Myocardial mechanics in hypertensive disorders of pregnancy: a systematic review and meta-analysis

O'Driscoll, J., Giorgione, V., Edwards, J., Wiles, Jonathan D., Sharma, Rajan and Thilaganathan, B.

Myocardial Mechanics in Hypertensive Disorders of Pregnancy: a Systematic Review and Meta-Analysis

Jamie M. O'Driscoll, Veronica Giorgione, Jamie J. Edwards, Jonathan D. Wiles, Rajan Sharma, Baskaran Thilaganathan

Originally published 17 Nov 2021

https://doi.org/10.1161/HYPERTENSIONAHA.121.18123

Hypertension. 2022;79:391–398

Myocardial mechanics in hypertensive disorders of pregnancy: a systematic review and meta-analysis.

Jamie M. O'Driscoll[*1,2], Veronica Giorgione[*3,4], Jamie J. Edwards[1], Jonathan D. Wiles[1], Rajan Sharma[2], Baskaran Thilaganathan[3,4].

[1]School of Psychology and Life Sciences, Canterbury Christ Church University, Kent, CT1 1QU

[2]Department of Cardiology, St George's Healthcare NHS Trust, Blackshaw Road, Tooting, London, SW17 0QT.

[3]Fetal Medicine Unit, St George's University Hospitals NHS Foundation Trust, University of London, London, United Kingdom.

[4]Molecular and Clinical Sciences Research Institute, St. George's University of London, London, UK

Correspondence to Dr Jamie O'Driscoll, School of Psychology and Life Sciences, Canterbury Christ Church University, North Holmes Road, Canterbury, Kent, CT1 1 QU. Email: jamie.odriscoll@canterbury.ac.uk; Telephone: 01227782711.

[*] = Authors contributed equally.

Running Title: Myocardial mechanics in HDP

Abstract

Global longitudinal strain (GLS) is becoming routinely used to direct the medical management of various cardiac diseases, but its application in pregnancy is unclear. Our objective was to perform a meta-analysis and pool multiple study data to consolidate the evidence base for the role of GLS in the assessment of women with hypertensive disorders of pregnancy (HDP). Electronic database searches were performed in PubMed/Medline and EMBASE for research articles reporting GLS in pregnancies complicated by HDP and normotensive pregnancies that have been published up to September 2021. The meta-analysis included 17 studies with a pooled sample size of 1723 participants, which included 951 women with HDP, of which 680 were pre-eclamptic (PE), and 772 controls. The primary random-effects pooled analysis demonstrated a statistically significant weighted mean difference (MD) in GLS between the HDP and control group (MD: 3.08%, CI=2.33-3.82, $p<0.001$). When analysed including only PE studies, there was also a statistically significant mean difference (MD: 2.98%, 95% CI=1.97-3.99, $p<0.001$). This meta-analysis demonstrates that HDP is associated with greater cardiac maladaptation, evidenced by a significantly reduced GLS compared to normal pregnancy. Echocardiography should be considered as a screening tool in women with HDP to enable early cardiovascular risk prevention through national initiatives.

Key Words: Cardiac mechanics, Hypertension, Pregnancy, Preeclampsia, Hypertensive disorders of pregnancy, Echocardiography, Meta-analysis

Introduction

Hypertensive disorders of pregnancy (HDP) are the most common complications of pregnancy and is estimated to affect 5–15% of all pregnancies.[1-3] It is increasingly recognized that women experiencing HDP are at increased risk of postnatal cardiovascular disease (CVD),[4] which is the leading non-obstetric cause of mortality in pregnancy and accounts for 18% of global maternal mortality.[5,6] As such, knowledge of the physiological adaptations and maladaptation's to pregnancy is important, to differentiate normal and abnormal responses. Early recognition may prove vital in order to plan appropriate interventions to reduce adverse outcomes.[7] A previous systematic review[6] provided important information surrounding the value of echocardiography to risk stratify and manage pre-clinical and clinical phases of HDP. Specifically, adverse changes in cardiac function and morphology, namely diastolic dysfunction and left ventricular remodelling were identified, which was shown to correlate with disease severity and adverse outcomes.[6] Indeed, overt cardiac dysfunction can occur in up to 40-45% of women with preeclampsia.[8] However, echocardiographic studies have shown that even healthy pregnant women at term may demonstrate signs of cardiac maladaptation and as such, a more sensitive marker of cardiac dysfunction is desirable.[9]

