Cardiovascular disease risk in women with a history of preeclampsia

General Introduction

INTRODUCTION

Preeclampsia (PE) is a pregnancy-related cardiovascular hypertensive disorder, complicating 3-5% of all pregnancies[1, 2]. Clinically, it is diagnosed as new-onset hypertension after 20 weeks of gestational age along with de novo proteinuria (0.3g/day)[3], although currently hypertension along with growth restriction or HELLP (hemolysis, elevated liver enzymes and low platelets) syndrome are also viewed upon as preeclampsia[4]. Preeclampsia has on the one hand major short time implications as it is one of the primary causes of fetal and maternal morbidity and mortality[5, 6]. On the other hand, PE has important long term sequela as it increases the risk for premature cardiovascular disease (CVD) later in life[7, 8]. Women with a history of PE have an about two – to sevenfold increased risk of developing ischemic cardiac disease compared with healthy controls within 15 years after pregnancy, with the highest risk accounting for early-onset PE[7]. Moreover, former preeclamptic women have a four-fold risk of developing chronic hypertension within 15 years after pregnancy[7].

Pregnancy is a women sensitive cardiovascular stress test that can, if valued appropriately, substantially change the remote cardiovascular health prognosis of women in the near future (Figure 1). Recent studies indicate that at least 1 in 4 former preeclamptic women have structural cardiac alterations, mostly concentric, consistent with heart failure stage B (HF-B) at least one year after delivery[8]. It is unknown whether or not these women are at one year postpartum still in their recovering phase from hypertensive complicated pregnancy or that this unfavorable state persists and preludes imminent cardiac dysfunction and disease.

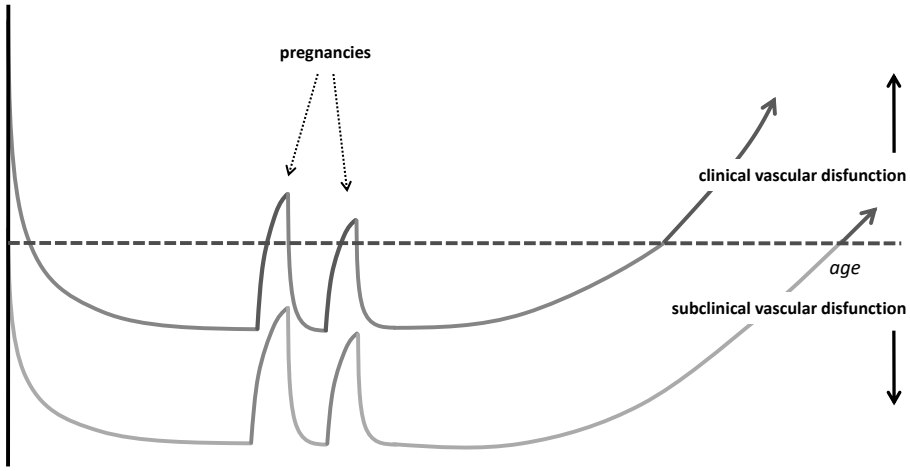


Figure 1: Pregnancy as cardiovascular risk test.

Despite the recognition by the American Heart Association of PE being an independent gender-specific CVD risk factor, no standardized follow-up screening or preventive programs are yet implemented in clinical care[9]. Several initiatives have emerged developing very divers and unstandardized CVD assessments programs at divergent intervals after PE.

CVD IN WOMEN

Cardiovascular disease is the number one cause of death in women[10, 11]. CVD include coronary heart disease, cerebrovascular disease, peripheral arterial disease, rheumatic heart disease, congenital heart disease, deep vein thrombosis and pulmonary embolism[12]. Although more men than women are affected by CVD, more women than men die of it. In the Netherlands, each day, 53 women and 50 men die each day due to CVD[13]. The number of patients worldwide affected by heart failure (HF) are over 23 million[14]. The prevalence is rising due to increased cardiovascular riskfactor comorbidities and higher life expectancy, thus the target group that is expected to benefit from therapy is growing[14]. HF is a major public health issue, associated with significant morbidity, mortality, and healthcare expenditures and costs in the past decade over $39 billion annually in the USA alone[14, 15]. The lifetime risk of developing HF is one in five with a 5-year mortality that corresponds to those of many cancers[14]. Instead of being a single entity, HF is a deadly clinical syndrome with possible different characteristics depending on age, sex, race or ethnicity, systolic and diastolic function and the underlying risk etiology. Once clinical, most of these HF entities (especially with preserved ejection fraction (EF)) do not respond to pharmacotherapy.

The American College of Cardiology Foundation/American Heart Association (ACCF/AHA) Task Force developed a new classification system of heart failure[16]. These stages represent the development and progression of the disease, from risk factors, to structural cardiac changes in absence of clinical complaint to clinical overt disease (Figure 2). Figure 2 is showing a simplistic reproduction of the four stages, using guidelines of the World Health Organization and the ACCF/AHA to determine the cut-off values of the different entities[16-18]. Using the term heart failure stage A and B is subject of discussion, because these are clearly not heart failure[16]. However, when viewed upon as tool to identify young women at risk for developing heart failure, this chronology may be helpful in timely detection of those at risk[16]. In the suggested chronology, heart failure progresses through four stages; the subclinical stages A and B and the clinical stages C and D[16]. The progression of the subclinical heart failure stage B to the clinical heart failure stage C is associated with a five-fold increased risk of death[19].

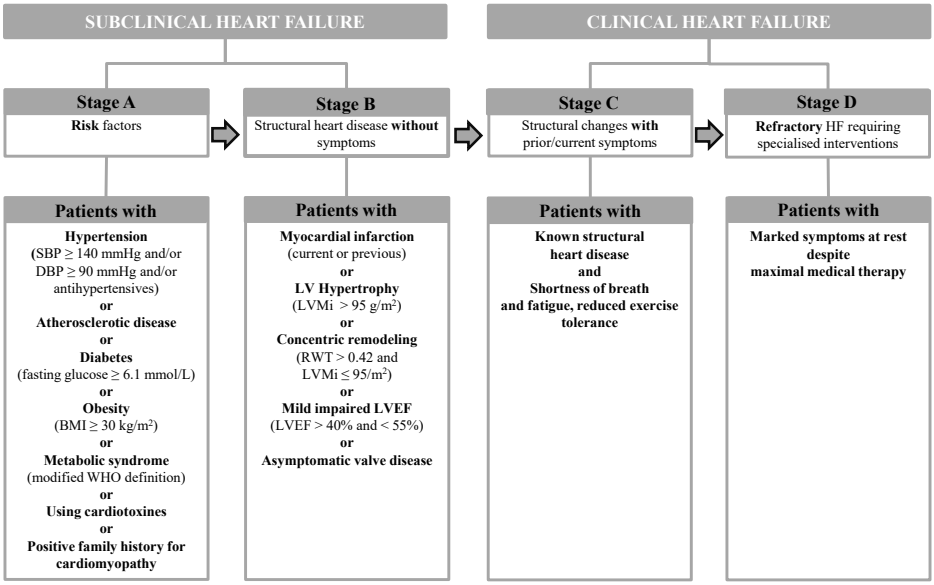


Figure 2: Heart failure stages[16-18].

There are risk models to calculate this person-specific CVD risk score, like the Framingham risk score, SCORE, CUORE and the Reynolds risk score[20, 21]. The Framingham risk score is the most widely used risk scoring calculator in North American Countries[20]. However, there are also a few disadvantages using this risk score. If preeclampsia is viewed upon as a cardiovascular incident, the Framingham risk score, originally developed in a population with elder men and women, may underestimate CVD risk in these relative young women[22, 23]. None of the other risk scores has been validated in a younger cohort.

CONVENTIONAL AND WOMEN SPECIFIC CV RISK FACTORS

PE and CVD share similar risk factors including hypertension, insulin resistance, obesity, lipid abnormalities and endothelial dysfunction[24-26]. With timely detection, these factors may be modifiable by lifestyle or pharmacological intervention[9, 27], emphasizing the importance of cardiovascular follow-up in these patients. Quantifying the person-specific CVD risk could be useful in counseling these patients.

The prevalence of hypertension after PE is 25% in the 4-10 years after delivery[28]. Prior to overt disease, elevated blood pressure preludes to left ventricular (LV) hypertrophy which can lead to ventricular diastolic dysfunction and is also a risk factor for myocardial infarction, which causes left ventricular systolic function[29]. As such, elevated blood pressure forms a major risk factor in the development of HF with clinical symptoms, both

with preserved ejection fraction (HFpEF) and reduced ejection fraction (HFrEF)[29-31]. Hypertension relates more to congestive HF in women than in men[30].

The prevalence of obesity in former preeclamptic women is 13% after their complicated pregnancy, in the first months postpartum[32]. Obesity is a major independent risk factor for CVD, particularly amongst women[33]. As excessive adipose tissue increases a variety of adaptations, alterations in cardiac structure will occur, even in absence of comorbidities[34, 35]. In women with a history of PE, dyslipidemia (impaired HDL and impaired triglycerides) occurred in approximately 18% of the women in the first years postpartum[36]. Dyslipidemia is a strong risk factor for CVD, by facilitating the formation of atherosclerotic soft plaques[25, 37]. The prevalence of insulin resistance after PE is 42%-53% in the first years postpartum[36]. Insulin resistance stimulates atherogenesis and plaque progression, the mechanisms which are likely to be involved in these processes include systemic factors (like dyslipidemia, hypertension, pro-inflammatory state) and a disturbed insulin signaling[38]. Moreover, insulin resistance drives the development of atherogenic dyslipidemia, creates a low-grade inflammatory state and rises the release of inflammatory markers[39]. Furthermore, insulin resistance also associates to increased blood pressure and intrinsic endothelial cell dysfunction[39]. Besides the influence of insulin resistance on the endothelium, all the above cardiovascular risk factors also extrinsically affect endothelial function[40]. Endothelial function seems to be significantly lower in preeclamptic women compared with women with uncomplicated pregnancies[41]. The endothelium, a monolayer of endothelial cells, functions as a protective barrier between the circulating blood and all tissues[42]. Preeclampsia is thought to be jeopardizing both placental and endothelial function, by an interaction between different mechanical and biochemical underlying disorders[43-46]. The flow-mediated dilation (FMD) is a well-established and non-invasive technique to assess part of the endothelial function by measuring the change in artery diameter in response to reactive hyperaemia, a function test indicative for cardiovascular health and disease[41, 47].

CARDIAC REMODELING DURING PREGNANCY

Cardiac remodeling is determined as change in size, shape and/or structure of the heart[2, 48]. To maintain adequate pumping capacity, in response to either volume or pressure overload, the heart uses cardiac remodeling as an important compensatory mechanism[2]. Cardiac remodeling can be divided in either eccentric or concentric remodeling[2, 49]. This division is based on the left ventricular mass (LVM) and the ratio of LV wall thickness to end-diastolic volume, the so-called relative wall thickness (RWT)[2, 18].

A first detectable systemic change during pregnancy is systemic arterial vasodilatation, leading to decreased vascular resistance and with it a decreased afterload, initiating

renin-angiotensin-aldosterone orchestrated plasma volume expansion[50-53]. The reduced afterload also stimulates baroreceptor activity, rising heart rate and cardiac contractility and with it stroke volume and cardiac output[53].

Elevated plasma volume during pregnancy increases venous return resulting in a higher preload, which is also reflected in elevated left atrial volumes[54, 55]. This high preload along with the vasoactive (neuro)hormonal environment, initiates a volume dependent remodeling response of the heart characterized by LV geometric changes and spherical dilatation along the LV short axis[49, 54, 56, 57]. At term, due to the persistent volume overload, the ventricle compensates this by enlargement to preserve stroke volume at the expense of a higher end systolic wall stress[54]. This results in an increase in the left ventricular mass by 35%[54]. This remodeling process is also called eccentric hypertrophy, which is an increase in cardiac mass with increased chamber volume[58].

Pregnancy complicated by preeclampsia is often paralleled by suboptimal plasma volume expansion, which could be inhibited in the absence of a concomitant increase in capacity of the venous storage due to an adverse response of the autonomic control of the cardiovascular system and or of a lack of rice in vascular compliance, which suggest that the adaptive capacity of the venous system is limited in these women[53, 59]. These women also have higher sympathetic activity to preserve the venous return at the expense of cardiovascular reserves[60, 61]. Women with preterm PE show a higher total vascular resistance index and a lower cardiac index in the phase prior to overt disease[62].

