts of interest and no relationship with industry.

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SHORT TWEET: Peripartum maternal clinical and echocardiographic data can identify women at risk of postpartum hypertension after hypertensive disorders of pregnancy #Hypertension #CardioObstetrics #ACCPrev

ACKNOWLEDGEMENTS: Central illustration created with Biorender.com

ABSTRACT

Background: Chronic hypertension (CHT) is the main risk factor for cardiovascular diseases (CVD) in women with a history of hypertensive disorders of pregnancy (HDP).

Objectives: To assess the effectiveness of peripartum screening in predicting CHT after HDP.

Methods: In this longitudinal prospective study, women with HDP underwent peripartum transthoracic echocardiographic (TTE) and were evaluated for CHT (blood pressure ≥140/90mmHg or on anti-hypertensive medications) at least three months postpartum. Univariable and multivariable analyses assessed the association between clinical and TTE data and CHT.

Results: At a median (IQR) postpartum follow-up of 124 (103-145) days, 70 out of 211 (33.2%) women remained hypertensive. Compared to normotensive women, women with CHT were older (35.5±5 vs 32.9±5.6 years, p=0.001), more likely to be Afro-Caribbean (27.1 vs 7.8%, p<0.0001), had higher body mass index (BMI) (33.4±5.9 vs 31.2±5.4 Kg/m^2, p=0.006), and higher mean arterial pressure (MAP) (106.5±8.4 vs 103.3±7.0 mmHg, p=0.004). Moreover, they showed significantly higher left ventricular mass index (LVMI) (84±17.9 vs 76.3±14.8 g/m^2, p=0.001) relative wall thickness (RWT) (0.46±0.1 vs 0.40±0.1, p<0.0001), and lower global longitudinal strain (-15.6±2.7 vs -16.6±2.2%, p=0.006) than normotensive women. A prediction model combining clinical (maternal age and first-trimester MAP) and echocardiographic features (LVMI >75g/m^2, RWT >0.42 and E/E' >7) showed excellent accuracy in identifying women with persistent hypertension after HDP (AUC 0.85, 95% CI 0.79-0.90).

Conclusions: This peripartum screening might be used to identify women at risk of CHT who would benefit from intensive blood pressure monitoring and pharmacological strategies from the early postpartum period to prevent CVD.

CONDENSED ABSTRACT

Chronic hypertension is one of the main mediators of the increased cardiovascular risk in women with a history of hypertensive disorder of pregnancy (HDP). In this prospective longitudinal study, women with HDP underwent peripartum transthoracic echocardiographic (TTE) and were evaluated postnatally to investigate the persistence of hypertension. Women with persistent hypertension showed significant peripartum differences in pregnancy-related clinical and TTE data from normotensive patients. Therefore, a cardiovascular screening could effectively identify those women with HDP at risk of postpartum hypertension who might warrant an early and more active primary cardiovascular prevention to improve their long-term cardiovascular risk.

KEYWORDS: preeclampsia, hypertensive disorders of pregnancy, pregnancy, cardiovascular prevention

ABBREVIATIONS

- BP=blood pressure
- BMI=body mass index
- CHT=chronic hypertension
- CVD=cardiovascular diseases
- GLS=global longitudinal strain
- GLS-R-E= early diastolic GLS rate
- HDP=hypertensive disorders of pregnancy
- HFpEF= heart failure with preserved left ventricular ejection fraction
- LV= left ventricular
- LVMI=left ventricular mass index
- MAP=mean arterial pressure
- RWT=relative wall thickness
- TTE=transthoracic echocardiography

INTRODUCTION

Women with a history of hypertensive disorders of pregnancy (HDP) are prone to develop cardiovascular diseases (CVD), the leading cause of mortality in the female population.[1,2] Before developing CVD, which typically manifests several decades after pregnancy, women with HDP first exhibit CVD risk factors such as chronic hypertension (CHT), diabetes and dyslipidemia.[3-5] In particular, CHT is the major mediator of the associations between gestational hypertension and preeclampsia with CVD.[4,5] More recent work has demonstrated that soon after a pregnancy complicated by HDP, women have persistent left ventricular (LV) diastolic dysfunction and abnormal geometry that may explain the predisposition to developing CVD.[6,7] As a consequence, the development of HDP might offer a unique opportunity for early identification of a group of women at risk of CVD later in life.[8]

Despite these findings, there are no specific guidelines on cardiovascular screening, monitoring and primary CVD prevention in this high-risk group of women.[9] While behavioral interventions such as diet, exercise and smoking cessation could be offered to all women with HDP, more complex cardiovascular assessments and pharmacological interventions need to be tailored for women who are most likely to develop cardiovascular risk factors and CVD.[10-12]

Therefore, this study aims to assess the effectiveness of clinical pregnancy-related data and peripartum maternal transthoracic echocardiographic (TTE) indices in the prediction of persistent postpartum hypertension after HDP.

METHODS

Study design and population

This observational longitudinal cohort study was conducted at St George's University Hospitals NHS Foundation Trust between February 2019 and August 2021. The Brent Research Ethics Committee (19/LO/0794) approved the study protocol, and all participants provided written informed consent. Women with a pregnancy complicated by HDP who were admitted to the Maternity Department were recruited consecutively. Pregnancies complicated by genetic syndromes or fetal abnormalities and patients affected by known cardiac conditions were not included. Patients with a diagnosis of CHT and on anti-hypertensive medications before pregnancy were excluded.

