Cardiac structure, function and mechanics in hypertensive disorders of pregnancy: a systematic review and meta-analysis.

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Running Title: Cardiac structure and function in HDP

Abstract

Background: Hypertensive disorders of pregnancy (HDP) are among the most common pregnancy complications and leading causes of maternal morbidity and mortality worldwide. This study aimed to perform the largest meta-analysis to date comparing conventional and advanced echocardiographic features in HDP against healthy pregnancy.

Methods: PubMed (MEDLINE) and EMBASE were systematically searched for research articles published up to March 2024. Included studies reported at least one relevant echocardiographic parameter in pregnancies complicated by HDP and normotensive healthy pregnancies separately. A total of 53-studies met the inclusion criteria, comprising 7168-participants (3381-HDP and 3787-controls).

Results: Myocardial mechanics as measured by global longitudinal strain (GLS; Weighted Mean Difference (WMD): -2.81%, CI=-3.70 to -1.91,p<0.001) and left atrial reservoir strain (LAr; WMD: -9.36%, CI=-12.73 to -5.99,p<0.001) were significantly impaired in HDP compared to healthy pregnancy. Furthermore, there were prominent cardiac structural differences, with significantly greater LVMI (WMD: 12.20,CI= 9.77 to 14.64,p<0.001), RWT (WMD: 0.055, CI=0.04 to 0.07, p<0.001), LA size (WMD: 2.34cm, CI=1.62 to 3.06,p<0.001) and LAVI (WMD: 2.38ml/m^2, CI=1.44 to 3.32,p<0.001) in HDP compared to healthy pregnancy. Finally, E/E' average was significantly greater in HDP (WMD: 1.90, CI=1.42 to 2.38,p<0.001), indicative of an elevated LV filling pressure.

Conclusions: This meta-analysis highlights clinically relevant differences in echocardiographic measures between HDP and healthy pregnancy. These results may enhance

the utilisation of echocardiography for the risk stratification and management of women with HDP. Advanced myocardial mechanics, including GLS and LAr, likely play a key role in detecting subclinical myocardial dysfunction and guidance for early intervention.

Key Words: HDP, preeclampsia, echocardiography, myocardial mechanics.

Abbreviations:

Hypertensive disorders of pregnancy, HDP

Global longitudinal strain, GLS

Pre-eclampsia, PE

Gestational hypertension, GH

left ventricular end diastolic volume, LVEDV

left ventricular end systolic volume, LVESV

the ratio of early to late diastolic peak blood flow velocity E/A ratio

deceleration time DT

the ratio between early mitral inflow velocity and early mitral annular velocity, E/E′

left ventricular mass, LVM

left ventricular mass index, LVMI

relative wall thickness, RWT

left atrial volume index, LAVI

left atrial size, LA size

LA reservoir strain, LAr

peak atrial longitudinal strain, PALS

tricuspid regurgitation velocity, TR velocity

tricuspid annular plane systolic excursion, TAPSE

Introduction

Hypertensive disorders of pregnancy (HDP) are among the leading causes of maternal morbidity and mortality worldwide.[1] With a prevalence of up to 15% of all pregnancies, HDP has significant global implications for female health, particularly in relation to long-term cardiovascular outcomes.[2–4] Extensive research has documented the increased cardiovascular risk associated with HDP,[1,5,6] with longitudinal studies demonstrating cardiac dysfunction that can persist for over a decade post-partum.[7] These findings highlight the clinical importance of continued cardiovascular surveillance and the need for effective therapeutic interventions.

Echocardiography is a safe, non-invasive tool for assessing cardiac structure and function in pregnancy with a plethora of previous review studies highlighting its potential role in the early detection, risk stratification and management of women with HDP.[8] Previous systematic reviews have explored echocardiographic parameters in HDP, but many lacked meta-analysis or, in research where it was included, focused narrowly on pre-specified measures. For instance, earlier research from our group investigated changes in global longitudinal strain (GLS) in HDP compared to healthy pregnancy, evidencing both statistically and clinically significant differences, with important prognostic implications.[9] However, this narrow focus on single parameters can overlook the broader clinical context of concurrent cardiac dysfunction. Indeed, limited previous work has provided comprehensive meta-analysis of the full spectrum of cardiac maladaptation, especially when considering more novel approaches such as left atrial mechanics, which have physiological and prognostic relevance in this population.[10,11] Addressing this gap through a comprehensive meta-analysis offers a valuable opportunity to integrate a broad spectrum of data, providing a more holistic understanding of cardiac structure, function and mechanics in the context of HDP. Meta-analysis results could

streamline the integration of echocardiography assessment into routine clinical practice by highlighting differences in commonly measured parameters, making it easier for clinicians to apply and interpret echocardiographic findings in HDP.