In women destined to develop preterm PE, this low cardiac output/ high total vascular resistance hemodynamic state suggests that there is even at mid-gestation, an elevated LV afterload and contracted circulating volume, which triggers also a cardiac remodeling process characterized by LV concentric remodeling or total altered geometry[62]. This process is needed to minimize the higher wall stress that occurs with the elevated afterload[62].

CARDIAC REMODELING AFTER PREGNANCY

During a normal pregnancy, the physiologic LV remodeling resolves in the first weeks postpartum[63]. In contrast, the cardiovascular implications of PE do not end with delivery[8]. The additional increase in LVM in women with PE does not always resolve after delivery[8, 63]. It was observed that four-in-ten former preterm PE women still present abnormal LV geometry 1 year after their complicated pregnancy[8]. Certain antihypertensive medication (mainly angiotensin-converting enzyme inhibitors and angiotensin receptor blockers) have a protective and inhibitory effect on adverse cardiac remodeling[16, 64].

Our group studied the relationship of PE and conventional modifiable cardiovascular risk factors that are related with asymptomatic structural and functional cardiac abnormalities postpartum[28]. After adjusting for conventional risk factors, preeclampsia

remained independently associated with a four-fold increased risk of having subclinical HF-B[28]. Currently, it is still unknown whether these women already had cardiovascular abnormalities prior to their pregnancy and that preeclampsia reveals this condition or that healthy women develop preeclampsia and that preeclampsia itself damages the cardiovascular system.

Currently, we suppose that hemodynamic assessments of both the vasculature and the heart is essential in the understanding, prediction and possible therapies of cardiovascular disease in this specific population[2].

AIM OF THIS THESIS

Although studies have indicated that preeclampsia increases the cardiovascular disease risk, the pathologic process and cardiovascular determinants of this increased risk remains unclear. We first assessed meta-analytically in a systematic review, the natural course of systolic function during normal pregnancy and during preeclamptic pregnancy (CHAPTER 2). In order to improve follow-up in former preeclamptic women it is of importance to gain more knowledge on factors that increase CV risk in these women. At present there is no tailored risk score available to predict cardiovascular disease in young, seemingly healthy former preeclamptic women. Therefore, we estimated the predicted risk of cardiovascular disease in the next 10 and 30 years as computed with the Framingham risk score calculator in former preeclamptic women and women with an uncomplicated pregnancy. Moreover, we compared subgroups based on onset of preeclampsia and/or whether hypertension was developed (CHAPTER 3). Thereafter, we studied the development and recovery of subclinical heart failure in former preeclamptic women between 1 and 4 years postpartum (CHAPTER 4). To obtain further insight in the relation between subclinical heart failure and impaired endothelial function after PE, we assessed flow mediated dilation and echocardiography in women with and without subclinical heart failure and a control group of healthy parous women (CHAPTER 5). Finally, we assessed whether cardiac preload, as indicated by low plasma volume measured in former preeclamptic women is related to concentric remodeling 4 years later (CHAPTER 6).

The main findings of this thesis are discussed in the context of each other in the last chapter (CHAPTER 7)

REFERENCES

1. Roberts JM and Cooper DW. Pathogenesis and genetics of pre-eclampsia. *Lancet*. 2001;357:53-6.
2. Ghossein-Doha C, Khalil A and Lees CC. Maternal hemodynamics: a 2017 update. *Ultrasound in obstetrics & gynecology : the official journal of the International Society of Ultrasound in Obstetrics and Gynecology*. 2017;49:10-14.
3. Brown MA, Lindheimer MD, de Swiet M, Van Assche A and Moutquin JM. The classification and diagnosis of the hypertensive disorders of pregnancy: statement from the International Society for the Study of Hypertension in Pregnancy (ISSHP). *Hypertension in pregnancy*. 2001;20:IX-XIV.
4. Brown MA, Magee LA, Kenny LC, Karumanchi SA, McCarthy FP, Saito S, Hall DR, Warren CE, Adoyi G and Ishaku S. The hypertensive disorders of pregnancy: ISSHP classification, diagnosis & management recommendations for international practice. *Pregnancy hypertension*. 2018;13:291-310.
5. Zhang J, Meikle S and Trumble A. Severe maternal morbidity associated with hypertensive disorders in pregnancy in the United States. *Hypertension in pregnancy*. 2003;22:203-12.
6. ACOG practice bulletin. Diagnosis and management of preeclampsia and eclampsia. Number 33, January 2002. *Obstetrics and gynecology*. 2002;99:159-67.
7. Bellamy L, Casas JP, Hingorani AD and Williams DJ. Pre-eclampsia and risk of cardiovascular disease and cancer in later life: systematic review and meta-analysis. *BMJ (Clinical research ed)*. 2007;335:974.
8. Melchiorre K, Sutherland GR, Liberati M and Thilaganathan B. Preeclampsia is associated with persistent postpartum cardiovascular impairment. *Hypertension*. 2011;58:709-15.
9. Mosca L, Benjamin EJ, Berra K, Bezanson JL, Dolor RJ, Lloyd-Jones DM, Newby LK, Pina IL, Roger VL, Shaw LJ, Zhao D, Beckie TM, Bushnell C, D'Armiento J, Kris-Etherton PM, Fang J, Ganiats TG, Gomes AS, Gracia CR, Haan CK, Jackson EA, Judelson DR, Kelepouris E, Lavie CJ, Moore A, Nussmeier NA, Ofili E, Oparil S, Ouyang P, Pinn VW, Sherif K, Smith SC, Jr., Sopko G, Chandra-Strobos N, Urbina EM, Vaccarino V and Wenger NK. Effectiveness-based guidelines for the prevention of cardiovascular disease in women--2011 update: a guideline from the american heart association. *Circulation*. 2011;123:1243-62.
10. Go AS, Mozaffarian D, Roger VL, Benjamin EJ, Berry JD, Blaha MJ, Dai S, Ford ES, Fox CS, Franco S, Fullerton HJ, Gillespie C, Hailpern SM, Heit JA, Howard VJ, Huffman MD, Judd SE, Kissela BM, Kittner SJ, Lackland DT, Lichtman JH, Lisabeth LD, Mackey RH, Magid DJ, Marcus GM, Marelli A, Matchar DB, McGuire DK, Mohler ER, 3rd, Moy CS, Mussolino ME, Neumar RW, Nichol G, Pandey DK, Paynter NP, Reeves MJ, Sorlie PD, Stein J, Towfighi A, Turan TN, Virani SS, Wong ND, Woo D, Turner MB, American Heart Association Statistics C and Stroke Statistics S. Heart disease and stroke statistics--2014 update: a report from the American Heart Association. *Circulation*. 2014;129:e28-e292.
11. Mosca L, Barrett-Connor E and Wenger NK. Sex/gender differences in cardiovascular disease prevention: what a difference a decade makes. *Circulation*. 2011;124:2145-54.
12. World Health Organization. Media centre. Cardiovascular diseases (CVDs). Fact Sheet. Reviewed may 2017. http://www.who.int/mediacentre/factsheets/fs317/en/.
13. Hartstichting. Cijfers hart- en vaatziekten. 2019. https://www.hartstichting.nl/hart-en-vaatziekten/feiten-en-cijfers-hart-en-vaatziekten.
14. Bui AL, Horwich TB and Fonarow GC. Epidemiology and risk profile of heart failure. *Nature reviews Cardiology*. 2011;8:30-41.
15. Lloyd-Jones D, Adams RJ, Brown TM, Carnethon M, Dai S, De Simone G, Ferguson TB, Ford E, Furie K, Gillespie C, Go A, Greenlund K, Haase N, Hailpern S, Ho PM, Howard V, Kissela B, Kittner S, Lackland D, Lisabeth L, Marelli A, McDermott MM, Meigs J, Mozaffarian D, Mussolino M, Nichol G, Roger VL, Rosamond W, Sacco R, Sorlie P, Roger VL, Thom T, Wasserthiel-Smoller S, Wong ND and Wylie-Rosett J.

Heart disease and stroke statistics—2010 update: a report from the American Heart Association. *Circulation*. 2010;121:e46-e215.

16. Jessup M, Abraham WT, Casey DE, Feldman AM, Francis GS, Ganiats TG, Konstam MA, Mancini DM, Rahko PS, Silver MA, Stevenson LW and Yancy CW. 2009 focused update: ACCF/AHA Guidelines for the Diagnosis and Management of Heart Failure in Adults: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines: developed in collaboration with the International Society for Heart and Lung Transplantation. *Circulation*. 2009;119:1977-2016.
17. Alberti KG and Zimmet PZ. Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: diagnosis and classification of diabetes mellitus provisional report of a WHO consultation. *Diabetic medicine : a journal of the British Diabetic Association*. 1998;15:539-53.
18. Lang RM, Bierig M, Devereux RB, Flachskampf FA, Foster E, Pellikka PA, Picard MH, Roman MJ, Seward J, Shanewise JS, Solomon SD, Spencer KT, Sutton MS and Stewart WJ. Recommendations for chamber quantification: a report from the American Society of Echocardiography's Guidelines and Standards Committee and the Chamber Quantification Writing Group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology. *Journal of the American Society of Echocardiography : official publication of the American Society of Echocardiography*. 2005;18:1440-63.
19. Ammar KA, Jacobsen SJ, Mahoney DW, Kors JA, Redfield MM, Burnett JC, Jr. and Rodeheffer RJ. Prevalence and prognostic significance of heart failure stages: application of the American College of Cardiology/American Heart Association heart failure staging criteria in the community. *Circulation*. 2007;115:1563-70.
20. Hermes W, Tamsma JT, Grootendorst DC, Franx A, van der Post J, van Pampus MG, Bloemenkamp KW, Porath M, Mol BW and de Groot CJ. Cardiovascular risk estimation in women with a history of hypertensive pregnancy disorders at term: a longitudinal follow-up study. *BMC pregnancy and childbirth*. 2013;13:126.
21. Berks D, Hoedjes M, Raat H, Duvekot JJ, Steegers EA and Habbema JD. Risk of cardiovascular disease after pre-eclampsia and the effect of lifestyle interventions: a literature based study. *BJOG : an international journal of obstetrics and gynaecology*. 2013;120:924-31.
22. D'Agostino RB, Sr., Vasan RS, Pencina MJ, Wolf PA, Cobain M, Massaro JM and Kannel WB. General cardiovascular risk profile for use in primary care: the Framingham Heart Study. *Circulation*. 2008;117:743-53.
23. Pencina MJ, D'Agostino RB, Sr., Larson MG, Massaro JM and Vasan RS. Predicting the 30- year risk of cardiovascular disease: the framingham heart study. *Circulation*. 2009;119:3078-84.
24. English FA, Kenny LC and McCarthy FP. Risk factors and effective management of preeclampsia. *Integrated blood pressure control*. 2015;8:7-12.
25. Benjamin EJ, Blaha MJ, Chiuve SE, Cushman M, Das SR, Deo R, de Ferranti SD, Floyd J, Fornage M, Gillespie C, Isasi CR, Jimenez MC, Jordan LC, Judd SE, Lackland D, Lichtman JH, Lisabeth L, Liu S, Longenecker CT, Mackey RH, Matsushita K, Mozaffarian D, Mussolino ME, Nasir K, Neumar RW, Palaniappan L, Pandey DK, Thiagarajan RR, Reeves MJ, Ritchey M, Rodriguez CJ, Roth GA, Rosamond WD, Sasson C, Towfighi A, Tsao CW, Turner MB, Virani SS, Voeks JH, Willey JZ, Wilkins JT, Wu JH, Alger HM, Wong SS and Muntner P. Heart Disease and Stroke Statistics-2017 Update: A Report From the American Heart Association. *Circulation*. 2017;135:e146-e603.
26. Craici I, Wagner S and Garovic VD. Preeclampsia and future cardiovascular risk: formal risk factor or failed stress test? *Therapeutic advances in cardiovascular disease*. 2008;2:249-59.