Global longitudinal strain (GLS), representing the magnitude of myocardial deformation, is an important emerging tool for the quantification of left ventricular (LV) function in clinical practice and is more sensitive and reproducible in detecting subclinical cardiac changes compared to conventional techniques.[10] Indeed, a recent study demonstrated that pregnant women with term preeclampsia and minimal changes on conventional echocardiography demonstrated significant reductions in GLS compared to healthy term pregnant women.[11] Importantly, longitudinal data has demonstrated significant differences in cardiac structure,

function and GLS between HDP and non-HDP patients persist a decade following pregnancy, highlighting the need for continued surveillance and therapeutic interventions.[12] Due to the short and long-term CVD risks of HDP, the aim of this study was to perform a meta-analysis and pool multiple study data to consolidate the evidence base for the role of GLS in the assessment of women with HDP.

Methods

The authors declare that all supporting data are available within the article and its Data Supplement. This systematic review and meta-analysis were performed in accordance with the PRISMA and MOOSE guidelines (PROSPERO Reg ID: CRD42021254571).[13, 14]

Protocol, eligibility criteria, information sources and search

Electronic database searches were performed in PubMed/Medline and EMBASE for research articles reporting GLS in pregnancies complicated by HDP and normotensive pregnancies that has been published up to September 2021. The search strategy included combinations of the relevant medical subject heading (MeSH) terms, key words, and word variants for "preeclampsia", "hypertensive disorders of pregnancy", "global longitudinal strain", "speckle tracking" 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.

Study selection, data collection and data items

Case-control studies reporting maternal left ventricle GLS assessed by a standard trans-thoracic echocardiography during pregnancy or <7 days post-partum in women affected by HDP were considered. Case reports and studies without a control group of normotensive pregnant women were excluded. HDP that include gestational hypertension and preeclampsia (PE) were defined by international guidelines.[15, 16] 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 (JE and VG) independently screened all papers for eligibility. Studies were initially screen 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 (JE and VG) 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. For those articles in which information was not reported but the methodology indicates that this information would have been recorded initially, the authors were contacted[17-19].

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).[20] 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 (JE and VG) independently scored each of the included papers and resolved any discrepancies via consensus.

Quantitative analysis

The extracted raw data was manually inputted into Comprehensive Meta-Analysis (Comprehensive Meta-Analysis Version 3, Biostat, Englewood, NJ, USA). A pooled analysis was performed on all recruited studies to establish the weighted mean difference in GLS% between HDP and control. Further, separate PE-only analysis was performed independently to

measure the weighted mean difference in GLS% between PE and control. Finally, independent subgroup analyses on study quality, severe PE, gestational hypertension, and pre-existing chronic hypertension were determined. Statistical heterogeneity was tested alongside the pooled analysis and reported as Cochran's *Q* and the I^2 statistic. Statistical significance for *Q* was P <0.01 and >40% for the I^2 statistic.[21] Once past this threshold, post-hoc tests such as Egger's test (1997) were systematically planned to assess the presence of funnel plot asymmetry to account for potential publication bias.[22] Random effects analysis was selected as suggested when inter-study variability is confirmed through significant heterogeneity[21]. The results of the pooled analysis were considered significant with a P value of <0.05 and a Z-value of >2.

A meta-regression was performed to ascertain if any moderator variables influenced GLS and explain any of the observed inter-study variance in outcomes. The moderators assessed independently were: control group systolic and diastolic blood pressure, strain software, gestational age at assessment, mother age and body mass index (BMI).

Results

Study and participant characteristics

Figure 1 details the PRISMA systematic review flowchart. Our initial search in December 2020 identified 520 studies, which when updated in September 2021 identified 44 new studies (564 studies), reducing to 403 upon removal of duplicates. After screening the records against the title and abstract, 373 studies were excluded, leaving 30 papers for full-text review. Of these, 11 were removed for containing the wrong outcome data, 1 for an irrelevant study population and 1 for insufficient data reporting. As such, the final meta-analysis included 17 studies with a pooled sample size of 1723 participants which included 951 women with HDP, of which 680 were pre-eclamptic, and 772 controls. All relevant study characteristics including NOS scores are presented in Table 1. Only three studies were classified as 'high' quality, and thus study quality could not be used for sub-group sensitivity analysis.