Pregnancy data and outcomes were ascertained from the maternity databases (ViewPoint version 5.6.26.148, ViewPoint Bildverarbeitung GMBH, Wessling, Germany, EuroKing E3, Wellbeing software group, Surrey, UK), discharge letters and by direct patient enquiry. All study data were collected and managed using REDCap electronic data capture tools hosted at St George's University.

Women with HDP underwent two cardiovascular assessments:

- The peripartum visit was conducted before delivery, or within one week after the delivery because we previously demonstrated that maternal hemodynamic changes that occur with the delivery do not affect cardiac indices in women with HDP.[13]
- The postpartum assessment was performed from three to twelve months after delivery.

Only women with both cardiovascular evaluations were included in the analysis.

Outcome and definitions

HDP were defined according to the International Society for the Study of Hypertension in Pregnancy.[14] Birthweight below the 10th centile was used to define small-for-gestational-age neonates. Delivery before 37 weeks' gestation was described as preterm. Persistent hypertension was classified according to the guidelines of the International Society of Hypertension, defining hypertension as a systolic blood pressure (SBP) ≥140 mmHg and/or diastolic BP (DBP) ≥90 mmHg

and/or the use of anti-hypertensive medication.[15] LV myocardial dysfunction was defined by a global longitudinal strain (GLS) 2 SDs below the expected mean for age.[16,17]

Cardiovascular assessment

Measurements at both peripartum and postpartum visits were performed in standardized environmental conditions according to a predetermined protocol, including anthropometric measurements, BP profile and maternal TTE. Body mass index (BMI) (kg/m^2) was calculated by dividing body weight (kg) by the squared height in meters (m^2), and body surface area (BSA, m^2) was measured using the following equation: $0.007184*height(cm)^{0.725}*weight(kg)^{0.425}$. BP profile with at least three measurements with one min between was obtained using an upper arm automatic BP monitor (Microlife®, Microlife AG Swiss Corporation, Widnau, Switzerland) with the woman in a resting state and sitting positioned with a cuff size appropriate for arm circumference. Mean arterial pressure (MAP) was calculated as (2*DBP+SBP)/3. The average of the last two measurements was used to diagnose hypertension.[15] Moreover, women with elevated BP but not already on hypertensive medication at postpartum follow-up were provided with a BP monitor (Microlife®, Microlife AG Swiss Corporation, Widnau, Switzerland) to confirm the diagnosis of CHT or identify white-coat hypertension, if BP at home was less than 135/85 mmHg.[15] They were instructed to check their BP at home once a day and to communicate their readings after one week.

TTE was performed in all participants at rest in the left lateral decubitus position using a commercially available ultrasound Doppler system (GE Vivid E95 with a M5Sc-D probe; GE Healthcare, Horten, Norway). Three cardiac cycles of non-compressed data for each acquisition were stored in cine-loop format and analyzed offline by one investigator (VG) who was blinded to patients' outcome on a dedicated workstation (EchoPAC version 203, GE Healthcare, Horten, Norway). Two-dimensional and Doppler TTE was performed following the American Society of Echocardiography guidelines.[18-20]. Speckle-tracking imaging was applied to the apical 2-, 3-, and 4-chamber views. The highest quality digital images were selected with a frame rate of 60-90 frames per second. GLS was obtained

by the average value of peak systolic longitudinal strain from all three views and peak global strain rate (GLS-R) during early and late diastole as indices of diastolic function were calculated.[21] LV radial and circumferential strain were obtained from parasternal short-axis views obtained from the LV base at the level of the mitral valve and the LV apex. These measurements were used to measure LV twist and twisting and untwisting rates were calculated as the time derivative of twist.[22]

Statistical analysis

This study has 80% power for statistically detecting a difference in LV mass index (LVMI) of 3 units and how the study's sample size was obtained is explained in Supplemental Material.[23] Variables were assessed for normality by the Shapiro-Wilk test and by visualizing their histograms. Continuous data were expressed as mean±standard deviation (SD) or median, interquartile range (IQR). According to the data distribution, they were compared using the Student t-test or Mann–Whitney U test. Categorical data were presented as numbers (%) and compared using the chi-square test of homogeneity or Fisher's exact test as appropriate.

Binomial logistic regression analyses were used to assess the association between clinical and echocardiography factors and persistent cardiovascular impairment. Multivariable models were also undertaken to compare if differences in TTE findings between cohorts persisted after adjusting for maternal age, Afro-Caribbean ethnicity, BMI and MAP assessed in pregnancy. In a supplementary analysis, Cox proportional hazard models estimated the association between persistent hypertension and peripartum data to adjust for different timing of the postpartum follow-up. Receiver Operating Characteristic (ROC) curves were performed to examine the efficacy of clinical and echocardiographic variables in detecting patients at risk of CHT, and the relative results were reported as the area under the curve (AUC) and 95% confidence interval (95% CI). Youden's index was used to define the best cut-offs for TTE variables included in the final models. Comparisons between area under the ROC between models was performed. Statistical significance was deemed a priori as $p<0.05$. P values and 95% CI presented in this report have not been adjusted for multiplicity, and

99 therefore inferences drawn from these statistics may not be reproducible. The analysis was performed
100 using SPSS 27.0 (SPSS Inc., Chicago, IL, USA) and MedCalc Statistical Software version 19.2.6
101 (MedCalc Software bv, Ostend, Belgium).