27. Brown MC, Best KE, Pearce MS, Waugh J, Robson SC and Bell R. Cardiovascular disease risk in women with pre-eclampsia: systematic review and meta-analysis. *European journal of epidemiology*. 2013;28:1-19.
28. Ghossein-Doha C, van Neer J, Wissink B, Breetveld NM, de Windt LJ, van Dijk AP, van der Vlugt MJ, Janssen MC, Heidema WM, Scholten RR and Spaanderman ME. Pre-eclampsia: an important risk factor for asymptomatic heart failure. *Ultrasound in obstetrics & gynecology : the official journal of the International Society of Ultrasound in Obstetrics and Gynecology*. 2017;49:143-149.
29. Vasan RS and Levy D. The role of hypertension in the pathogenesis of heart failure. A clinical mechanistic overview. *Archives of internal medicine*. 1996;156:1789-96.
30. Levy D, Larson MG, Vasan RS, Kannel WB and Ho KK. The progression from hypertension to congestive heart failure. *Jama*. 1996;275:1557-62.
31. Kostis JB. From hypertension to heart failure: update on the management of systolic and diastolic dysfunction. *American journal of hypertension*. 2003;16:18s-22s.
32. Hooijschuur MC, Ghossein-Doha C, Al-Nasiry S and Spaanderman ME. Maternal metabolic syndrome, preeclampsia, and small for gestational age infancy. *American journal of obstetrics and gynecology*. 2015;213:370 e1-7.
33. Hubert HB, Feinleib M, McNamara PM and Castelli WP. Obesity as an independent risk factor for cardiovascular disease: a 26-year follow-up of participants in the Framingham Heart Study. *Circulation*. 1983;67:968-77.
34. Poirier P, Giles TD, Bray GA, Hong Y, Stern JS, Pi-Sunyer FX and Eckel RH. Obesity and cardiovascular disease: pathophysiology, evaluation, and effect of weight loss: an update of the 1997 American Heart Association Scientific Statement on Obesity and Heart Disease from the Obesity Committee of the Council on Nutrition, Physical Activity, and Metabolism. *Circulation*. 2006;113:898-918.
35. Poirier P, Martin J, Marceau P, Biron S and Marceau S. Impact of bariatric surgery on cardiac structure, function and clinical manifestations in morbid obesity. *Expert review of cardiovascular therapy*. 2004;2:193-201.
36. Heidema WM, Scholten RR, van Drongelen J and Spaanderman MEA. Metabolic Syndrome After Preeclamptic Pregnancy: A Longitudinal Cohort Study. *Journal of women's health (2002)*. 2019;28:357-362.
37. Nelson RH. Hyperlipidemia as a risk factor for cardiovascular disease. *Primary care*. 2013;40:195-211.
38. Bornfeldt KE and Tabas I. Insulin resistance, hyperglycemia, and atherosclerosis. *Cell metabolism*. 2011;14:575-85.
39. Laakso M and Kuusisto J. Insulin resistance and hyperglycaemia in cardiovascular disease development. *Nature reviews Endocrinology*. 2014;10:293-302.
40. Hadi HA, Carr CS and Al Suwaidi J. Endothelial dysfunction: cardiovascular risk factors, therapy, and outcome. *Vascular health and risk management*. 2005;1:183-98.
41. Weissgerber TL, Milic NM, Milin-Lazovic JS and Garovic VD. Impaired Flow-Mediated Dilation Before, During, and After Preeclampsia: A Systematic Review and Meta-Analysis. *Hypertension*. 2016;67:415-23.
42. Verma S, Buchanan MR and Anderson TJ. Endothelial function testing as a biomarker of vascular disease. *Circulation*. 2003;108:2054-9.
43. Powe CE, Levine RJ and Karumanchi SA. Preeclampsia, a disease of the maternal endothelium: the role of antiangiogenic factors and implications for later cardiovascular disease. *Circulation*. 2011;123:2856-69.
44. Brennan LJ, Morton JS and Davidge ST. Vascular dysfunction in preeclampsia. *Microcirculation*. 2014;21:4-14.
45. Scholten RR, Hopman MT, Sweep FC, Van de Vlugt MJ, Van Dijk AP, Oyen WJ, Lotgering FK and Spaanderman ME. Co-occurrence of cardiovascular and prothrombotic risk factors in women with a history of preeclampsia. *Obstetrics and gynecology*. 2013;121:97-105.

46. Roberts JM. Endothelial dysfunction in preeclampsia. *Seminars in reproductive endocrinology*. 1998;16:5-15.
47. Weissgerber TL. Flow-mediated dilation: can new approaches provide greater mechanistic insight into vascular dysfunction in preeclampsia and other diseases? *Current hypertension reports*. 2014;16:487.
48. Gaasch WH and Zile MR. Left ventricular structural remodeling in health and disease: with special emphasis on volume, mass, and geometry. *Journal of the American College of Cardiology*. 2011;58:1733-40.
49. Cantor EJ, Babick AP, Vasanji Z, Dhalla NS and Netticadan T. A comparative serial echocardiographic analysis of cardiac structure and function in rats subjected to pressure or volume overload. *Journal of molecular and cellular cardiology*. 2005;38:777-86.
50. Andrietti S, Kruse AJ, Bekkers SC, Sep S, Spaanderman M and Peeters LL. Cardiac adaptation to pregnancy in women with a history of preeclampsia and a subnormal plasma volume. *Reprod Sci*. 2008;15:1059-65.
51. Duvekot JJ and Peeters LL. Renal hemodynamics and volume homeostasis in pregnancy. *Obstetrical & gynecological survey*. 1994;49:830-9.
52. de Haas S, Ghossein-Doha C, van Kuijk SM, van Drongelen J and Spaanderman ME. Physiological adaptation of maternal plasma volume during pregnancy: a systematic review and meta-analysis. *Ultrasound in obstetrics & gynecology : the official journal of the International Society of Ultrasound in Obstetrics and Gynecology*. 2017;49:177-187.
53. Spaanderman M, Ekhart T, van Eyck J, de Leeuw P and Peeters L. Preeclampsia and maladaptation to pregnancy: a role for atrial natriuretic peptide? *Kidney Int*. 2001;60:1397-406.
54. Melchiorre K, Sharma R, Khalil A and Thilaganathan B. Maternal Cardiovascular Function in Normal Pregnancy: Evidence of Maladaptation to Chronic Volume Overload. *Hypertension*. 2016;67:754-62.
55. Duvekot JJ and Peeters LL. Maternal cardiovascular hemodynamic adaptation to pregnancy. *Obstetrical & gynecological survey*. 1994;49:S1-14.
56. Ghossein-Doha C, Hooijschuur MCE and Spaanderman MEA. Pre-Eclampsia: A Twilight Zone Between Health and Cardiovascular Disease? *Journal of the American College of Cardiology*. 2018;72:12-16.
57. Spinale FG. Myocardial matrix remodeling and the matrix metalloproteinases: influence on cardiac form and function. *Physiological reviews*. 2007;87:1285-342.
58. Hill JA and Olson EN. Cardiac plasticity. *N Engl J Med*. 2008;358:1370-80.
59. Spaanderman ME, Willekes C, Hoeks AP, Ekhart TH and Peeters LL. The effect of pregnancy on the compliance of large arteries and veins in healthy parous control subjects and women with a history of preeclampsia. *American journal of obstetrics and gynecology*. 2000;183:1278-86.
60. Aardenburg R, Spaanderman ME, Ekhart TH, van Eijndhoven HW, van der Heijden OW and Peeters LL. Low plasma volume following pregnancy complicated by pre-eclampsia predisposes for hypertensive disease in a next pregnancy. *British journal of obstetrics and gynaecology*. 2003;110:1001-6.
61. Scholten RR, Sep S, Peeters L, Hopman MT, Lotgering FK and Spaanderman ME. Prepregnancy low-plasma volume and predisposition to preeclampsia and fetal growth restriction. *Obstetrics and gynecology*. 2011;117:1085-93.
62. Melchiorre K, Sutherland G, Sharma R, Nanni M and Thilaganathan B. Mid-gestational maternal cardiovascular profile in preterm and term pre-eclampsia: a prospective study. *BJOG : an international journal of obstetrics and gynaecology*. 2013;120:496-504.
63. Simmons LA, Gillin AG and Jeremy RW. Structural and functional changes in left ventricle during normotensive and preeclamptic pregnancy. *American journal of physiology Heart and circulatory physiology*. 2002;283:H1627-33.
64. Goldberg LR and Jessup M. Stage B heart failure: management of asymptomatic left ventricular systolic dysfunction. *Circulation*. 2006;113:2851-60.

Adaptation of cardiac systolic function to pregnancy: a systematic review and meta- analysis

S. de Haas[1], N.M. Breetveld[1], L. Geerts[1], S.M.J. van Kuijk[2], J. van Drongelen[3], Z. Mohseni[1], M.E.A. Spaanderman[1], C. Ghossein-Doha[4]

[1] *Department of Obstetrics and Gynaecology, Research School GROW, Maastricht University Medical Centre (MUMC+), Maastricht, The Netherlands*

[2] *Department of Clinical Epidemiology and Medical Technology Assessment (KEMTA), Maastricht University Medical Centre (MUMC+), Maastricht, The Netherlands*

[3] *Department of Obstetrics and Gynecology, Radboud University Medical Centre (Radboudumc), Nijmegen, The Netherlands*

[4] *Department of Cardiology, Maastricht University Medical Center (MUMC+), The Netherlands*

To be submitted to Journal of Hypertension

ABSTRACT

Background

During pregnancy, the maternal cardiovascular system undergoes significant adaptive changes in response to a substantial drop in vascular resistance that are thought to be pivotal for uncomplicated pregnancy. These adaptations also affects systolic cardiac function. We aimed to meta-analytically determine the adaptation of cardiac systolic function in singleton normotensive pregnancies and gestational hypertensive complicated pregnancies.

Methods and Results

We performed a systematic review and meta-analysis on systolic function during pregnancy using PubMed and Embase. As we tried to quantify healthy gestational changes, we only included studies that reported a non-pregnant reference measurement and the indices of interest, which were left ventricular chamber volumes, ejection fraction (EF) and fractional shortening (FS). Mean differences between pregnant and reference measurements and weighted means of the absolute values were calculated for predefined gestational age intervals using a random-effects model.

The final analysis included 48 studies (of 10706 initially screened). In normal pregnancy, left ventricular end-diastolic and end-systolic volumes started to increase in the second trimester, with a maximum increase of 15.6 ml (16.9%) and 5.9 ml (17.9%), respectively. EF only increased by 2.6% (4.1% compared to reference) in the second trimester. In hypertensive pregnancies, left ventricular end-systolic volume increased more while EF decreased more compared to normotensive pregnancies ($P < 0.0001$ and $P= 0.007$, respectively).

Conclusions

During normotensive pregnancies, there is a rise in LVEDV and LVESV while EF remains preserved. In hypertensive pregnancies, the increase of LVESV increase and decrease of EF suggest the inability to maintain contractility.

Keywords

Systolic function, pregnancy, hypertensive pregnancy, preeclampsia, physiology.

INTRODUCTION

Up to 10-20% of pregnancies are complicated by cardiovascular (CV) complications including preeclampsia, gestational hypertension and fetal growth restriction. Unfortunately, (bio)chemical tests still lack sufficient predictive performance to timely identify those pregnancies at risk. Early maladaptation of the CV system is thought to play an essential role in the development of these complications. Therefore, understanding the moment and magnitude of the physiological adaptation during healthy pregnancy may enable early recognition of maladaptation in hypertensive pregnancies and may improve early predictive models and guide targeted interventions.

Early in the course of pregnancy, structural and functional changes in CV functioning occur which later benefit both maternal circulatory health and adequate uteroplacental perfusion. One of the earliest alterations observed in the first trimester of pregnancy is systemic arterial vasodilatation leading to a decreased arterial pressure. Subsequently, this decrease initiates plasma volume expansion[1-3]. The extra circulatory volume facilitates the needed increase in preload and subsequently enlarges left ventricular dimensions[4]. In parallel, the afterload reduction initiates a rise in baroreceptor activity, raising heart rate and cardiac contractility[3]. Both, altered volume–and pressure load as well as a rise in baroreceptor activity modify systolic and diastolic cardiac functioning[4]. Unfortunately, there are no reference values available describing the physiologically pattern of systolic cardiac function during pregnancy and it is therefore not yet possible to detect early deviating pathophysiological adaptation.