Primary analysis

The primary random-effects pooled analysis demonstrated a statistically significant weighted mean difference in GLS between the HDP and control group (MD: 3.08%, CI=2.33-3.82, $p<0.001$, Z=8.1) (Figure 2). When analysed including only PE studies, there was also a statistically significant mean difference (MD: 2.98%, 95% CI=1.97-3.99, $p<0.001$, Z=5.79) (Figure 3). There was statistically significant heterogeneity in both the PE ($p<0.001$, Q=188.7, I^2=93%) and HDP ($p<0.001$, Q=200.1, I^2=90%) primary analyses. As such, the post-hoc Egger's test (1997) was performed, suggesting no evidence of publication bias (p=0.235) (see figure S1).

Subgroup and moderator analysis

When studies including women with pre-existing chronic hypertension were excluded, there was a significant mean difference in GLS between HDP and control (MD: 3.19%, 95% CI= 2.37-4.01, p<0.001, Z=7.66), and PE and control (MD: 3.15%, 95% CI=2.1-4.2, p<0.001, Z=5.9) (see figures S2 and S3). Analysis of gestational hypertension-only cohorts revealed a significant mean difference in GLS from the control group (MD: 3.25%, 95% CI= 2.78-3.71, p<0.001, Z=13.73) (figure S4). Furthermore, subgroup analysis of severe-only PE showed a significant mean difference in GLS between severe PE and control (MD: 1.26%, 95% CI= 0.79-1.72, p<0.001, Z=5.30) (figure S5). There was no statistical significance for the moderator variables: strain software, gestational age and mother age. Control group BP did explain some variance, however, not to statistical significance (p=0.05, R^2 0.09). As such, BMI was the only significant moderator (p=0.029, R^2 0.46), with an increase in BMI producing a decrease in mean difference in GLS between HDP and control (see figure S6).

Discussion

This meta-analysis has demonstrated that HDP is associated with greater cardiac maladaptation, evidenced by a significantly reduced GLS compared to normal pregnancy. The mean GLS in women with HDP was -17.4±2.8% vs -20.6±2.3% for normal pregnancy, which is greater than two standard deviations below normal GLS values reported in the general population <40 years of age, and falls below the lowest percentile.[23] This result may have significant clinical implications, since GLS values within the lowest quartile were associated with a 5-fold higher risk of heart failure, 4-fold higher risk of myocardial infarction and 2-fold higher risk of CVD in a low risk general population.[24] Indeed, each 1% reduction in GLS was associated with a 12% increase in the risk of adverse outcomes,[24] which based on our results may translate to a 37% (3.08% weighted mean difference in GLS between HDP and control) increased risk of adverse outcomes in women with HDP compared to normal pregnancy. This assumption is close to the 31% increased 10-year CVD risk (Framingham score) reported in women with preeclampsia compared to women without preeclampsia.[4]

Echocardiography assessment and reporting of GLS is not widely used in the clinical management of HDP or as a screening tool, except for research settings, which enables clinical escalation. Pregnancy may be an important opportunity for early identification of women at increased risk of CVD later in life.[25, 26] Previous work suggests that echocardiography can improve the management of patients with HDP and categorize women into high and low risk.[6] This is not surprising, since a number of studies have reported that women with HDP present with impaired diastolic and systolic myocardial function, adverse biventricular remodelling, hypertrophy, haemodynamic instability and indirect signs of myocardial ischaemia and

fibrosis,[8, 27, 28] which can remain significantly different from women without HDP up to a decade following pregnancy.[12]