RESULTS

Comparison of clinical peripartum data between normotensive and hypertensive women in the postpartum

Two hundred and fifty-eight patients affected by HDP were enrolled in the study and underwent maternal TTE in the peripartum period. 211/258 (81.8%) patients were included in the final analysis because they had both peripartum and postpartum cardiovascular evaluation. Baseline pregnancy characteristics of this HDP cohort and a comparison between patients who attended the postpartum follow-up and those who did not are shown in Supplemental Table 1 and 2.

70 out of 211 (33.2%) were found to remain hypertensive or on anti-hypertensive medication at post-partum follow-up. The postpartum evaluation was performed at a median (IQR) of 126 (108-155) days in normotensive women and 123.5 (98-147) days in hypertensive women (p=0.192). Six (8.6%) cases of white-coat syndrome were identified and included in the hypertensive group. 134 (63.5%) women had hypertension and/or persistent LV myocardial dysfunction on postpartum TTE. Women with LV myocardial dysfunction (103/211, 48.8%) at the postpartum assessment had worse cardiac indices compared to those with normal myocardial function (Supplemental Table 3). Women with persistent hypertension were significantly older, more likely to be Afro-Caribbean, and had a higher BMI and MAP in early pregnancy and at the time of HDP diagnosis compared to the normotensive group (Table 1).

Comparison of peripartum echocardiographic data between normotensive and hypertensive women in the postpartum

Table 2 shows that hypertensive women had significantly higher LVMI, RWT and proportion of concentric hypertrophy compared to normotensive women in the peripartum. GLS and early diastolic GLS-R (GLS-R-E) obtained from peripartum TTE were significantly lower in hypertensive than normotensive patients, while diastolic parameters showed significantly lower E', higher E/E' and peak velocity of tricuspid regurgitation in the hypertensive group (Table 2). The results of univariate

and multivariate analysis for the association between clinical and echocardiographic parameters with the postpartum persistence of hypertension are shown in Table 3. When adjusted for maternal age, Afro-Caribbean ethnicity, BMI, peripartum MAP, the following echocardiographic findings – LVM, RWT, myocardial performance index, peak velocity or tricuspid regurgitation, GLS-R-E and twist rate – remained associated with postpartum hypertension.

ROC curve analyses

The AUC for LVMI, RWT, E/E' in the identification of women with postpartum hypertension were 0.66 (95% CI 0.59-0.74), 0.74 (95% CI 0.68-0.81) and 0.67 (95% CI 0.60-0.75), respectively. When these echo indices were combined, the AUC was 0.76 (95% CI 0.70-0.83) (Figure 1). An AUC of 0.79 (95% CI 0.72-0.85) was obtained when LVMI, RWT and E/E' were combined with GLS and GLS-R-E (Supplemental Figure 1). The following cut-off for echocardiographic parameters with the best sensitivity and specificity were identified from ROC curves: 75 g/m^2 for LVMI, 0.42 for RWT, 11 cm/s for average E', 7 for E/E', -14% for GLS and 1.18 for GLS-R-E. They were used to carry out univariate and multivariable analyses, and the results are illustrated in Supplemental Table 4. Timing of postpartum follow-up did not affect the association between clinical or echocardiographic findings with persistent postpartum hypertension, as similar results were demonstrated by Cox regression analysis (Supplemental Table 5).

Prediction models

Five prediction models (1 through to 5) were built using various combinations of i) clinical data obtained in pregnancy at diagnosis of HDP, ii) clinical data from the first trimester to diagnosis of HDP, iii) clinical data at diagnosis of HDP and conventional echocardiography, iv) clinical data from the first trimester and conventional echocardiography, and v) clinical data, conventional and speckle tracking echocardiography (Table 4, Figure 2). Model 4 was statistically significant ($\chi^2(4) = 79.048$, $p<0.0001$) and explained 42.0% of the variance for persistent hypertension and correctly classified

79.2% of postpartum hypertension cases. The model had good performance; sensitivity 48.5%, specificity 91.5%, positive predictive value 69.6% and negative predictive value 81.6% (Table 4). After exclusion of women with hypertension in the first trimester of pregnancy (n=24), the model had the following results: $\chi^2(4) = 39.881$, $p<0.0001$, sensitivity 33.3% and specificity 90.9%. Of the four predictor variables, only three were statistically significant: maternal age, booking MAP, abnormal LV geometry with an AUC of 0.79 (95% CI 0.72-0.86). Differences between AUCs of models 1 and 2 (0.08, 95% CI 0.02-0.13, p=0.005), 1 and 3 (0.06, 95% CI 0.01-0.11, p=0.019), 1 and 4 (0.10, 95% CI 0.03-0.18, p=0.009), 1 and 5 (0.12, 95% CI 0.04-0.20, p=0.002) and 3 and 5 (0.06, 95% CI 0.01-0.11, p=0.027) were all statistically significant. There were no significant differences between AUCs of models 2 and 3 (0.01, 95% CI -0.05-0.07, p=0.654), 2 and 4 (0.03, 95% CI -0.02-0.08, p=0.255), 2 and 5 (0.05, 95% CI -0.01-0.10, p=0.077), 3 and 4 (0.04, 95% CI -0.01-0.09, p=0.226) and 4 and 5 (0.02, 95% CI -0.00-0.04, p=0.100).