This systematic review and meta-analysis aimed to compare echocardiographic features in HDP against a healthy pregnancy control. This work also aimed to establish the independent cardiac effects across the HDP spectrum with sub-analysis of pre-eclampsia (PE) and gestational hypertension (GH).

Methods

Protocol, eligibility criteria, information sources and search

This systematic review and meta-analysis were performed in accordance with the PRISMA guidelines [12]. The authors declare that all supporting data are available within the article and its supplementary file. PubMed/Medline and EMBASE were systematically searched for research articles published up to March 2024. Studies were required to report at least one relevant echocardiographic parameter in pregnancies complicated by HDP and normotensive healthy pregnancies separately. The search strategy included combinations of the relevant medical subject heading (MeSH) terms, key words, and word variants for "preeclampsia", "hypertensive disorders of pregnancy", "echocardiograph*", and an array of their synonyms (see supplementary file). No search filters on language or date of publication were applied. Reference lists of relevant articles and reviews were hand searched for additional reports.

Echocardiographic parameters of interest were: left ventricular ejection fraction (LVEF), GLS, left ventricular end diastolic volume (LVEDV), left ventricular end systolic volume (LVESV), the ratio of early to late diastolic peak blood flow velocity (E/A ratio), deceleration time (DT), the ratio between early mitral inflow velocity and early mitral annular velocity (E/E′), left ventricular mass (LVM), left ventricular mass index (LVMI), relative wall thickness (RWT), ascending aorta size, left atrial volume index (LAVI), left atrial size (LA size), LA reservoir strain (LAr), peak atrial longitudinal strain (PALS), LA conduit strain, LA contractile strain, LA stiffness, right ventricular size (RV size), right ventricular free-wall strain, tricuspid regurgitation velocity (TR velocity) and tricuspid annular plane systolic excursion (TAPSE). Where there were <3 studies with sufficient data, parameters were omitted from analyses.

Studies that did not report data separately for both HDP/PE/GH and healthy control were excluded.

Study selection, data collection and data items

Case-control studies reporting the outlined parameters from a standard transthoracic echocardiography during pregnancy or <7 days post-partum in women affected by HDP were considered. Case reports and studies without a control group of a normotensive pregnant women were excluded. HDP that include gestational hypertension and preeclampsia (PE) were defined by international guidelines [13,14]. Women with new-onset hypertension (≥140mm/Hg systolic or ≥90mm/Hg diastolic on two separate occasions 12 h apart) were classified as gestational hypertension or preeclampsia according to the presence of systemic involvement (significant proteinuria or maternal organ dysfunction).

Two authors independently screened all papers for eligibility. Studies were initially screened by title and abstract, and subsequently by full text if they met the relevant inclusion criteria. Any inconsistency and disagreement were discussed by the researchers and a consensus was reached. Following study recruitment, the respective data of all included studies was extracted independently by two researchers for the analysis. If more than one study was published for the same cohort, the study containing the most comprehensive information was included to avoid overlapping populations. In cases where articles measured the same cohort but different parameters, both were included.

Study quality assessment

The risk of bias and methodological quality of the included studies was measured using the Newcastle-Ottawa Quality Assessment Form for Case-Control Studies (NOS)[15]. NOS is a tool

designed for the assessment of non-randomised studies, judged on the categories: selection, comparability and exposure; with a maximum achievable score of 9 stars. For the purpose of subgroup analysis, study quality was determined as 'high' with a NOS of 8 or 9. Two researchers independently scored each of the included papers and resolved any discrepancies via consensus.