Timely detection of aberrant cardiac adjustments early in pregnancy would allow timely instituted interventions to prevent vascular complications and improve fetal and maternal health. Therefore, we performed a systematic review with meta-analysis of the current literature to estimate the extent and time course of changes in cardiac systolic function during human singleton normotensive pregnancies and hypertensive complicated pregnancies.

METHODS

Literature search

We performed an extensive literature search on articles evaluating cardiac systolic function during normal and complicated pregnancies using PubMed (NCBI) and Embase (Ovid). These databases provided publications from 1946 and 1974 to August 2017 for PubMed and Embase, respectively. The search strategy was originally designed for a series of meta-analysis on cardiac geometry, systolic function, diastolic function with a focus on normotensive and hypertensive pregnancies, as detailed in Supplemental Table 1.

Selection of studies

The identified studies were assessed for eligibility in two phases (Figure 1). First, all studies were independently screened for eligibility based on the title and abstract by two authors (primary investigator SdH and secondary investigator CGD or NMB). Second, full text articles were screened independently for eligibility based on the inclusion and exclusion criteria by the same authors. Discrepancies were resolved by mutual agreement. Studies were included if they reported a reference measurement, either estimated before conception, at or after 6 weeks postpartum, or in non-pregnant controls, and at least one measurement during pregnancy at any gestational age. Studies needed to report numerical values (mean) with standard deviation (SD), standard error (SE), or a 95% confidence interval (95% CI). Data was requested in the correct format from authors if they reported their data differently. Exclusion criteria included studies with a study population consisting of women with pre-existing cardiovascular disease, or with a history of a hypertensive pregnancy in a previous pregnancy, articles in other languages than English or Dutch, and case reports.

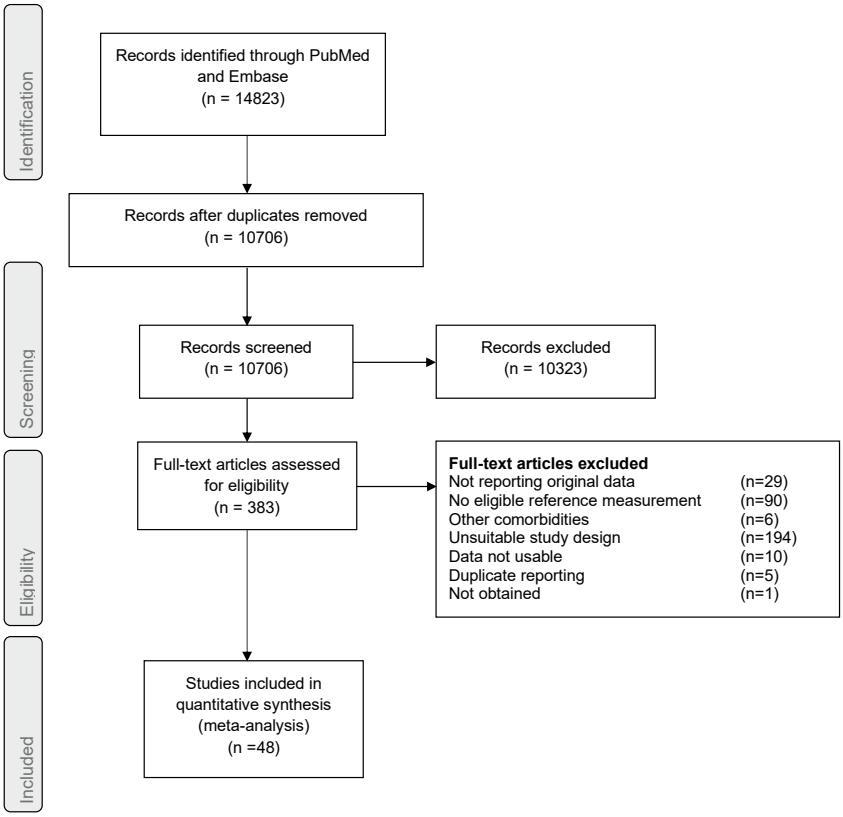


Figure 1. Flowchart summarizing the process of study selection.

Data extraction

Study characteristics (study design, sample size and methods), anthropometric measures (age, non-pregnant weight, height, parity and duration of amenorrhea), and effect measures with SD, SE, or 95% CI were collected from the eligible studies in predesigned data collection forms. Systolic function indices of interest were left ventricular end-diastolic volume (LVEDV), left ventricular end-systolic volume (LVESV), left ventricular ejection fraction (EF), and left ventricular fractional shortening (FS).

Quality assessment

The studies that were included were assessed for quality and risk of bias using a modified list of items described in the Quality In Prognosis Studies (QUIPS) tool, made most suitable for the purposes of this review[5]. Studies were scored with a '+' or '-' for risk of bias on six domains including study participation, study attrition, variable measurement, data reporting, and study design (Supplemental Table 2). Items that were not applicable for a study were assigned a '?'. Studies were only scored for study attrition in case of lost to follow-up in longitudinal study designs. Studies with a positive score greater than 60% were identified as high quality (HQ) studies, whereas studies with a score lower than 30% were identified as low quality (LQ) studies. Studies were identified as moderate quality (MQ) studies if the study scored between 30% and 60%.

Data and statistical analysis

The systolic function indices were categorized in five different intervals of gestational age (<14, 15-21, 22-28, 29-35, and 36-41 weeks). These gestational age intervals were adapted from Abudu *et al.* and enabled a most precise categorization of almost all indices[6]. SD was obtained from SE or 95% CI and calculated for combined groups according to the Cochrane handbook for systematic review of interventions whenever necessary[7]. The change of the different cardiac systolic function indices were calculated separately for these predefined intervals using a random-effects model as described by DerSimonian and Laird[8]. The random-effects model allows for inter-study variation and was chosen since observational data of different pregnant populations were used in terms of anthropometric and clinical characteristics. Hereby, we would not expect a common effect size.

The primary outcome for each study was the mean difference (MD) of the indices between pregnancy and reference and is reported with 95% CI. Relative increase from reference in percentage is reported in parenthesis. The Egger's regression test for funnel plot asymmetry was performed to test for the presence of publication bias[9]. If publication bias was statistically significant for an interval, the MD was corrected for publication bias using the Trim and Fill method, as described by Duval and Tweedie[10].

The ratio between total heterogeneity and total variability (I-squared statistic (I^2)) is presented as measure for heterogeneity. I^2 can distinguish true heterogeneity from

sampling variance and is expressed as a percentage[11]. Sources of heterogeneity (type of reference, study quality, and formula used to calculate left ventricular chamber volumes) and differences between normotensive and hypertensive complicated pregnancies were investigated by meta-regression analyses using a Mixed-Effects Model. The meta-analyses and meta-regression analyses were performed in R version 3.6.0 using the meta package. Reference curves were constructed using the ggplot2 package.

RESULTS

Study and data selection

The search strategy resulted in 10706 unique studies. After screening based on title and abstract, 10323 articles were excluded. In the second phase the remaining 383 articles were screened in full text and assessed for eligibility. Eventually, 48 studies were eligible and reported cardiac systolic function parameters (Figure 1). One study contained data that had to be converted to the desired format according to the recommendations in the Cochrane handbook for systematics reviews of interventions[12]. We excluded studies based on not reporting original data (n = 29), not reporting an eligible reference measurement (n = 90), study populations with other comorbidities (n = 6), unsuitable study designs (n = 194), studies without usable data (n = 10). We suspected double reporting in five articles and excluded these articles from analyses[13-17]. One article was excluded because we were unable to assess the eligibility since the article could not be retrieved[18].

Of the 48 studies, 9 reported data on pregnancies complicated by hypertension. Two studies included pregnant subjects with pregnancy-induced hypertension[19, 20] and seven studies included subjects with preeclampsia[21-27]. All studies reported data on normotensive pregnancies. One study also reported data on pregnancies complicated by gestational diabetes mellitus[28]. The data of the latter study was not used in this meta-analysis for the evaluation. Three studies used a pre-pregnant measurement as reference group, 25 studies used postpartum measurements as reference and 20 studies used a separate non-pregnant control group.

Study characteristics

The study characteristics and anthropometric measures of the study subjects included in this meta-analysis are summarized in Supplemental Tables 3 and 4 for normotensive and hypertensive pregnancies, respectively. Studies that were included in this meta-analysis rarely reported a complete overview of clinically relevant anthropometric measures of the study population.

With the exception of two studies, left ventricular volumes were determined using transthoracic echocardiography (TTE). One study determined left ventricular volumes

using cardiac magnetic resonance imaging (CMRI)[29], while the other presented both TTE and CMRI measures of left ventricular volumes[30]. Because the majority of the studies presented TTE measures we decided to use the TTE measurements.

Quality assessment

The quality assessment of the included studies is presented in Supplemental Table 2. Of the 48 included studies, 31 (65%) were classified as moderate quality, 12 (25%) as high quality and five (10%) as low quality studies. All included studies adequately described the method of measurement, either by stating that echocardiograms were recorded according to the recommendations of the American Society of Echocardiography or by extensively reporting the methods in their methods section. The item that scored lowest among all studies was a pre-pregnant value as reference measurement ($n = 3$). Moreover, in case of lost to follow-up, studies most often failed to mention reasons for loss follow-up and/or did not adequately describe the participants who dropped out.

Left ventricular end-diastolic volume

In normotensive pregnancies, LVEDV increased in the first 14 weeks of pregnancy by 6.3 ml [95% CI, 1.6 to 11.1 ml] (relative change of 7.3% [95% CI, 1.8 to 12.7%], absolute value 96.1 ml [95% CI, 89.3 to 103.0 ml]). The LVEDV continued to increase between 29 and 35 weeks of pregnancy with a maximum increase of 15.6 ml [95% CI, 9.9 to 21.2 ml] (relative change of 16.9% [95% CI, 10.8 to 23.0%]), absolute value 110.8 ml [95% CI, 103.4 to 118.3ml] (Table 1, Supplemental Figures 1 and 2).

Publication bias was present in the <14 weeks interval ($P = 0.03$). The corrected MD is presented in Table 1. There was no statistically significant difference in LVEDV between the type of reference measurement (prepregnant vs. NP and PP ($P = 0.66$) and PP vs. NP and prepregnant ($P = 0.46$), nor for the study qualities (LQ vs. HQ and MQ ($P = 0.46$) and MQ vs. LQ and HQ ($P = 0.53$). Only the MD of LVEDV calculated with the Noninvasive Continuous Cardiac Output Monitor (NNCOM) was statistically significantly different ($P = 0.0032$) from the other methods (Area-length method, Bullet method, Cardiac magnetic resonance imaging (CMRI), Pombo method, Simpson method, Teichholz method, or the estimation by (left ventricular end-diastolic diameter)^3) ($0.10 \leq P \leq 0.95$).

Only four studies reported on LVEDV in hypertensive complicated pregnancy. Moreover, there were no data available for the period before 22 weeks of pregnancy. Absolute LVEDV values ranged from 114.7 ml [95% CI, 109.4 to 120.0 ml] to 98.9 ml [95% CI, 93.7 to 104.2 ml]. One study reported data on LVEDV between 22 and 28 weeks gestation showing no change. LVEDV increased with 22.0 ml [95% CI, 9.9 to 34.2 ml] (relative change, 24.8% [95% CI, 11.1 to 38.6%]) between 29 and 35 weeks gestation compared to normotensive pregnancies. Between the interval of 36 to 41 weeks gestation, one study reported an increase, whereas another study reported a decrease in LVEDV compared to

Table 1. Pooled changes of cardiac systolic function indices in normotensive pregnancies.