DISCUSSION

Summary of the main findings

Persistent postpartum hypertension after HDP affected around one-third of patients in our cohort. Hypertension was associated with specific demographic, clinical and echocardiographic parameters such as age, ethnicity, early pregnancy BP, LVM, RWT and GLS. A prediction model based on demographic, clinical and echocardiographic indices showed good/excellent discrimination in identifying women with HDP who went on to exhibit persistent hypertension in the postpartum period.

Interpretation of study findings and comparison with published literature

The rate of persistent hypertension (33.2%) and impaired LV function (48.8%) in the postpartum in our cohort are consistent with previously published studies.[3,7,24] The most critical clinical variables associated with persistent postpartum hypertension were Afro-Caribbean ethnicity, advancing maternal age and obesity, which are recognized risk factors for CHT.[25] Additionally, increased MAP in the first trimester and at the time of HDP diagnosis were also associated with persistent postpartum hypertension. Maternal hypertension before 20 weeks' gestation is one of the criteria to define CHT in pregnancy, and this could explain the strong association with hypertension persistence beyond 12 weeks postpartum.[26] After excluding women with hypertension in the first trimester, models including combined clinical and echocardiographic data still performed well, producing AUCs with either good or excellent discrimination. Hence, women with increase BP in the first trimester were retained in the final analysis. It is crucial to consider that not all women have a BP check in the first trimester, there is a normal physiologic decrease in BP at mid-gestation that might mask CHT, and presumably, these women may well have as yet undiagnosed CHT.[27] They, therefore, warrant cardiovascular screening when they develop HDP. Consistently with other studies, an early-onset hypertension in pregnancy and preterm delivery were significantly more common in CHT women than in normotensive women.[28,29] We did not find associations of smoking or a diagnosis of pre-

194 eclampsia with postpartum CHT, as it was shown by a retrospective Korean study on 600 HDP
195 patients with a 6-month postpartum follow-up.[28] These could be related to nationwide differences in
196 population and/or healthcare systems.
197
198 Our data showed that women with persistent hypertension after HDP presented more profound
199 changes in LV geometry, diastolic function and GLS at maternal peripartum TTE assessment.
200 Previous studies have also described these changes in pregnancies complicated by pre-eclampsia. [30,31]
201 However, only one small study has correlated these antenatal echocardiographic findings with
202 incident hypertension four years after delivery, and they found, similarly to our data, that the
203 hypertensive group (16 out 33 patients, 48%) had thicker LV posterior walls on the antenatal TTE
204 compared with the normotensive group.[32] An increase in RWT appears to be an early response to LV
205 pressure overload, and concentric remodeling generally exhibits a trend toward higher LV mass.[33]
206 LVM has been associated with cardiovascular-related death in both general population and patients
207 affected by hypertension.[34] Moreover, women destined to remain hypertensive showed altered
208 myocardial relaxation that interferes with normal LV diastolic filling and lower myocardial function
209 assessed by GLS. Pathophysiological changes of diastole can occur early in arterial hypertension,
210 even when ejection fraction is still preserved.[35] LV diastolic dysfunction and, in particular, E/E' ratio
211 are strong predictors of heart failure and cardiovascular events, independently of several confounders,
212 including LVM.[36] LV diastolic dysfunction is strongly related to LV myocardial dysfunction, which
213 might occur even before developing LV concentric geometry and LV systolic dysfunction.[37]
214 Hypertension and LV diastolic dysfunction are critical features for developing heart failure,
215 particularly in the presence of preserved LV ejection fraction (HFpEF), which is particularly
216 prevalent in women. HFpEF was historically defined as diastolic heart failure because it is generally
217 characterized by abnormal diastolic function. Emerging models have suggested a more complex and
218 heterogeneous pathophysiology, and highlighted the role of cardiometabolic comorbidities including
219 hypertension, obesity, and insulin resistance.[38] Therefore, in asymptomatic patients with a history of

HDP, early identification of LV diastolic dysfunction by using TTE may be a unique opportunity to prevent progression to HFpEF. Furthermore, impaired LV GLS is common among HFpEF patients, indicating the presence of covert LV systolic dysfunction despite normal LV ejection fraction.[37] Interestingly, impaired GLS only during exercise has been independently associated with increased all-cause mortality and heart failure hospitalizations,[39] and it is well-known the response of the maternal cardiovascular system to the prolonged volume load of pregnancy, even in uncomplicated pregnancies.[40] As indicated by previous studies, pregnancy affected by HDP is associated with a lower GLS.[30] In our cohort, 48.8% of patients showed persistently impaired GLS, regardless of their BP level, at postpartum follow-up.

Clinical and Research Implications

The opportunity offered by HDP and the subsequent development of persistent hypertension after delivery cannot be ignored at any healthcare level.[2] Cardiovascular screening of women affected by HDP in the peripartum instead of postpartum period (4-6 months after delivery) would benefit patients and healthcare providers. First, pregnancy cardiovascular demand and hypertension in pregnancy unmask maternal cardiac impairment by causing more profound changes than in the postpartum period. The postpartum period can be a difficult time for a new mum who has to deal with substantial changes in her life, and many studies have shown low uptake of postpartum screening. For instance, the postpartum clinical check at 4 to 6 weeks after delivery and subsequent follow-up for anti-hypertensive medication management has a visit attendance rate of only 45% to 60%.[41] Therefore, cardiovascular screening conducted during the antenatal admission for delivery has the potential to provide effective universal screening for women with HDP and allows the implementation of early intervention strategies tailored for postpartum women.