The addition of GLS may identify the most vulnerable patients and through a tailored medical management programme, provide an opportunity to improve both maternal and fetal outcomes; for example, reduce utero-placenta hypoperfusion with benefits for fetal growth and therefore prolongation of the pregnancy, reducing prematurity, which may play a key role in ameliorating perinatal morbidity and mortality in pregnancies complicated by HDP. Indeed, abnormalities in myocardial deformation indices are seen early in the development of many pathophysiological states and is highly sensitive at detecting even mild myocardial damage.[24] Previous work has demonstrated that cardiac dysfunction detected using myocardial strain was observable early in pregnancy with relatively normal BP and which predated complications such as pre-eclampsia.[29] This is consistent with other studies, which demonstrated that women at high risk of pre-eclampsia (pre-existing chronic hypertension or history of pre-eclampsia) and who developed recurrent pre-eclampsia showed higher rates of left ventricle remodelling and diastolic dysfunction in mid-gestation compared to those who did not have recurrent pre-eclampsia.[25, 30, 31] It is likely that cardiovascular dysfunction is involved in the pathophysiology of preeclampsia; however, a prospective study using GLS is required in order to attempt to answer this important question. In circumstances where image quality is sub-optimal, it may not be possible to acquire GLS measures, which can be in up to 20% of individuals.[11] However, the use of contrast combined with recent software capable of measuring GLS may eliminate this limitation.[32]

The pathophysiological mechanisms relating HDP with escalated CVD risk in later years is poorly understood, which limits the development of appropriate interventions to prevent future

CVD in these women. Medical management of HDP is well documented[33] and exercise training interventions are established as effective for reducing CVD risk in the general population[34] and in numerous CVD conditions.[35] Importantly, although the mechanisms are unclear, prenatal exercise has been shown to reduce the odds of developing HDP by 40%.[36] As such, exercise interventions that produce advantageous cardiac (improved systolic, diastolic, left ventricular remodelling and myocardial mechanics) and vascular (peripheral vascular resistance) adaptations, which ultimately reduces blood pressure should be regarded as viable interventions for the management and/or prevention of HDP and not limited to traditional aerobic training interventions. Physiological interventions may reduce the requirement for pharmacological management strategies and therefore reduce any unfavourable medical side effects. As such, future prospective research is required to ascertain if GLS has a role in highlighting women who present the greatest risk of persistent cardiac dysfunction and/or hypertension, as well as the role of exercise training during and following HDP.

Limitations

We found significant heterogeneity for both primary outcomes. Attributing this variance to methodological differences, our meta-regression accounted for control group blood pressure, BMI, gestational age, strain software, and mother age, with BMI being the only moderator to explain any of the observed variance to statistical significance (R^2 0.46, p=0.029). Previous research has demonstrated that a higher BMI is associated with worse GLS.[37] The mechanisms underlying obesity associated cardiac dysfunction are likely multifaceted; however, circulating adipose derived hormones, such as leptin, may influence both diastolic function and systolic mechanics.[37,38] Nonetheless, random-effects models were applied to account for such heterogeneity. In addition, only three of the analysed studies were classified as high quality

(NOS of 8 or 9) and thus study quality sensitivity analysis could not be performed, suggesting the need for future publications of greater methodological rigour. The HDP cohorts of two studies in the present analysis[39, 40] did not exclude women with chronic hypertension, resulting in an overlap of participants with gestational hypertension and chronic hypertension.

Perspectives

GLS is significantly impaired in women with HDP and combined with traditional echo parameters may aid the antenatal and postnatal medical management. Longitudinal data suggests HDP women have sustained markers of cardiac impairment, which suggests additional clinical interventions are warranted. Lifestyle changes and exercise training, including novel interventions, which have demonstrated improvements in cardiac and vascular health through improved blood pressure regulation should be investigated.

Sources of Funding: Veronica Giorgione has received funding from the European Union's Horizon 2020 research and innovation programme under the Marie Skłodowska-Curie grant agreement No 765274 (iPLACENTA project).

Disclosures: None.