		Gestational age interval (weeks)					
		Reference	***<14***	***15-21***	***22-28***	***29-35***	***36-41***
LVEDV (mL)	Abs	99.3 (93.0 to 105.5)	96.1 (89.3 to 103.0)	112.1 (100.4 to 123.8)	100.5 (94.5 to 106.4)	110.8 (103.4 to 118.3)	112.7 (103.6 to 121.8)
	MD	--	6.3 (1.6 to 11.1)	8.5 (4.5 to 12.5)	12.7 (9.7 to 15.7)	15.6 (9.9 to 21.2)	11.9 (6.0 to 17.8)
	%	--	7.3 (1.8 to 12.7)	9.2 (4.9 to 13.6)	15.4 (11.7 to 19.0)	16.9 (10.8 to 23.0)	12.1 (6.1 to 18.1)
	cMD	--	10.0 (4.8 to 15.2)	--	--	--	--
LVESV (mL)	Abs	32.0 (29.4 to 34.6)	32.0 (29.6 to 34.4)	40.9 (26.8 to 55.1)	33.2 (31.2 to 35.2)	34.0 (32.2 to 35.7)	39.0 (32.9 to 45.2)
	MD	--	3.3 (2.3 to 4.2)	0.6 (-5.0 to 6.2)	4.2 (1.5 to 7.0)	5.0 (2.3 to 7.6)	5.9 (1.4 to 10.4)
	%	--	12.3 (8.7 to 15.9)	1.7 (-15.1 to 18.6)	14.6 (5.2 to 24.1)	17.1 (8.0 to 26.2)	17.9 (4.2 to 31.6)
	cMD	--	3.5 (2.6 to 4.4)	--	--	--	--
EF (%)	Abs	64.9 (63.1 to 66.6)	64.2 (62.4 to 65.9)	66.2 (63.9 to 68.5)	65.6 (63.7 to 67.6)	64.1 (61.5 to 66.8)	64.5 (60.6 to 68.4)
	MD	--	0.9 (-0.4 to 2.2)	2.6 (1.0 to 4.2)	1.0 (-1.0 to 2.9)	-0.2 (-2.8 to 2.5)	-1.0 (-2.5 to 0.5)
	%	--	1.4 (-0.7 to 3.5)	4.1 (1.6 to 6.6)	1.5 (-1.5 to 4.5)	-0.2 (-4.4 to 3.9)	-1.5 (-3.8 to 0.8)
	cMD	--	--	--	--	4.0 (1.3 to 6.7)	--
FS (%)	Abs	35.5 (34.5 to 36.5)	37.5 (37.0 to 38.0)	36.9 (34.9 to 38.9)	36.4 (34.8 to 38.0)	35.1 (33.5 to 36.8)	36.9 (35.7 to 38.2)
	MD	--	1.4 (0.7 to 2.1)	1.4 (-0.2 to 3.0)	0.7 (-0.9 to 2.3)	0.1 (-1.6 to 1.7)	0.9 (-0.1 to 1.9)
	%	--	3.9 (1.8 to 5.9)	3.8 (-0.7 to 8.4)	2.0 (-2.5 to 6.4)	0.2 (-4.4 to 4.9)	2.6 (-0.2 to 5.4)
	cMD	--	--	--	--	-1.9 (-3.4 to -0.4)	0.1 (-1.0 to 1.2)

Values are reported as mean difference (MD) and relative change (%) with 95% CI compared to the reference group and absolute values (Abs) with 95% CI. MD corrected for publication bias (cMD) is also presented for intervals with statistically significant funnel plot asymmetry.
LVEDV, Left ventricular end-diastolic volume. LVESV, Left ventricular end-systolic volume. EF, Ejection fraction. FS, Fractional shortening.

normotensive pregnancies (Table 2, Supplemental Figure 3 and 4). The study showing a decrease in LVEDV was distinguishable by the use of antihypertensive drugs (alphamethyldopa, hydralazine and nifedipine) and the inclusion of all preeclamptic pregnancies after 20 weeks of pregnancy, while the other study included late-onset preeclamptic pregnancies and ceased antihypertensive medication at least 3 days before the measurement.

Absolute LVEDV values were not statistically significantly different between hypertensive and normotensive pregnancies ($P = 0.95$). The change of LVEDV in pregnancies complicated by hypertension was not different from normotensive pregnancies ($P = 0.76$).

Left ventricular end-systolic volume

In normotensive pregnancy, LVESV increased significantly in the first trimester compared to reference values with 3.3 ml [95% CI, 2.3 to 4.2 ml] (relative change 12.3% [95% CI, 8.7 to 15.9%] and absolute value 32.0 ml [95% CI, 29.6 to 34.4 ml]). From 22 weeks of pregnancy onwards, LVESV increased with 4.2 ml [95% CI, 1.5 to 7.0 ml] (relative change 14.6% [95% CI, 5.2 to 24.1%] and absolute value, 33.2 ml [95% CI, 31.2 to 35.2 ml]). The maximal increase was observed between 36 and 41 weeks of pregnancy of 5.9 ml [95% CI,

Table 2. Pooled changes of cardiac systolic function indices in hypertensive complicated pregnancies.

		Gestational age interval (weeks)					
		Reference	***22-28***	***29-35***	***36-41***	***P-value†***	***P-value‡***
LVEDV (mL)	Abs	104.0 (84.1 to 123.8)	114.7 (109.4 to 120.0)	110.5 (100.7 to 120.4)	98.9 (93.7 to 104.2)		
	MD	--	11.8 (-1.7 to 25.3)	22.0 (9.9 to 34.2)	-7.1 (-65.8 to 51.7)	0.95	0.76
	%	--	11.5 (-1.6 to 24.6)	24.8 (11.1 to 38.6)	-6.5 (-61.0 to 47.9)		
LVESV (mL)	Abs	33.4 (29.1 to 37.7)	39.0 (35.9 to 42.1)	48.7 (36.6 to 60.8)	48.0 (44.2 to 51.8)		
	MD	--	9.4 (2.5 to 16.3)	14.1 (-3.0 to 31.3)	16.0 (11.4 to 20.6)	<0.0001	<0.0001
	%	--	31.8 (8.3 to 55.2)	41.0 (-8.6 to 90.5)	50.0 (35.7 to 64.3)		
EF (%)	Abs	64.3 (58.3 to 70.3)	65.9 (64.0 to 67.8)	54.3 (51.8 to 56.8)	55.6 (46.6 to 64.6)		
	MD	--	-5.3 (-8.9 to -1.7)	-5.9 (-8.8 to -3.0)	-5.4 (-12.8 to 1.9)	0.003	0.007
	%	--	-7.4 (-12.5 to -2.4)	-9.8 (-14.6 to -4.9)	-8.9 (-21.0 to 3.2)		
FS (%)	Abs	35.5 (33.4 to 37.7)	37.3 (35.8 to 38.8)	36.4 (33.1 to 39.8)	41.0 (38.5 to 43.5)		
	MD	--	-4.6 (-8.6 to -0.6)	1.1 (-0.6 to 2.9)	6.0 (2.7 to 9.3)	0.34	0.50
	%	--	-11.0 (-20.6 to -1.4)	3.3 (-1.8 to 8.4)	17.1 (7.7 to 26.6)		

Values are reported as mean difference (MD) and relative change (%) with 95% CI compared to the reference group.

LVEDV, Left ventricular end-diastolic volume. LVESV, Left ventricular end-systolic volume. EF, Ejection fraction. FS, Fractional shortening.

† P-value of difference between the absolute values in normotensive pregnancies compared to pregnancies complicated by hypertension, estimated by meta-regression analysis.

‡ *P*-value of difference between the MD in normotensive pregnancies compared to pregnancies complicated by hypertension, estimated by meta-regression analysis.

1.4 to 10.4 ml] (relative change 17.9% [95% CI, 4.2 to 31.6%] and absolute value, 39.0 ml [95% CI 32.9 to 45.2 ml]) (Table 1, Supplemental Figures 5 and 6).

Publication bias was present in the <14 weeks interval ($P = 0.04$). The corrected MD is presented in Table 1. Study quality statistically significantly contributed to the observed heterogeneity (LQ studies vs MQ and HQ studies, $P < 0.0001$ and MQ studies vs LQ and HQ studies, $P = 0.003$), as did the reference group (PP vs NP and prepregnant group, $P = 0.03$, prepregnant vs NP and PP, $P = 0.41$). The used formula to calculate chamber volumes did not contribute to the observed heterogeneity ($0.30 \leq P \leq 0.53$).

In hypertensive complicated pregnancies, one study reported data in the 22 to 28 weeks gestation interval. This study reported an increase of 9.4 ml [95% CI, 2.5 to 16.3 ml] (relative change 31.8% [95% CI, 8.3 to 55.2%] and absolute value 39.0 ml [95% CI, 35.9 to 42.1ml]). No change in LVESV was found between the 29 and 35 weeks interval compared to reference. In the 36 and 41 weeks interval, LVESV increased compared to reference with 16.0 ml [95% CI, 11.4 to 20.6 ml] (relative change of 50.0% [95% CI, 35.7 to 64.3%] and absolute value 48.0 ml [95% CI, 44.2 to 51.8 ml]). In the latter interval, only one study was included (Table 2, Supplemental Figure 7 and 8).

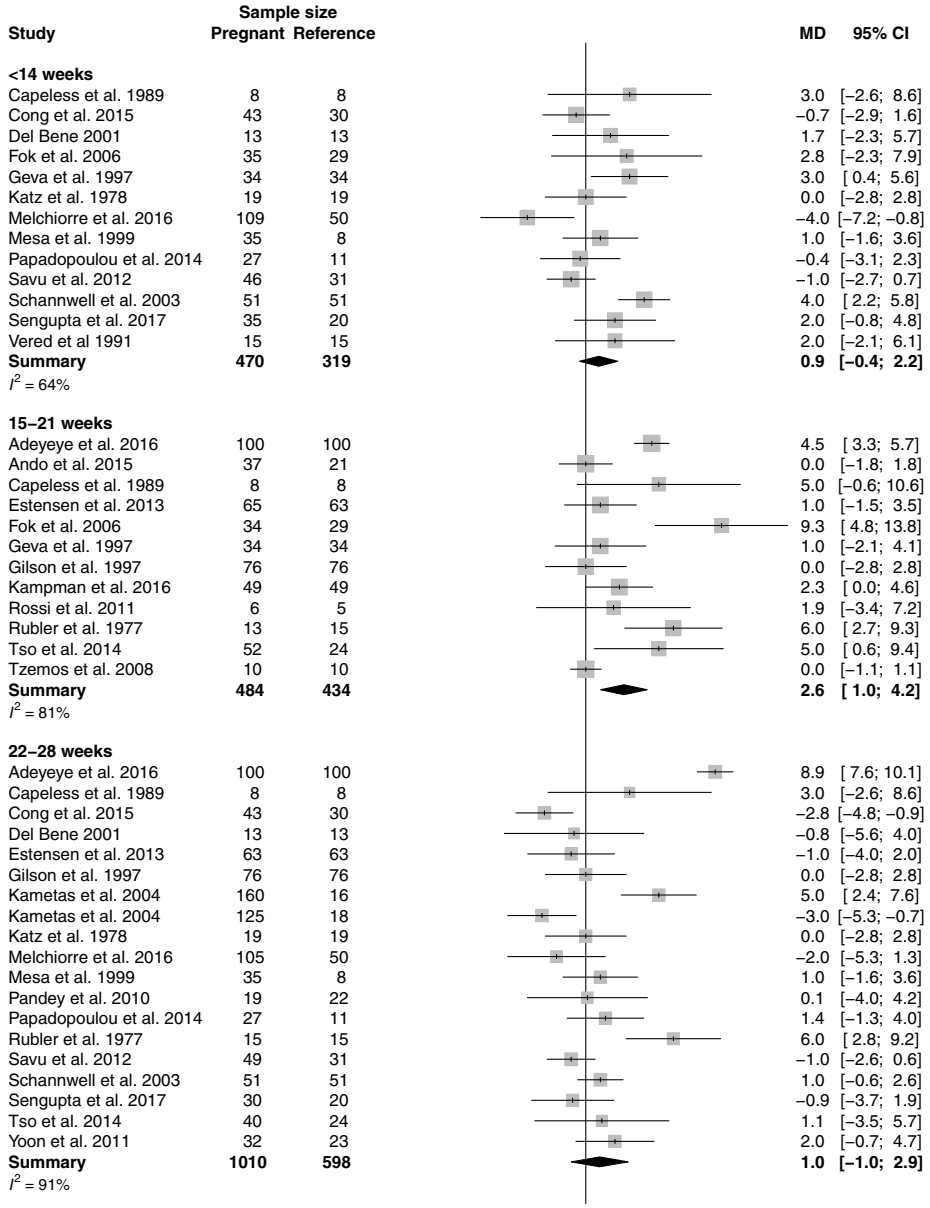


Figure 2. Forest plot of EF change during normotensive pregnancy.

Absolute LVESV and LVESV change were statistically significant different between hypertensive and normotensive pregnancies ($P < 0.0001$).