It has been demonstrated that home BP monitoring and self-management of anti-hypertensive medications commenced after delivery discharge was feasible and associated with a better DBP

control at six months postpartum, even after stopping anti-hypertensive treatment.[11] Interestingly, this reduction in DBP was also maintained 3.6 years later, as showed by 24-hour ambulatory BP monitoring.[12]

Anti-hypertensive treatment is helpful to improve LV geometry and diastolic indices[42] and, in particular, regression of LV hypertrophy, which is a good predictor of improved prognosis.[43] A single-center randomized controlled trial of six-months treatment with Enalapril in women with preterm pre-eclampsia reported an improvement in cardiac remodeling and diastolic function.[10] Postnatal treatment with Enalapril was acceptable to women, but further studies are necessary to assess whether these improvements in cardiac function would improve the maternal cardiovascular outlook in the long term. Furthermore, family planning for each patient should also be considered because of the teratogenicity of ACE inhibitors. The ideal medical therapy in this group is still unknown and, regardless of the use of specific anti-hypertensive medications, it is paramount to obtain optimal BP control in the "four trimesters".[11,12,44]

Postpartum lifestyle modification and bundled quality-improvement initiatives have been proved to be effective in improving maternal cardiometabolic risk factors in women with HDP.[41,45] Whereas lifestyle modification advice is effective and could potentially be provided to all women with HDP, postpartum home BP monitoring and tailored anti-hypertensive treatment should be offered to a selected high-risk population among HDP patients. Our study demonstrates that screening based on clinical features and TTE findings in the peripartum would be able to ascertain those women with HDP who could benefit the most from intensive monitoring and treatment (Central Illustration).

Strengths and limitations

This was a prospective longitudinal study that has, for the first time, found cardiovascular peripartum biomarkers of persistent hypertension in women with pregnancies complicated by HDP. The HDP

cohort with complete postpartum follow-up reached a good sample size using a heterogeneous population, paradigmatic of real life.

Regarding the main limitations of the study, being a single centre study limits the widespread applicability of the findings. Data were not adjusted for different types of anti-hypertensive treatment used in pregnancy and in the postpartum and, because of the shortness of the postpartum follow-up, the associations that were found between peripartum echo findings and persistent short-term cardiovascular impairment are not necessarily accurate for long-term cardiovascular diseases in women with a history of HDP. Moreover, we did not measure left atrial reservoir strain, which has been shown to be very accurate in detecting LV diastolic alterations and elevated LV filling pressure in patients with preserved ejection fraction.[46]

Conclusion

Peripartum cardiovascular screening, including maternal TTE, could effectively identify women with HDP at increased risk of persistent postpartum hypertension and/or asymptomatic LV myocardial dysfunction. In this subgroup of pregnant women, our findings support the application of more intensive BP self-monitoring and early therapeutic interventions – for example, prescribing ACE-inhibitors - not only to achieve optimal BP control but also to improve cardiac remodeling. These could potentially reduce the risk of CVD, such as HFpEF, later in life. Further study is required to externally validate the predictive models and evaluate the short- and long-term effectiveness of guided early cardiovascular interventions after pregnancies complicated by HDP.

CLINICAL PERSPECTIVE

- Competency in medical knowledge: The cardiovascular legacy of hypertensive disorders of pregnancy (HDP) appears in the first months after delivery as one-third of HDP patients showed persistent chronic hypertension and two-thirds persistent hypertension and/or impaired left ventricular myocardial function.
- Competency in patient care: Maternal age, BMI, blood pressure, and echocardiographic parameters such as left ventricular mass, wall thickness and indices of diastolic function assessed in the peripartum period can identify women with hypertensive disorders of pregnancy at risk of postpartum hypertension.
- Translational Outlook: Further studies are needed to validate these predictive models and define optimum strategies to reduce long-term cardiovascular risk in women with hypertensive disorders of pregnancy..

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FIGURE LEGENDS

Commented [VG1]: New figure legends

Figure 1. Performance of peripartum echocardiographic parameters for prediction of postpartum CHT. The blue line represents ROC curve for LVMI alone (AUC=0.66, 95% CI 0.59-0.74), the green line represents ROC curve for RWT alone (AUC=0.74, 95% CI 0.68-0.81), and the yellow line represents ROC curve for E/E' alone (AUC=0.67, 95% CI 0.60-0.75). A combination of LVMI, RWT and E/E' increases the AUC of the ROC curve (AUC=0.76, 95% CI 0.70-0.83), as shown by the red line. AUC=area under the curve, CHT=chronic hypertension, LVMI=left ventricular mass index, ROC=receiver operative characteristic, RWT=relative wall thickness.