Quantitative analysis

The extracted raw data were manually entered into Comprehensive Meta-Analysis (Version 3, Biostat, Englewood, NJ, USA). A pooled analysis was conducted on all included studies to determine the weighted mean difference with 95% confidence intervals (CI) for each echocardiographic parameter between HDP and control groups. Additionally, separate sub-analyses were independently performed for PE-only and GH-only groups where reported. Weighted mean differences for each pairwise comparative analysis were calculated using the difference in group means, weighted by the inverse of the variance for each study. Statistical heterogeneity was assessed alongside the pooled analysis and reported as the I^2 statistic, with a significance threshold set at >40% . If this threshold was exceeded, post-hoc tests, such as Egger's test [16], were systematically planned to evaluate funnel plot asymmetry and account for potential publication bias. Random effects analysis was applied, as recommended when significant heterogeneity between studies is confirmed[17]. The pooled analysis results were considered significant with a P value of <0.05 and a Z-value of >2.

Results

Study and participant characteristics

Figure 1 details the PRISMA systematic review process. The initial search identified 2773 studies, reducing to 2740 with the removal of duplicates. Following all exclusions, 53 studies (70 effect sizes) were ultimately included in the final meta-analysis, constituting an analysed sample of 7168 participants (3381 with HDP and 3787 controls). The characteristics of the included studies and NOS scores can be seen in Table 1. There was significant heterogeneity (>40% I^2) for all primary analyses, resulting in a random-effects analysis approach.

Primary and sub-group analyses

There was a statistically significantly lower LVEF in HDP compared to the control group (WMD: -1.06%, CI= -1.77 to -0.34, p=0.004, Effect sizes (ES)=40). However, sub-group analyses revealed no significant differences between PE and control (WMD: -0.56%, CI= -1.18 to 0.07, p=0.079, ES=24) or GH and control (WMD: -0.22%, CI= -1.40 to 0.97, p=0.722, ES=5). GLS was significantly worse in HDP (WMD: -2.81%, CI= -3.70 to -1.91, p<0.001, ES=20) and the PE sub-group (WMD: -2.88%, CI= -3.96 to -1.80, p<0.001, ES=15) compared to the control groups.

There was a significant difference in E/A ratio for GH (WMD: -0.11, CI= -0.20 to -0.02, p=0.023, ES=5), but not HDP (WMD: -0.04, CI= -0.11 to 0.02, p=0.193, ES=40) or PE (WMD: 0.01, CI= -0.08 to 0.11, p=0.767, ES=26) when compared to the controls. There were also no significant differences in DT for HDP (WMD: 4.65ms, CI= -9.35 to 18.66, p=0.515, ES=15) or PE (WMD: 11.82ms, CI= -3.04 to 26.68, p=0.119, ES=10) compared to the control groups. E/E' average was significantly greater in HDP compared to the control group (WMD: 1.90, CI= 1.42 to 2.38, p<0.001, ES=23), which remained consistent in the subgroup

analyses of PE (WMD: 1.94, CI= 1.36 to 2.52, p<0.001, ES=17) and GH (WMD: 1.32, CI= 1.02 to 1.63, p<0.001, ES=4).

LVEDV was significantly greater in HDP (WMD: 5.84ml, CI= 3.38 to 8.30, p<0.001, ES=23) and PE (WMD: 6.87ml, CI= 3.39 to 10.35, p<0.001, ES=14) compared to the control groups. LVESV was also significantly greater in HDP (WMD: 5.15ml, CI= 3.21 to 7.09, p<0.001, ES=25) and PE (WMD: 5.69ml, CI= 3.26 to 8.13, p<0.001, ES=15), but GH (WMD: 0.121ml, CI= -4.31 to 4.55, p=0.957, ES=4) when compared to the controls.