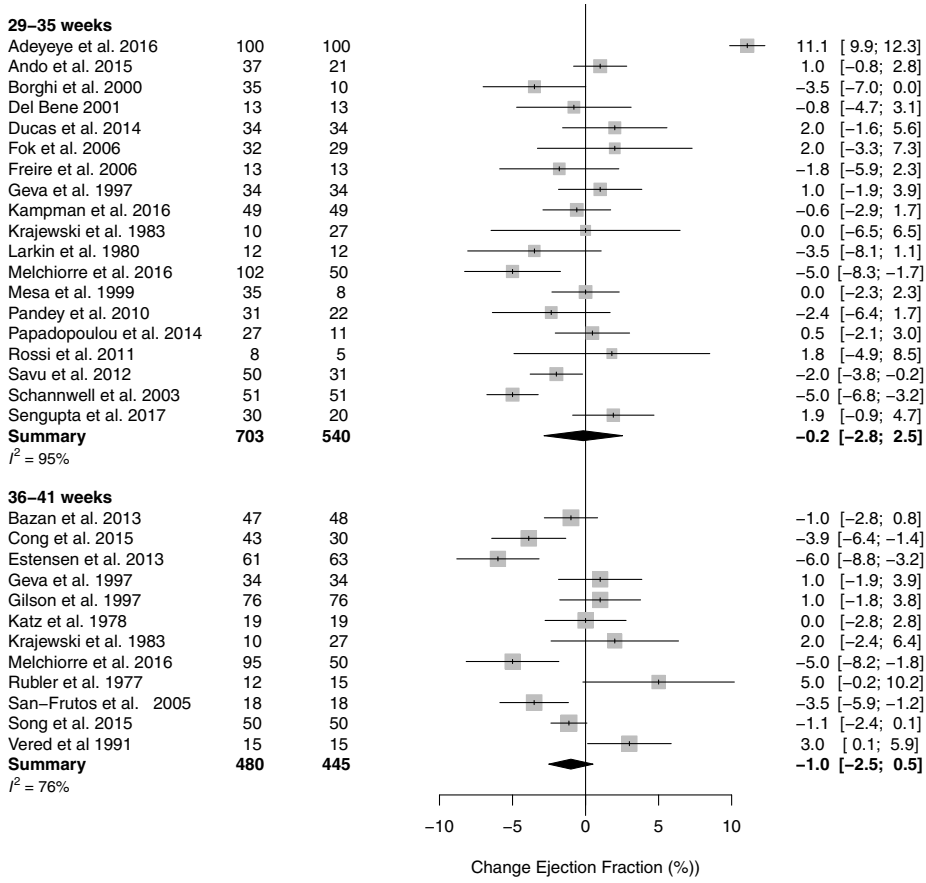


Figure 2. Forest plot of EF change during normotensive pregnancy. *(continued)*

Left ventricular ejection fraction

In normotensive pregnancies, EF did not change during the first trimester. EF only increased statistically significantly between 15 and 21 weeks gestation with 2.6% [95% CI, 1.0 to 4.2%] (relative change 4.1% [95% CI, 1.6 to 6.6%] and absolute value 66.2%, [95% CI 63.9 to 68.5%]). No change was observed in the subsequent intervals (Table 1, Figure 2 and 3).

Publication bias was present in the 29 to 35 weeks interval ($P = 0.048$). The corrected MD is presented in Table 1. No statistically significant contributors to the heterogeneity were found (type of reference (pre-pregnant vs. NP and PP, $P = 0.32$; PP vs pre-pregnant and NP, $P = 0.16$); study quality (LQ vs. MQ and HQ, P=0.11 MQ vs. LQ and HQ, P = 0.08) and formula used to calculate left ventricular volumes ($0.28 \leq P \leq 0.97$).

In hypertensive pregnancies, no data was available before 22 weeks of pregnancy. The 22 to 28 weeks of pregnancy and 29 to 35 weeks of pregnancy interval consisted of only one study. Both reported a decreased EF of -5.3% [95% CI, -8.9 to -1.7%] (relative change -7.4% [95% CI, -12.5 to -2.4%] and absolute value 65.9% [95% CI, 64.0 to 67.8%]) and

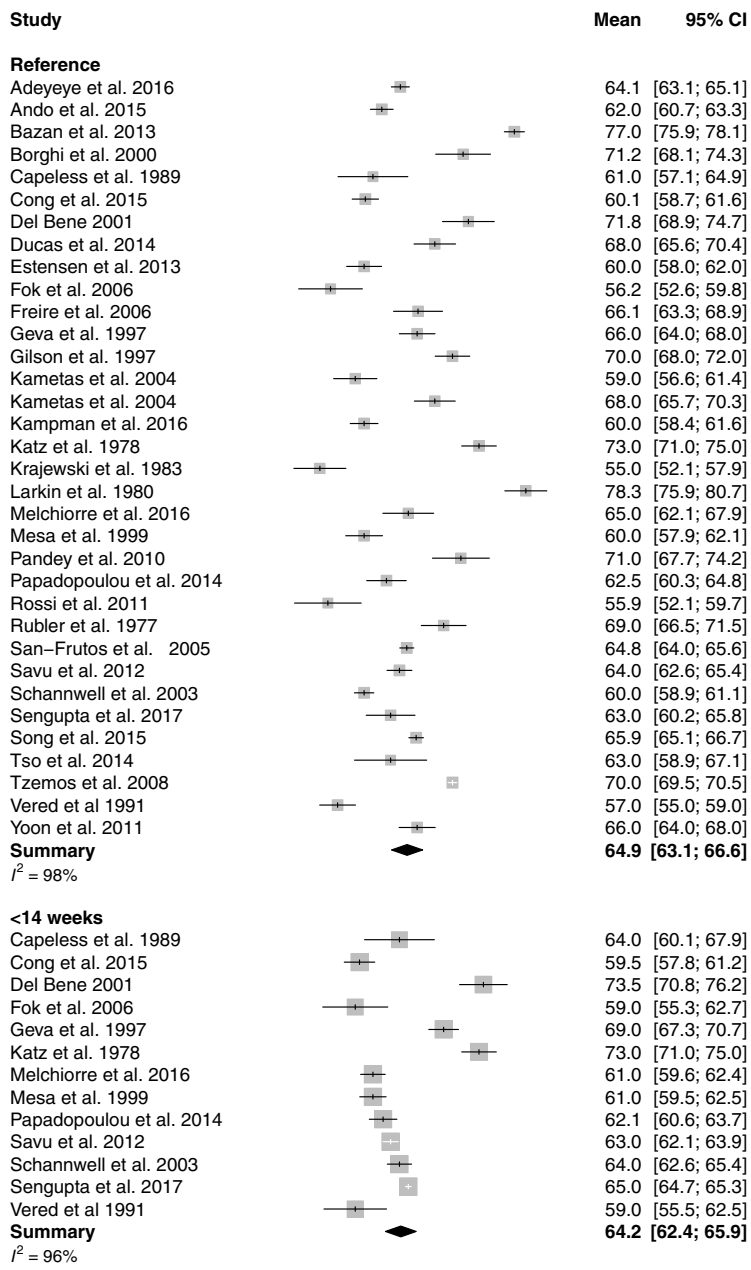


Figure 3. Forest plot of absolute EF values during normotensive pregnancy.

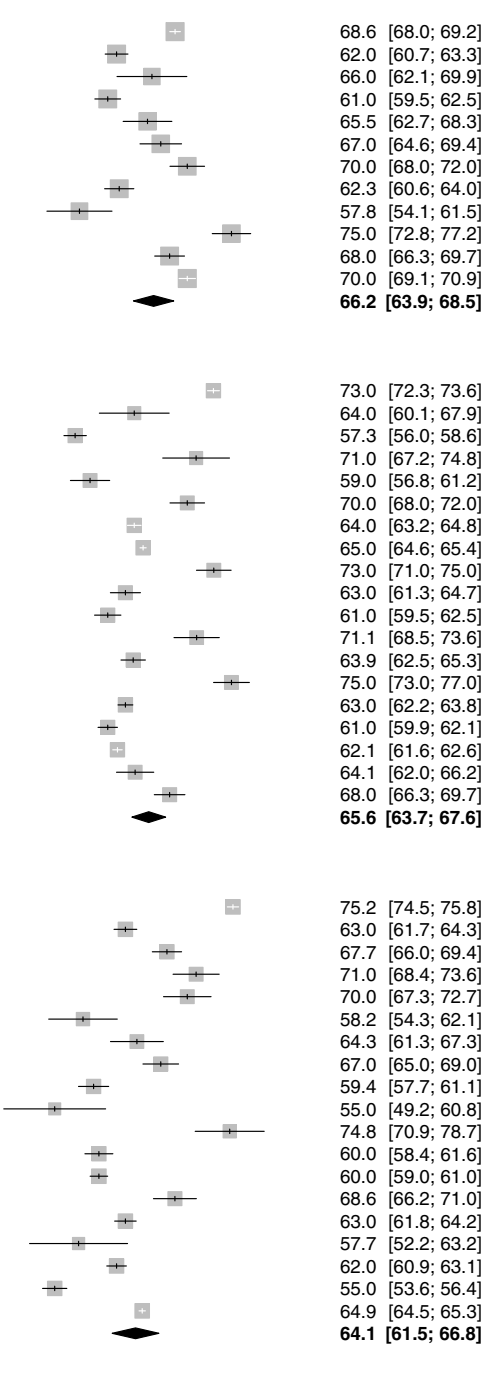


Figure 3. Forest plot of absolute EF values during normotensive pregnancy. *(continued)*

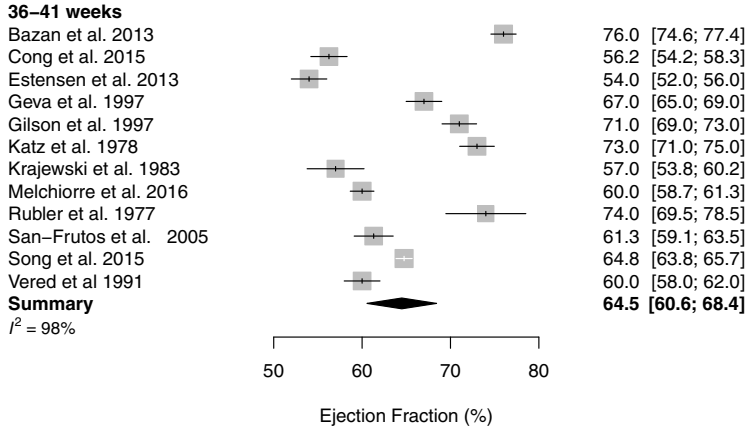


Figure 3. Forest plot of absolute EF values during normotensive pregnancy. *(continued)*

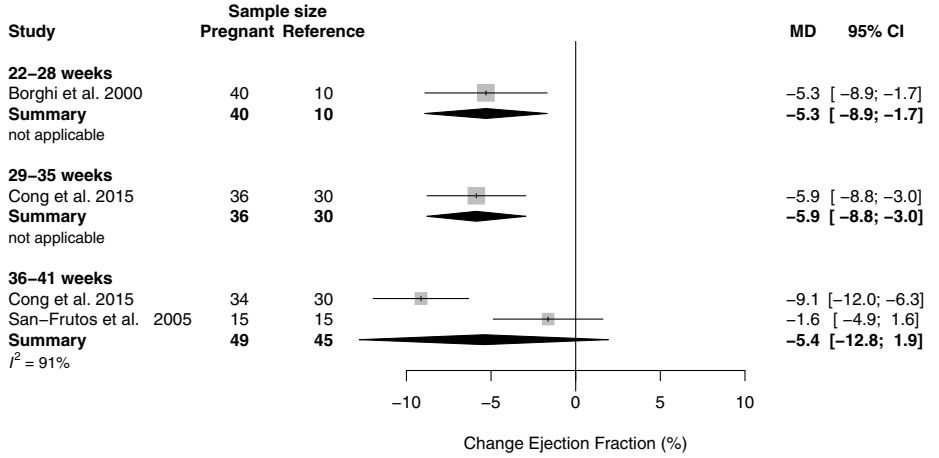


Figure 4. Forest plot of EF change during hypertensive pregnancy.

-5.9% [95% CI, -8.8 to -3.0%] (relative change -9.8% [95% CI, -14.6 to -4.9%] and absolute value 54.3% [95% CI, 51.8 to 56.8%]), respectively. The EF did not change between 36 and 41 weeks gestation in hypertensive pregnancies compared to reference values (Table 2, Figure 4 and Figure 5).