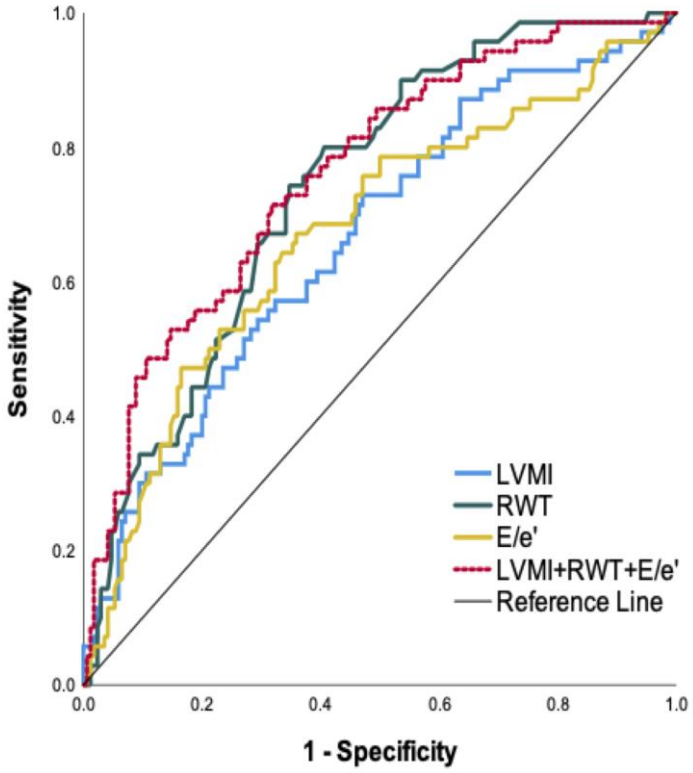
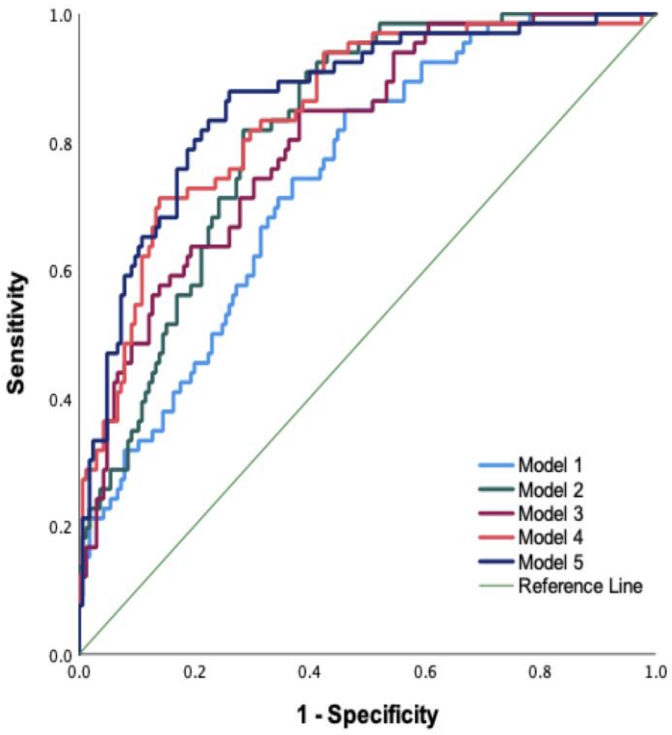
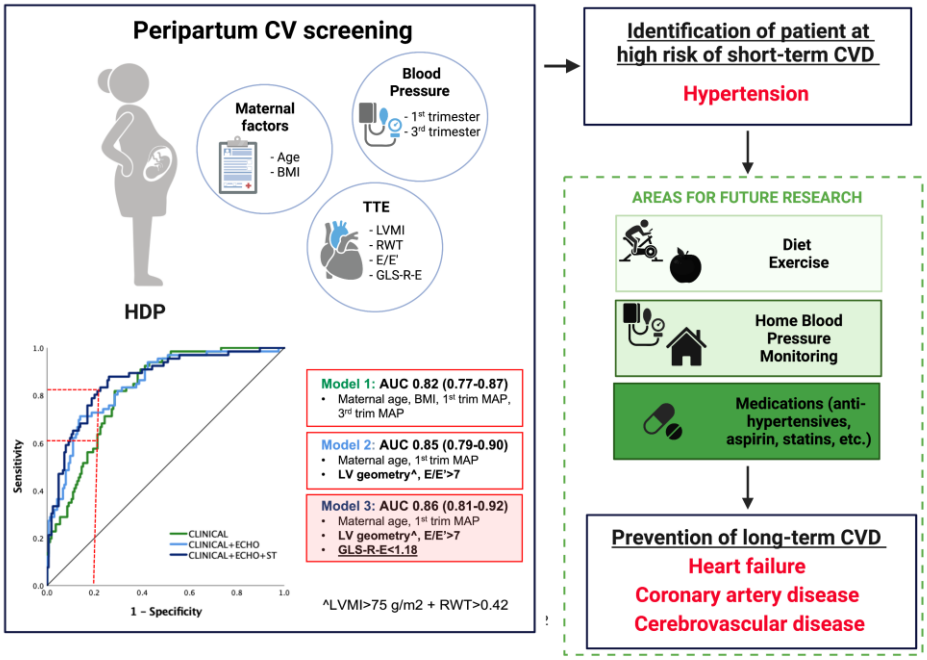


Figure 2. Performance of peripartum models for prediction of postpartum CHT.

The light blue ROC curve represents Model 1 (age, BMI and 3rd trimester MAP). The green ROC curve represents Model 2 (age, BMI, 1st and 3rd trimester MAP). The dark red ROC curve represents Model 3 (age, BMI, 3rd trimester MAP, abnormal LV geometry and E/E'>7). The pink ROC curve represents Model 4 (age, 1st trimester MAP, abnormal LV geometry and E/E'>7). The dark blue line represents Model 5 (age, 1st trimester MAP, abnormal LV geometry, E/E'>7 and GLS-R-E <1.18). BMI=body mass index, CHT=chronic hypertension, GLS-R-E= Early diastolic global longitudinal strain rate, LV=left ventricular, MAP= mean arterial pressure, ROC=receiver operative characteristic.