Reference List

1. Gillon TE, Pels A, von Dadelszen P, MacDonell K, Magee LA. Hypertensive disorders of pregnancy: A systematic review of international clinical practice guidelines. *PLoS One*. 2014;9:e113715
2. Ying W, Catov JM, Ouyang P. Hypertensive disorders of pregnancy and future maternal cardiovascular risk. *J Am Heart Assoc*. 2018;7:e009382
3. Wu R, Wang T, Gu R, Xing D, Ye C, Chen Y, Liu X, Chen L. Hypertensive disorders of pregnancy and risk of cardiovascular disease-related morbidity and mortality: A systematic review and meta-analysis. *Cardiology*. 2020;145:633-647
4. Fraser A, Nelson SM, Macdonald-Wallis C, Cherry L, Butler E, Sattar N, Lawlor DA. Associations of pregnancy complications with calculated cardiovascular disease risk and cardiovascular risk factors in middle age: The avon longitudinal study of parents and children. *Circulation*. 2012;125:1367-1380
5. Khan KS, Wojdyla D, Say L, Gulmezoglu AM, Van Look PF. Who analysis of causes of maternal death: A systematic review. *Lancet*. 2006;367:1066-1074
6. 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
7. Leon LJ, McCarthy FP, Direk K, Gonzalez-Izquierdo A, Prieto-Merino D, Casas JP, Chappell L. Preeclampsia and cardiovascular disease in a large uk pregnancy cohort of linked electronic health records: A caliber study. *Circulation*. 2019;140:1050-1060
8. Melchiorre K, Sutherland GR, Baltabaeva A, Liberati M, Thilaganathan B. Maternal cardiac dysfunction and remodeling in women with preeclampsia at term. *Hypertension*. 2011;57:85-93

9. Cong J, Fan T, Yang X, Squires JW, Cheng G, Zhang L, Zhang Z. Structural and functional changes in maternal left ventricle during pregnancy: A three-dimensional speckle-tracking echocardiography study. *Cardiovasc Ultrasound*. 2015;13:6

10. Leitman M, Lysyansky P, Sidenko S, Shir V, Peleg E, Binenbaum M, Kaluski E, Krakover R, Vered Z. Two-dimensional strain-a novel software for real-time quantitative echocardiographic assessment of myocardial function. *J Am Soc Echocardiogr*. 2004;17:1021-1029

11. Buddeberg BS, Sharma R, O'Driscoll JM, Kaelin Agten A, Khalil A, Thilaganathan B. Cardiac maladaptation in term pregnancies with preeclampsia. *Pregnancy Hypertens*. 2018;13:198-203

12. Countouris ME, Villanueva FS, Berlacher KL, Cavalcante JL, Parks WT, Catov JM. Association of hypertensive disorders of pregnancy with left ventricular remodeling later in life. *J Am Coll Cardiol*. 2021;77:1057-1068

13. Moher D, Liberati A, Tetzlaff J, Altman DG, Group P. Preferred reporting items for systematic reviews and meta-analyses: The prisma statement. *Ann Intern Med*. 2009;151:264-269, W264

14. Stroup DF, Berlin JA, Morton SC, Olkin I, Williamson GD, Rennie D, Moher D, Becker BJ, Sipe TA, Thacker SB. Meta-analysis of observational studies in epidemiology: A proposal for reporting. Meta-analysis of observational studies in epidemiology (moose) group. *JAMA*. 2000;283:2008-2012

15. Hypertension in pregnancy. Report of the american college of obstetricians and gynecologists' task force on hypertension in pregnancy. *Obstet Gynecol*. 2013;122:1122-1131

16. Tranquilli AL, Dekker G, Magee L, Roberts J, Sibai BM, Steyn W, Zeeman GG, Brown MA. The classification, diagnosis and management of the hypertensive

disorders of pregnancy: A revised statement from the isshp. *Pregnancy Hypertens*. 2014;4:97-104