There was a statistically significantly greater LVM (WMD: 23.58g, CI= 17.70 to 29.46, p<0.001, ES=18) and LVMI (WMD: 12.20, CI= 9.77 to 14.64, p<0.001, ES=38) in HDP compared to the control groups. There were consistent LVM (WMD: 24.23g, CI= 16.18 to 32.28, p<0.001, ES=11) and LVMI (WMD: 13.73, CI= 10.74 to 16.71, p<0.001, ES=22) differences in the PE sub-analysis, as well as LVMI in the GH (WMD: 12.13, CI= 4.86 to 19.39, p<0.001, ES=7). There was a significantly greater RWT in HDP (WMD: 0.055, CI= 0.04 to 0.07, p<0.001, ES=21), PE (WMD: 0.066, CI= 0.04 to 0.09, p<0.001, ES=11), and GH (WMD: 0.043, CI= 0.02 to 0.07, p<0.001, ES=4) compared to the control groups. The RV size was also significantly greater in the HDP analysis compared to the control group (WMD: 12.63mm, CI= 3.65 to 21.60, p=0.006, ES=7). There were no significant differences in TAPSE for HDP (WMD: 0.94, CI= -0.09 to 1.98, p=0.075, ES=13) or PE (WMD: 1.09, CI= -0.44 to 2.62, p=0.162, ES=8) compared to the control groups.

LA size was significantly greater in HDP (WMD: 2.34cm, CI= 1.62 to 3.06, p<0.001, ES=20) and PE (WMD: 2.79cm, CI= 1.77 to 3.82, p<0.001, ES=11) compared to the control groups. LAVI was also significantly greater in HDP (WMD: 2.38ml/m^2, CI= 1.44 to 3.32, p<0.001, ES=12) and PE (WMD: 2.37ml/m^2, CI= 0.85 to 3.98, p=0.002, ES=8) compared to the

control groups. LAr strain was significantly attenuated in the HDP group compared to control (WMD: -9.36%, CI= -12.73 to -5.99, p<0.001, ES=4).

Discussion

This meta-analysis included 53 studies consisting of 7168 patients, of whom 3381 were diagnosed with HDP. Notably, LV mechanics, LV function and LAr were significantly impaired in HDP compared to healthy pregnancy. Furthermore, there were prominent functional and structural differences with significantly greater LVM, LVMI, RWT, LA size and LAVI in HDP. Finally, E/E' average was significantly greater in HDP, indicative of an elevation in estimated left ventricular filling pressure. Overall, the findings of this work provide the general differences in routine echocardiographic parameters in patients with HDP compared to those with healthy pregnancy, which supports informed utilisation of echocardiography in the risk stratification and management of women with HDP.

Following from prior analyses, this study continues to evidence the impairments in myocardial structure, function and mechanics that accompany HDP.[8,9] O'Driscoll et al.[9] found a similar weighted magnitude of GLS impairment, which is understood to carry important clinical implications as an established prognostic marker.[18] Interestingly, previous prospective work has shown GLS impairments in HDP despite minimal changes on conventional echocardiographic parameters such as LVEF.[19] The differences in LVEF between HDP and healthy pregnancy observed in this analysis support this finding. Although statistically significant, the impairment in LVEF in HDP was minimal and would be generally regarded as clinically insignificant (1.06%), especially when considering reproducibility.[20] The findings of this study therefore add further context regarding the importance of incorporating GLS as an advanced measure for the assessment of subclinical

myocardial dysfunction to conventional echocardiographic assessment in HDP. This is further supported from the significant impairments in LAr seen in this analysis. Certainly, larger-scale prospective research is needed to fully understand the future utility of LAr in HDP screening and management, with a potentially similar role to GLS as a sensitive early marker of subclinical myocardial dysfunction. However, conflicting previous smaller-scale research,[21] the observed LAr impairment was accompanied by significant structural changes in LA size and LAVI. Despite the presence of such structural alterations in this study, there is wider potential for LAr as a more sensitive marker for monitoring in HDP patients for early targeted intervention prior to the delayed consequences of LA functional alternations which cascade to adverse structural remodelling. As such, the early detection of GLS and/or LAr impairment, prior to conventional echocardiographic changes, could enhance the consideration of early non-pharmacological approaches, such as targeted exercise training,[22] while also providing information on the potential indication for more aggressive pharmacological management.