Absolute EF were statistically significantly different between hypertensive and normotensive pregnancies (P = 0.003). The change of the EF in pregnancies complicated by hypertension was statistically significantly different compared to normotensive pregnancies (P = 0.007).

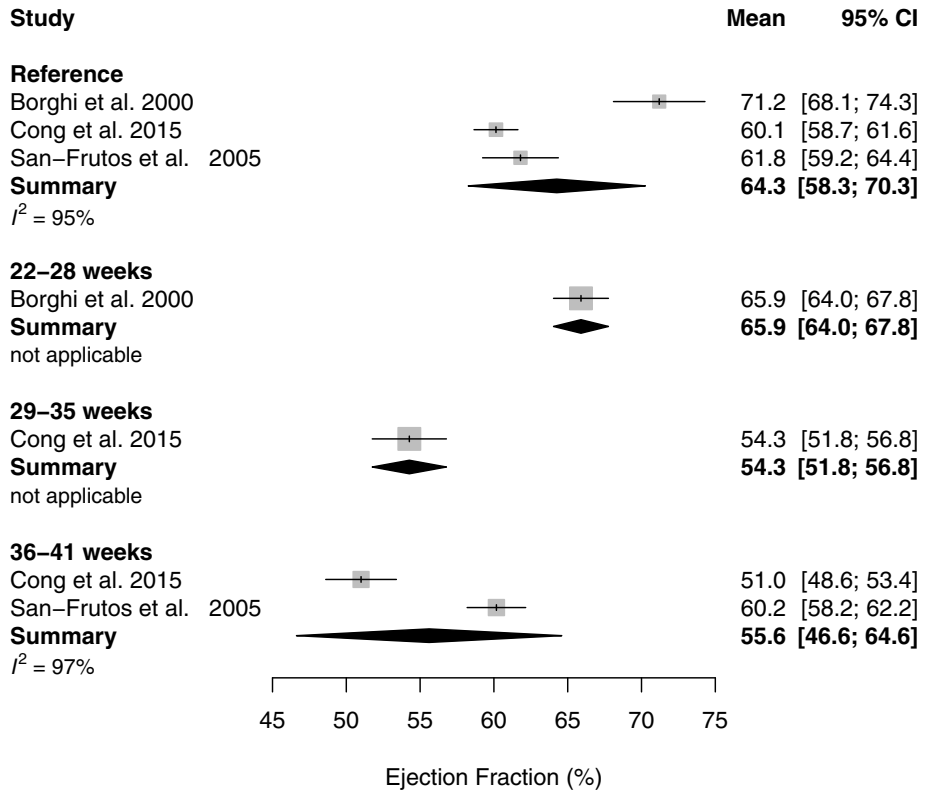


Figure 5. Forest plot of absolute EF values during hypertensive pregnancy.

Left ventricular fractional shortening

In normotensive pregnancy, FS increased with 1.4% [95% CI, 0.7 to 2.1%] (relative change 3.9 % [95% CI, 1.8 to 5.9%] and absolute value 37.5% [95% CI, 37.0 to 38.0%]) in the first 14 weeks of pregnancy. The FS did not change from 14 weeks of pregnancy onwards (Table 1, Supplemental Figures 9 and 10).

Publication bias was present in the 29 to 35 weeks interval (P=0.003) and in the 36 to 41 weeks interval (P = 0.045). The corrected MD is presented in Table 1. The type of reference group (PP vs pre-pregnant and NP, P = 0.002, pre-pregnant vs NP and PP, P = 0.08) and study quality (LQ vs MQ and HQ P = 0.02, MQ vs LQ and HQ, P = 0.06) contributed to the observed heterogeneity.

In hypertensive complicated pregnancies, only the 29 to 25 weeks of pregnancy interval included more than one study. The FS did not change in this interval. One study in the 22 to 28 weeks of pregnancy interval showed a decrease of -4.6% (95% CI, -8.6 to -0.6%] (absolute value 37.3% [95% CI, 35.8 to 38.8%], relative change -11.0 % [95% CI, -20.6 to -1.4%]). One other study in the 36 to 41 weeks of pregnancy interval showed an increase

of 6.0% [95% CI, 2.7 to 9.3%] (absolute value, 41.0% [95% CI 38.5 to 43.5%], relative change 17.1% [95% CI, 7.7 to 26.6%]) (Table 2, Supplemental Figures 11 and 12).

Absolute FS were not statistically different between hypertensive and normotensive pregnancies ($P = 0.34$). The change of the FS in pregnancies complicated by hypertension was not statistically different compared to normotensive pregnancies ($P = 0.50$).

Reference Curves

Reference curves were constructed based on the data from normotensive pregnancies for each variable. These reference curves are depicted in Figures 6 and S13 – S15. To establish reference values, 5th, 50th, and 95th percentiles weighted by study sample size were computed. Each point estimate is indicated as a value from a low-, moderate- or high-quality study as determined by the quality assessment.

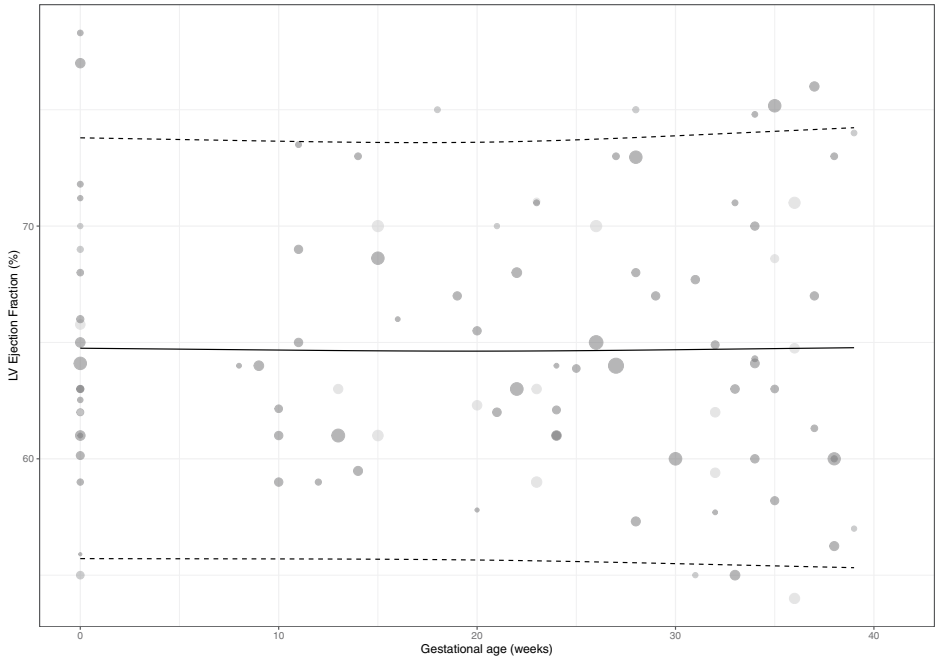


Figure 6. Reference curve for EF in normotensive pregnancy.

DISCUSSION

This systematic review and meta-analysis comprehensively describes the adaptation of cardiac systolic function in normotensive and hypertensive complicated pregnancy. To the best of our knowledge, this is the first meta-analysis on this topic. Cardiac systolic function is dependent on cardiac loading conditions (preload and afterload) and in-

otropy. In normotensive pregnancy, LVEDV and LVESV both progressively increased with a maximal increase of 17% and 18% respectively. LV EF slightly increased by 4% in the early second trimester, but decreased towards reference values in the second half of pregnancy. In hypertensive complicated pregnancy, LVESV increased three-fold more compared to normotensive pregnancy, reaching a maximal increase of 50%. Moreover, LV EF decreased 10% more compared to normotensive pregnancies.

Predicting Preeclampsia

Preeclampsia, a vascular hypertensive pregnancy disorder, is one of the leading causes of maternal and perinatal morbidity and mortality in the western world[31]. It accounts for 3.5 maternal deaths per 100.000 live births, of which 85% is thought to be related to inadequate blood pressure control[32, 33]. Initiating treatment in order to prevent or delay the development of preeclampsia is desirable in order to decrease maternal and fetal morbidity and mortality. Current prediction models, mainly relying on biochemical markers, still lack sufficient predictive power. A large body of evidence shows that early in pregnancy, differences in hemodynamic and cardiac adjustments between normotensive and hypertensive pregnancies are discernible, even when blood pressure measurements are still within the normotensive range. Therefore determining hemodynamics along with cardiac function can aid in recognizing circulatory maladaptation to pregnancy and have great potential to improve targeted prevention and intervention opportunities[34]. Although it is currently known that cardiac function changes during pregnancy, studies have not been able to consistently report the magnitude and time-course of change of indices reflecting cardiac function[12]. Inconsistencies may relate to different cardiac ultrasound measurements used, heterogeneity in the studied population, longitudinal or cross-sectional design and the used comparison groups. In order to detect maladaptation, it is necessary to gain specific insight in the normotensive course of hemodynamic and cardiac function variables in pregnancies ending uncomplicated, as initiated in this series of meta-analyses.

Physiological background

During normotensive pregnancy, an early-pregnancy drop in total peripheral vascular resistance triggers compensatory mechanisms, activation of humoral (RAAS system), central autonomic mechanisms and venous tone, all in order to restore circulatory volume and blood pressure and to meet the demands in compensatory rise in cardiac output[1, 35]. The increased volume load explains the rise in ventricular radius, mirrored in our study by a progressive increase in LVEDV. According to the Frank-Starlin mechanism, an increased LVEDV may increase force of ventricular contraction, resulting in increased stroke volume and consequently increased cardiac output. On the one hand, studies investigating LV contractility by the use of Speckle-Tracking Echocardiography (STE)

did not consistently report increased LV contractility[21, 36, 37]. STE data of the included articles in this meta-analysis show that changes in LV contractility differs between strains and regions of the left ventricle. We found that he LV EF remained unchanged except for a relative increase in the early second trimester. This reflects enhanced LV pump function in the early second trimester. On the other hand, the increased volume load on the left ventricle results in compensatory LV dilatation and hypertrophy, as detailed in a previous meta-analysis[38]. It is expected that changes in cardiac geometry affects cardiac systolic function. Previous studies with STE reported decreased longitudinal and circumferential LV strains in pregnancy suggesting loss of contractility during normotensive pregnancy[36, 39]. However, we show that LV EF is largely maintained stable throughout pregnancy. This suggests maintained LV EF results from increased volume load and reduced pressure load rather than substantial changes in cardiac contractility.

In hypertensive complicated pregnancies we show that LVEDV does not change statistically significantly differently compared to normotensive pregnancy, suggesting adequate rise in preload, which can be functionally reached by increased plasma volume or increased venous tone. In contrast, LVESV increased about three-fold more compared to normotensive pregnancy. This reflects higher residual systolic volume which may result from increased pressure load and larger loss in contractility during gestational hypertensive pregnancy. This is in line with previous studies on STE showing more extensive loss in contractility during preeclamptic pregnancies compared to normotensive pregnancies, reflected by decreased radial, circumferential and longitudinal LV strain[40, 41]. The decreased contractility is also reflected in this meta-analysis by a 10% larger loss in EF compared to normotensive pregnancy. Although still in the clinical acceptable range, the lost contractility may suggest subtle changes in cardiac energy metabolism either consistent with intrinsic cellular changes, progressive muscular hypertrophic architecture that goes along with gestational hypertension or relative oxidative coronary dysfunction, especially when preeclampsia-related global endothelial dysfunction arises. Impaired contractility, measured as decreased EF appears in end-stage cardiac disease expression, although early stages of impaired myocardial contractility and relaxation may precede the development of overt systolic dysfunction. Less load-dependent measurement modalities, such as STE may be capable to assess more subtle functional myocardial abnormalities in regional and global systolic function while conventional echocardiographic parameters such as EF are still in normal range[40, 42]. Therefore, we highly recommend the use of STE in future research in both normotensive and hypertensive pregnancies. Ideally, measurements are performed longitudinally starting in an early stage of pregnancy, enabling us to gain better knowledge in the pattern of pathological adaptation.