17. Ajmi H, Abid D, Milouchi S, Louati D, Sghaier A, Choura D, Chaaben K, Abid L, Kammoun S. Interest of speckle tracking in the detection of cardiac involvement in pregnant women with hypertensive disorder. *Pregnancy Hypertens*. 2018;11:136-141
18. Ambrozic J, Lucovnik M, Prokselj K, Toplisek J, Cvijic M. Dynamic changes in cardiac function before and early postdelivery in women with severe preeclampsia. *J Hypertens*. 2020;38:1367-1374
19. Yu L, Zhou Q, Peng Q, Yang Z. Left ventricular function of patients with pregnancy-induced hypertension evaluated using velocity vector imaging echocardiography and n-terminal pro-brain natriuretic peptide. *Echocardiography*. 2018;35:459-466
20. Wells GA, Shea B, O'Connell D, Peterson J, Welch V, Losos M, Tugwell P. The newcastle-ottawa scale (nos) for assessing the quality of nonrandomised studies in meta-analyses. http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp#:~:text=The%20Newcastle%2DOttawa%20Scale%20(NOS,nonrandomised%20studies%20in%20meta%2Danalyses&text=It%20was%20developed%20to%20assess,interpretation%20of%20meta%2Danalytic%20results. 2021
21. Huedo-Medina TB, Sanchez-Meca J, Marin-Martinez F, Botella J. Assessing heterogeneity in meta-analysis: Q statistic or i2 index? *Psychol Methods*. 2006;11:193-206
22. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ*. 1997;315:629-634

23. Kuznetsova T, Herbots L, Richart T, D'Hooge J, Thijs L, Fagard RH, Herregods MC, Staessen JA. Left ventricular strain and strain rate in a general population. *Eur Heart J*. 2008;29:2014-2023

24. Biering-Sorensen T, Biering-Sorensen SR, Olsen FJ, Sengelov M, Jorgensen PG, Mogelvang R, Shah AM, Jensen JS. Global longitudinal strain by echocardiography predicts long-term risk of cardiovascular morbidity and mortality in a low-risk general population: The copenhagen city heart study. *Circ Cardiovasc Imaging*. 2017;10 (3):e005521.

25. Thilaganathan B, Kalafat E. Cardiovascular system in preeclampsia and beyond. *Hypertension*. 2019;73:522-531

26. Giorgione V, Ridder A, Kalafat E, Khalil A, Thilaganathan B. Incidence of postpartum hypertension within 2 years of a pregnancy complicated by pre-eclampsia: A systematic review and meta-analysis. *BJOG*. 2021;128:495-503

27. Melchiorre K, Sutherland GR, Watt-Coote I, Liberati M, Thilaganathan B. Severe myocardial impairment and chamber dysfunction in preterm preeclampsia. *Hypertens Pregnancy*. 2012;31:454-471

28. Valensise H, Vasapollo B, Gagliardi G, Novelli GP. Early and late preeclampsia: Two different maternal hemodynamic states in the latent phase of the disease. *Hypertension*. 2008;52:873-880

29. Shahul S, Ramadan H, Mueller A, Nizamuddin J, Nasim R, Lopes Perdigao J, Chinthala S, Tung A, Rana S. Abnormal mid-trimester cardiac strain in women with chronic hypertension predates superimposed preeclampsia. *Pregnancy Hypertens*. 2017;10:251-255

30. Melchiorre K, Sutherland G, Sharma R, Nanni M, Thilaganathan B. Mid-gestational maternal cardiovascular profile in preterm and term pre-eclampsia: A prospective study. *BJOG*. 2013;120:496-504

31. Thilaganathan B. Maternal cardiac dysfunction precedes development of preeclampsia. *Hypertension*. 2020;76:321-322

32. Karagodin I, Carvalho Singulane C, Woodward GM, Xie M, Tucay ES, Tude Rodrigues AC, Vasquez-Ortiz ZY, Alizadehasl A, Monaghan MJ, Ordonez Salazar BA, Soulat-Dufour L, Mostafavi A, Moreo A, Citro R, Narang A, Wu C, Descamps T, Addetia K, Lang RM, Asch FM, Investigators W-C. Echocardiographic correlates of in-hospital death in patients with acute covid-19 infection: The world alliance societies of echocardiography (wase-covid) study. *J Am Soc Echocardiogr*. 2021; S0894-7317(21)00483-1.