Central illustration. Peripartum screening for postpartum CHT in women with HDP. The green ROC curve represents a model based on only clinical data, the light blue ROC curve represents a model based on clinical data and conventional TTE and the dark blue ROC curve shows a model based on clinical data, conventional and speckle tracking TTE. The dotted red line illustrates that 80% specificity corresponds to a sensitivity of ~60% in the first model and of ~80% in the last one. AUC=area under the curve, BMI=body mass index, CHT=chronic hypertension, GLS-R-E= Early diastolic global longitudinal strain rate, CVD=cardiovascular diseases, HDP=Hypertensive disorders of pregnancy, LVMI=left ventricular mass index MAP= mean arterial pressure, ROC=receiver operative characteristic, RWT=relative wall thickness, TTE=transthoracic echocardiography.



TABLES

Table 1. Comparisons of clinical data between normotensive and hypertension women in the postpartum.

		Normotensive (n=141)	BP≥140/90 or on medications (n=70)	p-value
Clinical data				
Maternal age (years)		32.91±5.55	35.50±5.00	**0.001**
Ethnicity	Caucasian	108 (76.6%)	34 (48.6%)	**<0.0001**
	Afro-Caribbean	11 (7.8%)	19 (27.1%)	
	Asian	16 (11.3%)	11(15.7%)	
	Mixed/other	6 (4.3%)	6 (8.6%)	
Family history of CVD or CHT		59 (41.8%)	38 (54.3%)	0.088
Smoking (before or during pregnancy)		15 (10.6%)	8 (11.4%)	0.862
Pregnancy-related data				
1st trimester MAP[a]		93.33 (88.33-97.67)	98.33 (94.00-102.67)	**<0.0001**
Diagnosis of pre-eclampsia		87 (61.7%)	37 (52.9%)	0.219
Diagnosis of HDP <34 weeks		31 (22.0%)	30 (42.9%)	**0.002**
≥2 anti-hypertensives		28 (19.9%)	28 (40.0%)	**0.002**
Preterm birth		37 (26.2%)	29 (41.4%)	**0.025**
Gestational age at delivery (weeks)		38.29 (36.43-39.71)	37.36 (35.71-39.29)	0.107
Birthweight centile		20.94 (4.56-56.42)	23.07 (6.97-48.50)	0.804
Small-for-gestational-age neonates		50 (35.5%)	26 (37.1%)	0.811

Data at peripartum CV assessment			
BMI (kg/m^2)	31.15±5.35	33.41±5.94	**0.006**
MAP (mmHg)[a]	103.33±6.98	106.51±8.44	**0.004**

Data are expressed as median (IQR), mean±SD, n (%). No corrections for multiple testing were applied. HDP hypertensive disorders of pregnancy, BW birthweight, BMI body mass index, MAP mean arterial pressure, CV cardiovascular, CVD cardiovascular diseases, CHT chronic hypertension.

[a] Only clinic blood pressure values were included.

Table 2. Echocardiographic data at peripartum cardiovascular assessment between normotensive and hypertensive women in the postpartum period.

	Normotensive (n=141)	**BP≥140/90 or on medication (n=70)**	**p-value**
LV geometry			
LVMI (g/m^2)	76.31±14.83	84.30±17.88	**0.001**
RWT	0.40 ±0.09	0.46±0.08	**<0.0001**
LV remodeling	62 (44%)	51 (72.9%)	**<0.0001**
LV ESVI (ml/m^2)	25.65±6.15	25.68±7.14	0.997
LV EDVI (ml/m^2)	61.96±12.21	61.03±12.38	0.612
Diastolic function			
LAVI (ml/m^2)	27.30±5.89	27.63±6.92	0.724
E/A	1.25±0.27	1.17±0.25	0.055
PV A-MV A duration (ms)	-17.91±39.23	-13.21±38.44	0.418
PV S/D	1.21±0.27	1.31±0.31	**0.026**
Average E' (m/s)	0.12±0.02	0.11±0.02	**0.001**
Lateral E' (m/s)	0.13±0.03	0.12±0.03	**0.004**
Septal E' (m/s)	0.10±0.02	0.09±0.02	**0.003**
E/E'	7.11±1.82	7.95±1.99	**0.002**
MPI	0.49±0.09	0.53±0.11	**0.005**
Peak TR velocity (m/s)	2.03±0.36	2.16±0.34	**0.010**
LV systolic function			
LV EF (%)	58.91±4.16	58.26±4.55	0.317
LV GLS (%)	-16.55±2.16	-15.58±2.74	**0.006**

LV GLS-R-E (s^{-1})	1.26±0.29	1.07±0.25	**<0.0001**
LV GLS-R-A (s^{-1})	0.67± 0.15	0.68 ±0.22	0.808
LV GLS-R-S (s^{-1})	-0.98± 0.14	-0.95±0.18	0.287
LV mechanics			
Twist (deg)	14.83±5.26	16.76±7.36	0.055
Twist rate (deg/s)	107.02±31.92	122.05±41.26	**0.005**
Untwist rate (deg/s)	-120.01±41.80	-127.36±50.48	0.271

Data are expressed as mean±SD. No corrections for multiple testing were applied. LV: left ventricular, LVMI: left ventricular mass index, RWT: relative wall thickness, EDVI: end-diastole volume index, ESVI: end-systole volume index, LAVI: left atrial volume index, MPI: myocardial performance index, PV: pulmonary vein, MV: mitral valve, TR: tricuspid regurgitation, EF: ejection fraction, GLS: global longitudinal strain, GLS-R-E: global longitudinal early diastolic strain rate, GLS-R-A: global longitudinal late diastolic strain rate, GLS-R-S: global longitudinal systolic strain rate.