As is extensively documented,[23] this study also identified cardiac remodelling and diastolic dysfunction in patients with HDP, PE and GH. Previous research, such as work by Rafik Hamad et al.[24] has reported an LVMI at $15 g \cdot m^2$ greater than that seen in healthy pregnancy, as well as being one of many studies to report evidence of diastolic dysfunction [25–27]. To our knowledge, this study presents the largest analysis to-date to measure such cardiac changes in HDP, which provides an effective framework for understanding these broad cardiac differences across a large dataset of heterogeneous HDP studies. Given the statistically and clinically significant increases in LVM, LVMI and RWT and E/E', the pattern of cardiac remodelling and diastolic dysfunction in HDP, including PE and GH, remains consistent. Specifically, E/e' has been evidenced to progressively increase in healthy pregnancy past the first trimester, and our work suggests a clear exaggeration of such progression in the context

of altered loading conditions in HDP [28]. As evidenced in the recent POP-HT trial,[29] effective anti-hypertensive control in the early postpartum period is associated with reversal of these maladaptation's, further evidencing the utility of cardiac monitoring.

Despite the benefits of echocardiography, it is not widely applied in the clinical management of HDP or with postpartum management in recovery from HDP, which remains a missed opportunity for early risk stratification for both cardiovascular complications peripartum,[30] and future cardiovascular disease progression [8,11,31,32]. In addition to screening, echocardiography may offer an opportunity to monitor the effectiveness of therapeutic interventions. It's application to detect early sub-clinical dysfunction, cardiac remodelling and changes in diastolic function could guide intervention timing and ultimately help prevent long-term cardiovascular complications. While medical management in HDP is well-documented, future research investigating the effectiveness of novel anti-hypertensive lifestyle approaches are also necessary. Furthermore, future longitudinal investigation is needed to effectively document the development of peripartum cardiomyopathy in this high-risk group, with implications for the discussed interventional approaches in the pursuit of favourable reverse remodelling.

Limitations

There was significant heterogeneity across all primary and secondary analyses in this work. Although speculative, this heterogeneity is likely attributable to the broad inclusion criteria of this study design as necessary to provide such a wide pool of data. Methodological differences between studies, such as differences in blood pressure, BMI and gestational age, as well as differences in echocardiographic accuracy are likely culprits in this context. While we attempted to account for such heterogeneity through random-effects models this limitation

should be considered in the interpretation of this work. Furthermore, only 4 studies of the included 53 were considered high quality by NOS score. There were limitations in the sub-analyses where not all studies reported by HDP status, therefore the effects for PE or GH were a subset of the included studies and should be interpreted with caution. Finally, important parameters relevant to diastology, particularly tricuspid regurgitation velocity, were not included in this analysis due to insufficient reporting. This subsequently limits inferences relating to diastolic functional differences between HDP and healthy pregnancy, particularly in the context of changing diastolic assessment guidelines.[33]

Perspectives

This study is the largest-scale analysis to-date to characterise echocardiographic features of HDP compared to healthy pregnancy, demonstrating significant differences in myocardial mechanics, structural maladaptation and diastolic dysfunction. Understanding the broad cardiac alterations in HDP using echocardiography can facilitate early detection and subsequently improve clinical management – not only in pregnancy, but also in postpartum recovery from HDP. Advanced assessment of myocardial mechanics including GLS and LAr may have a key role in the detection of subclinical dysfunction and the need for early intervention. However, further prospective research is required to validate these findings.

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Pathophysiological Novelty and Relevance section with the sub-sections:

What is new?

This large-scale analysis provides the clinically relevant differences in routine and advanced echocardiographic parameters in patients with hypertensive disorders of pregnancy compared to healthy pregnancy.

What is Relevant?

We found significant impairments in left ventricular function, mass, geometry, estimated filling pressures and myocardial mechanics in women with hypertensive disorders of pregnancy compared to healthy pregnancy.

Left atrial pathology was also demonstrated with significant greater left atrial size and indexed volumes, concurrent to significantly worse left atrial reservoir strain in hypertensive disorders of pregnancy.

Clinical/Pathophysiological Implications?

The findings of this work evidence the potential for enhanced utilisation of echocardiography in the risk stratification and management of women with hypertensive disorders of pregnancy. The implementation of advanced measures of myocardial mechanics, including global longitudinal strain and left atrial reservoir strain, may play a key role in detecting subclinical myocardial dysfunction with implications for clinical management.

Figure legends

Figure 1: PRISMA systematic review and meta-analysis flowchart.