33. Brown MA, Magee LA, Kenny LC, Karumanchi SA, McCarthy FP, Saito S, Hall DR, Warren CE, Adoyi G, Ishaku S, International Society for the Study of Hypertension in P. Hypertensive disorders of pregnancy: Isshp classification, diagnosis, and management recommendations for international practice. *Hypertension*. 2018;72:24-43

34. Schroeder EC, Franke WD, Sharp RL, Lee DC. Comparative effectiveness of aerobic, resistance, and combined training on cardiovascular disease risk factors: A randomized controlled trial. *PLoS One*. 2019;14:e0210292

35. Gielen S, Laughlin MH, O'Conner C, Duncker DJ. Exercise training in patients with heart disease: Review of beneficial effects and clinical recommendations. *Prog Cardiovasc Dis*. 2015;57:347-355

36. Davenport MH, Ruchat SM, Poitras VJ, Jaramillo Garcia A, Gray CE, Barrowman N, Skow RJ, Meah VL, Riske L, Sobierajski F, James M, Kathol AJ, Nuspl M,

Marchand AA, Nagpal TS, Slater LG, Weeks A, Adamo KB, Davies GA, Barakat R, Mottola MF. Prenatal exercise for the prevention of gestational diabetes mellitus and hypertensive disorders of pregnancy: A systematic review and meta-analysis. *Br J Sports Med*. 2018;52:1367-1375

37. Ho JE, McCabe EL, Wang TJ, Larson MG, Levy D, Tsao C, Aragam J, Mitchell GF, Benjamin EJ, Vasan RS, Cheng S. Cardiometabolic traits and systolic mechanics in the community. *Circ Heart Fail*. 2017;10

38. Abel ED, Sweeney G. Modulation of the cardiovascular system by leptin. *Biochimie*. 2012;94:2097-2103

39. Shahul S, Medvedofsky D, Wenger JB, Nizamuddin J, Brown SM, Bajracharya S, Salahuddin S, Thadhani R, Mueller A, Tung A, Lang RM, Arany Z, Talmor D, Karumanchi SA, Rana S. Circulating antiangiogenic factors and myocardial dysfunction in hypertensive disorders of pregnancy. *Hypertension*. 2016;67:1273-1280

40. Shahul S, Rhee J, Hacker MR, Gulati G, Mitchell JD, Hess P, Mahmood F, Arany Z, Rana S, Talmor D. Subclinical left ventricular dysfunction in preeclamptic women with preserved left ventricular ejection fraction: A 2d speckle-tracking imaging study. *Circ Cardiovasc Imaging*. 2012;5:734-739

Novelty and Significance

What Is New?

This is the first meta-analysis, which pooled multiple study data to assess differences in global longitudinal strain between women with and without hypertensive disorder of pregnancy.

What is Relevant?

Hypertensive disorders of pregnancy is associated with a clinically significant difference in global longitudinal strain compared to normal pregnancy. The addition of global longitudinal strain in the echocardiographic assessment may identify the most vulnerable patients and provide an opportunity to improve both maternal and fetal outcomes.

Summary

Global longitudinal strain is significantly impaired in women with hypertensive disorders of pregnancy and combined with traditional echo parameters may aid the antenatal and postnatal medical management. Echocardiography should be considered as a screening tool in women with hypertensive disorders of pregnancy to enable early cardiovascular risk prevention through national initiatives.

Figure legends

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

Figure 2: Random-effects meta-analysis of the weighted mean difference in GLS between HDP and control.

Figure 3: Random-effects meta-analysis of the weighted mean difference in GLS between PE and control.

Table 1. Characteristics of included studies

Authors (year)	Country	Study type	Exclusion criteria	Software	NOS	Group	N°	GLS±SD (%)	Mean GA±SD (weeks)
Ajmi et al. (2018)	Tunisia	Case-control	Ejection fraction <55%, poor quality pictures, pre-existing cardiac, pulmonary, renal disease	NR	7	HDP	30	-18±3	32
						Control	30	-21±2	33
Ambrožič et al. (2020)	Slovenia	Case-control	Pre-existing or gestational hypertension and/or diabetes mellitus, congenital or acquired heart disease or a history of smoking, alcohol or drug abuse	GE EchoPac	7	PE	30	-21.4±2	4 days postpartum
						Control	30	-23±1.4	4 days postpartum
Buddeberg et al. (2018)	UK	Case-control	Any cardiovascular co-morbidity, multiple gestations	GE EchoPac	5	PE	30	-13.32±2.37	38.26±1.54
						Control	40	-17.61±1.89	39.31±1.02
Cho et al. (2011)	South Korea	Case-control	Pre-existing diabetes mellitus, essential hypertension or symptomatic coronary artery disease	GE EchoPac	4	GH	106	-17.6±2.95	33.3±3.6
						Control	93	-21.2±2.14	3.6±3.4
Cong et al. (2015)	China	Case-control	NR	GE EchoPac (3D STE)	7	EOPE	43	-15.74±3.19	28.94±2.71
						Control	41	-19.74±2.39	28.2±2.93
						LOPE	41	-15.41±2.7	36.43±1.29