24 **Table 3. Logistic regression for persistent hypertension in the postpartum.**

	OR (95% CI)	p-value	Adjusted OR* (95% CI)	p-value
Clinical data				
Maternal age (years)	1.11 (1.05-1.18)	**0.001**	-	-
Afro-Caribbean ethnicity	4.60 (2.07-10.18)	**<0.0001**	-	-
≥2 anti-hypertensive medications	3.17 (1.71-5.87)	**<0.0001**	-	-
Preterm birth	2.09 (1.16-3.78)	**0.015**	-	-
BMI (kg/m^2)	1.06 (1.01-1.12)	**0.018**	-	-
MAP (mmHg)	1.05 (1.01-1.10)	**0.009**	-	-
1^{st} trimester MAP (mmHg)	1.14 (1.10-1.20)	**<0.0001**	-	-
Echocardiographic parameters				
LVM (g)	1.02 (1.01-1.03)	**<0.0001**	1.01 (1.00-1.024)	**0.006**
RWT	1.07 (1.04-1.11)	**<0.0001**	1.05(1.01-1.09)	**0.011**
PV S/D	2.94 (1.03-8.37)	**0.044**	1.46 (0.44-4.80)	0.537
Average E' (m/s)	0.81 (0.72-0.92)	**0.001**	0.90 (0.78-1.03)	0.131
Lateral E' (m/s)	0.86 (0.78-0.95)	**0.003**	0.93 (0.83-1.04)	0.195
Septal E' (m/s)	0.84 (0.74-0.95)	**0.006**	0.91 (0.79-1.04)	0.175

E/E’	1.30 (1.11-1.53)	**0.001**	1.16 (0.98-1.37)	0.080
MPI	1.05 (1.02-1.08)	**0.003**	1.05 (1.01-1.03)	**0.011**
Peak TR velocity (m/s)	3.19 (1.36-7.46)	**0.007**	3.46 (1.37-8.72)	**0.008**
LV GLS (%)	1.17 (1.04-1.32)	**0.010**	1.08 (0.94-1.23)	0.268
LV GLS-R-E (s^{-1})	0.10 (0.03-0.30)	**<0.0001**	0.18 (0.06-0.56)	**0.003**
Twist (deg)	1.05 (1.00-1.10)	**0.045**	1.05 (0.99-1.10)	0.096
Twist rate (deg/s)	1.01 (1.00-1.02)	**0.012**	1.01 (1.00-1.02)	**0.025**
Untwist rate (deg/s)	0.98 (0.99-1.00)	0.312	-	-

*Regression analyses for each echocardiographic parameters with adjustment for maternal age, Afro-Caribbean ethnicity, BMI and MAP at peripartum echocardiography.

No corrections for multiple testing were applied. BMI: body mass index, MAP: mean arterial pressure, LV: left ventricle, LVM: left ventricle mass, RWT: relative wall thickness, PV: pulmonary vein, MPI: myocardial performance index, TR: tricuspid regurgitation, GLS: global longitudinal strain, GLS-R-E: global longitudinal early diastolic strain rate.

Table 4. Predictions model for persistent postpartum hypertension based on peripartum clinical and/or echocardiographic data.

Model	**Model 1**		**Model 2**		**Model 3**		**Model 4**		**Model 5**	
Description	**Clinical (peripartum only)**		**Clinical (peripartum and 1st trimester)**		**Clinical (peripartum only) and TTE data**		**Clinical (1st trimester only) and TTE data**		**Clinical (1st trimester only) and ST TTE data**	
Variables	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value
First-trimester MAP (mmHg)			1.15 (1.08-1.22)	<0.0001			1.17 (1.10-1.24)	<0.0001	1.16 (1.09-1.24)	<0.0001
Maternal age (years)	1.11 (1.05-1.18)	0.001	1.11 (1.04-1.19)	0.003	1.10 (1.03-1.17)	0.004	1.09 (1.01-1.16)	0.017	1.07 (1.00-1.15)	0.042
BMI (Kg/m^2)	1.09 (1.03-1.15)	0.002	1.06 (1.00-1.13)	0.058	1.07 (1.00-1.13)	0.035				

Peripartum MAP (mmHg)	1.10 (1.05-1.14)	<0.0001	1.06 (1.08-1.13)	0.001	1.08 (1.04-1.13)	<0.001				
Abnormal LV geometry					3.52 (1.81-6.82)	<0.0001	4.13 (2.02-8.44)	<0.0001	3.96 (1.90-8.26)	<0.0001
E/E'>7					2.12 (1.09-3.12)	0.026	2.29 (1.13-4.63)	0.022	2.05 (0.99-4.23)	0.052
GLS-R-E <1.18 s^{-1}									3.04 (1.43-6.43)	0.004
AUC (95% CI)	**0.74 (0.68-0.81)**	**-**	**0.82 (0.77-0.87)**	**-**	**0.80 (0.75-0.86)**	**-**	**0.85 (0.79-0.90)**	**-**	**0.86 (0.81-0.92)**	**-**

No corrections for multiple testing were applied. LV: left ventricular, LVMI: left ventricular mass index, RWT: relative wall thickness, ST: speckle tracking, GLS-R-E: global longitudinal early diastolic strain rate, TTE: transthoracic echocardiography.