						Control	40	-18.28±3.14	36.39±1.29
Levine et al. (2019)	USA	Case-control	Pre-existing cardiovascular disease, chronic hypertension or multiple gestations	TomTec	8	PE	29	-12.94±3.4	31.3±3.9
						Control	29	-15.06±3.1	31.7±3.61
Mostafavi et al. (2019)	Iran	Case-control	Low imaging quality, high blood pressure, pre-existing diabetes, and other abnormal findings such as 1) abnormal dilation in at least one of the 4 cardiac chambers; 2) ejection fraction < 55%, 3) right ventricular dilatation or hypokinesia, 4) moderate or worse valvular disorders, 4) pericardial effusion, 5) uncorrected cognitive state, 6) congenital heart disease, and 6) diastolic disturbances	Philips Epic 7	6	PE	60	-18.69±2.28	33.4±3.54
						Control	40	-19.39±3.49	32.25±4.65
Pan et al. (2019)	China	Case-control	Pre-existing co-morbidities, smoking, multiple gestations	GE EchoPac	7	PE	33	-15.8±3.2	34.7±5
						Control	20	-16.8±3	34.7±3.4
Paudel et al. (2020)	Turkey	Case-control	Pre-existing hypertension or cardiac disease, gestational diabetes, renal or hepatic disease, multiple gestations, alcohol or cigarette users	QLAB Philips	7	PE	55	-18±2.6	33±4
						Control	35	19.8±2.1	34±3
Shahul et al. (2016)	USA	Case-control	Pre-existing ischemic or valvular heart disease, pulmonary disease, diabetes mellitus, or labor.	Tomtec	7	PE	62	-18.9±3.3	32.8±3.7
						GH or CHT	40	-21.2±3.6	34.4±5.2
						Control	105	-23.9±2.7	30.7±4.3

Shahul et al. (2012)	USA	Case-control	Pre-existing cardiovascular disease, pulmonary disease, and diabetes mellitus	TomTec	5	PE	11	-13.7±4.6	36.6±3.34
						GH or CHT	11	-15.9±1.33	36.4±3.48
						Control	17	-20.1±3.48	38±2.97
Sun et al. (2020)	China	Case-control	Pre-existing chronic hypertension, multiple gestations, heart disease, pulmonary hypertension, renal disease, diabetes, systemic lupus erythematosus, any connective tissue disease, antiphospholipid syndrome, indeterminate diastolic function	Tomtec	8	PE	132	-19.15±2.65	30.64±4.92
						Control	87	-21.09±2.74	31.87±3.62
Vaught et al. (2018)	USA	Case-control	Pre-existing valvular or congenital heart disease, cardiomyopathy, pulmonary hypertension, prior cardiac surgery, pulmonary embolism, systemic lupus erythematosus, any connective tissue disease, antiphospholipid syndrome, or interstitial lung disease, multiple gestations	Epsilon	8	PE	63	-19.1±1.5	33.1±3.6
						Control	36	-20.1±1.5	31.8±4.9
Yu et al. (2018)	China	Case-control	Gestational diabetes, or pre-existing hypertension or cardiovascular disease, multiple gestations	VVI	5	PE	25	-13.7±3.1	32±6
						GH	27	-17.4±3.31	34±3
						Control	30	-21.9±3.88	33±4
Zamen et al. (2018)	India		GA less than 34 weeks, cardiac disease (e.g., structural heart disease coronary	QLAB Philips	4	PE	30	-15.63±1.69	35±2.8

		Case-control	heart disease, cardiomyopathies, etc.), chronic or gestational hypertension, renal impairment, multiple gestations, Diabetes mellitus, Obesity, Moderate to severe anemia.			Control	30	-20.86±1.52	35±1.1