Limitations

There are several shortcomings that need to be addressed. First, definitions for gestational hypertension and preeclampsia were not consistent between the included studies. The international definition for different hypertensive complications in pregnancy somewhat vary over the past decades and probably reflect the heterogeneity of the disease and the growing understanding of the syndrome. Second, some included longitudinal studies reported the investigated indices of reference and pregnant values from the same women. The results from these studies often did not present sufficient information to determine the covariance between both measurements. We ignored their dependence, instead of estimating (a range of) covariances. Since the variance of the mean difference decreases as the covariance between the two measurements increases, not taking the covariance into account can only have resulted in slightly conservative estimates of precision. Point estimates are unaffected by these dependent observations. Third, we are aware that there was not always enough power to test for funnel plot asymmetry. Therefore, the corrected effect sizes should be interpreted carefully.

CONCLUSION

This systematic review and meta-analysis on healthy gestational adjustments of cardiac systolic function showed that during normotensive pregnancies, LVEDV and LVESV increased while EF showed an initial small rise in early second trimester to normalize towards reference afterwards. In contrast to normotensive pregnancies, during hypertensive pregnancies, the left ventricle is apparently unable to maintain contractility, reflected by 10% reduced ejection fraction. The underlying mechanisms leading to the reduction in cardiac contractility needs to be elucidated.

ACKNOWLEDGEMENTS

Not applicable.

SOURCES OF FUNDING

Not applicable.

DISCLOSURES

Not applicable.

AFFILIATIONS

From Department of Obstetrics and Gynaecology, Maastricht University Medical Center, Maastricht, The Netherlands (S.d.H., N.M.B, L.G, Z.M., M.S.); Department of Clinical Epidemiology and Medical Technology Assessment, Maastricht University Medical Center, Maastricht, The Netherlands (S.v.K.); Department of Obstetrics and Gynaecology, Radboud University Medical Center, Nijmegen, The Netherlands (J.v.D.); Department of Cardiology, Maastricht University Medical Center, Maastricht, The Netherlands (C.G.).

REFERENCES

1. Duvekot JJ, Cheriex EC, Pieters FA, Menheere PP and Peeters LL. Early pregnancy changes in hemodynamics and volume homeostasis are consecutive adjustments triggered by a primary fall in systemic vascular tone. *American journal of obstetrics and gynecology*. 1993;169:1382-1392.
2. Andrietti S, Kruse A-J, Bekkers SC, Sep S, Spaanderman M and Peeters LL. Cardiac adaptation to pregnancy in women with a history of preeclampsia and a subnormal plasma volume. *Reproductive Sciences*. 2008;15:1059-1065.
3. Spaanderman M, Ekhart T, van Eyck J, de Leeuw P and Peeters L. Preeclampsia and maladaptation to pregnancy: a role for atrial natriuretic peptide? *Kidney international*. 2001;60:1397-1406.
4. Valensise H, Novelli GP, Vasapollo B, Di Ruzza G, Romanini ME, Marchei M, Larciprete G, Manfellotto D, Romanini C and Galante A. Maternal diastolic dysfunction and left ventricular geometry in gestational hypertension. *Hypertension*. 2001;37:1209-1215.
5. Hayden JA, van der Windt DA, Cartwright JL, Côté P and Bombardier C. Assessing bias in studies of prognostic factors. *Annals of internal medicine*. 2013;158:280-286.
6. Abudu O and Sofola O. Plasma volume in normal pregnant Nigerian primigravidae. *International Journal of Gynecology & Obstetrics*. 1985;23:137-142.
7. Higgins J and Green S. Cochrane Handbook for Systematic Reviews of Interventions. 7732 Obtaining standard deviations from standard errors and confidence intervals for group means. 2011;2016.
8. DerSimonian R and Laird N. Meta-analysis in clinical trials. *Controlled clinical trials*. 1986;7:177 188.
9. Egger M, Smith GD, Schneider M and Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ*. 1997;315:629-634.
10. Duval S and Tweedie R. Trim and fill: a simple funnel-plot–based method of testing and adjusting for publication bias in meta-analysis. *Biometrics*. 2000;56:455-463.
11. Higgins JP, Thompson SG, Deeks JJ and Altman DG. Measuring inconsistency in meta-analyses. *BMJ: British Medical Journal*. 2003;327:557.
12. Melchiorre K, Sharma R, Khalil A and Thilaganathan B. Maternal Cardiovascular Function in Normal Pregnancy. Hypertension. 2016;67:*HYPERTENSIONAHA*. 115.06667.
13. Schannwell CM, Zimmermann T, Schneppenheim M, Plehn G, Marx R and Strauer BE. Left ventricular hypertrophy and diastolic dysfunction in healthy pregnant women. *Cardiology*. 2002;97:73-8.
14. Kametas N, McAuliffe F, Hancock J, Chambers J and Nicolaides K. Maternal left ventricular mass and diastolic function during pregnancy. *Ultrasound in obstetrics & gynecology*. 2001;18:460-466.
15. Cong J, Fan T, Yang X, Squires JW, Cheng G, Zhang L and Zhang Z. Structural and functional changes in maternal left ventricle during pregnancy: a three-dimensional speckle-tracking echocardiography study. *Cardiovascular ultrasound*. 2015;13:6.
16. Pandey A, Banerjee A, Das A, Bhawani G, Kumar A, Majumadar B and Bhattacharya A. Evaluation of maternal myocardial performance during normal pregnancy and post partum. *Indian heart journal*. 2010;62:64-67.
17. Larkin H, Gallery E, Hunyor S, Gyory A and Boyce E. Cardiac and haemodynamic measurements in hypertensive pregnancy. *Clinical science (London, England: 1979)*. 1980;59:357s-360s.
18. Sudha M, Tripathy PC, Rajkumar D, Chidambaram N and Umarani. Study of hemodynamic changes during pregnancy and postpartum period in women of twenty to thirty-five years of age. *Biomedicine*. 2007;27:11-14.
19. Escudero E, Favaloro L, Moreira C and Plastino J. Study of the left ventricular function in pregnancy-induced hypertension. *Clinical cardiology*. 1988;11:329-333.

20. Sánchez RA, Glenny JE, Marcó E, Voto LS, Lapidus AM, Iglesias GH, Moledo LV and Margulies M. Two-dimensional and M-mode echocardiographic findings in hypertensive pregnant women. *American journal of obstetrics and gynecology.* 1986;154:910-913.
21. Cong J, Yang X, Zhang N, Shen J, Fan T and Zhang Z. Quantitative analysis of left atrial volume and function during normotensive and preeclamptic pregnancy: a real-time three-dimensional echocardiography study. *The international journal of cardiovascular imaging*. 2015;31:805-812.
22. Dennis A, Castro J, Carr C, Simmons S, Permezel M and Royse C. Haemodynamics in women with untreated pre-eclampsia. *Anaesthesia*. 2012;67:1105-1118.
23. Hamad RR, Larsson A, Pernow J, Bremme K and Eriksson MJ. Assessment of left ventricular structure and function in preeclampsia by echocardiography and cardiovascular biomarkers. *Journal of hypertension*. 2009;27:2257-2264.
24. San-Frutos LM, Fernández R, Almagro J, Barbancho C, Salazar F, Pérez-Medina T, Bueno B and Bajo J. Measure of hemodynamic patterns by thoracic electrical bioimpedance in normal pregnancy and in preeclampsia. *European Journal of Obstetrics & Gynecology and Reproductive Biology*. 2005;121:149-153.
25. Simmons LA, Gillin AG and Jeremy RW. Structural and functional changes in left ventricle during normotensive and preeclamptic pregnancy. *American Journal of Physiology-Heart and Circulatory Physiology*. 2002;283:H1627-H1633.
26. Borghi C, Degli Esposti D, Immordino V, Cassani A, Boschi S, Bovicelli L and Ambrosioni E. Relationship of systemic hemodynamics, left ventricular structure and function, and plasma natriuretic peptide concentrations during pregnancy complicated by preeclampsia. *American journal of obstetrics and gynecology*. 2000;183:140-147.
27. Kuźniar J, Piela A and Skręt A. Left ventricular function in preeclamptic patients: an echocardiographic study. *American journal of obstetrics and gynecology*. 1983;146:400-405.
28. Airaksinen K, Ikäheimo M, Salmela P, Kirkinen P, Linnaluoto M and Takkunen J. Impaired cardiac adjustment to pregnancy in type I diabetes. *Diabetes care*. 1986;9:376-383.
29. Rossi A, Cornette J, Johnson MR, Karamermer Y, Springeling T, Opic P, Moelker A, Krestin GP, Steegers E and Roos-Hesselink J. Quantitative cardiovascular magnetic resonance in pregnant women: cross-sectional analysis of physiological parameters throughout pregnancy and the impact of the supine position. *Journal of Cardiovascular Magnetic Resonance*. 2011;13:31.
30. Ducas RA, Elliott JE, Melnyk SF, Premecz S, Cleverley K, Wtorek P, Mackenzie GS, Helewa ME and Jassal DS. Cardiovascular magnetic resonance in pregnancy: insights from the cardiac hemodynamic imaging and remodeling in pregnancy (CHIRP) study. *Journal of Cardiovascular Magnetic Resonance*. 2014;16:1.
31. Kuklina EV, Ayala C and Callaghan WM. Hypertensive disorders and severe obstetric morbidity in the United States. *Obstet Gynecol*. 2009;113:1299-306.
32. Schutte J, Steegers E, Schuitemaker N, Santema J, De Boer K, Pel M, Vermeulen G, Visser W and Van Roosmalen J. Rise in maternal mortality in the Netherlands. *BJOG: An International Journal of Obstetrics & Gynaecology*. 2010;117:399-406.
33. Schutte JM, Schuitemaker N, Van Roosmalen J, Steegers E and Committee DMM. Substandard care in maternal mortality due to hypertensive disease in pregnancy in the Netherlands. *BJOG: An International Journal of Obstetrics & Gynaecology*. 2008;115:732-736.
34. McLaughlin K, Scholten RR, Kingdom JC, Floras JS and Parker JD. Should maternal hemodynamics guide antihypertensive therapy in preeclampsia? *Hypertension*. 2018;71:550-556.
35. Meah VL, Cockcroft JR, Backx K, Shave R and Stöhr EJ. Cardiac output and related haemodynamics during pregnancy: a series of meta-analyses. *Heart*. 2016;102:heartjnl-2015-308476.

36. Estensen M, Beitnes J, Grindheim G, Aaberge L, Smiseth O, Henriksen T and Aakhus S. Altered maternal left ventricular contractility and function during normal pregnancy. *Ultrasound in Obstetrics & Gynecology*. 2013;41:659-666.
37. Sengupta SP, Bansal M, Hofstra L, Sengupta PP and Narula J. Gestational changes in left ventricular myocardial contractile function: new insights from two-dimensional speckle tracking echocardiography. *The international journal of cardiovascular imaging*. 2017;33:69-82.
38. de Haas S, Ghossein-Doha C, Geerts L, van Kuijk SMJ, van Drongelen J and Spaanderman MEA. Cardiac remodelling during normotensive and hypertensive complicated pregnancies: a systematic review and meta-analysis. *Ultrasound in Obstetrics & Gynecology*. 2017;50:683-696.
39. Papadopoulou E, Kaladaridou A, Agrios J, Matthaiou J, Pamboukas C and Toumanidis S. Factors influencing the twisting and untwisting properties of the left ventricle during normal pregnancy. *Echocardiography*. 2014;31:155-163.
40. Buddeberg BS, Sharma R, O'Driscoll JM, Kaelin Agten A, Khalil A and Thilaganathan B. Cardiac maladaptation in term pregnancies with preeclampsia. *Pregnancy Hypertens*. 2018;13:198-203.
41. Shahul S, Rhee J, Hacker MR, Gulati G, Mitchell JD, Hess P, Mahmood F, Arany Z, Rana S and Talmor D. Subclinical left ventricular dysfunction in preeclamptic women with preserved left ventricular ejection fraction: a 2D speckle-tracking imaging study. *Circulation Cardiovascular imaging*. 2012;5:734-739.
42. D'andrea A, Radmilovic J, Ballo P, Mele D, Agricola E, Cameli M, Rossi A, Esposito R, Novo G and Mondillo S. Left ventricular hypertrophy or storage disease? the incremental value of speckle tracking strain bull's-eye. *Echocardiography*. 2017;34:746-759.
43. Adeyeye V, Balogun M, Adebayo R, Makinde O, Akinwusi P, Ajayi E, Ogunyemi S, Akintomide A, Ajayi E and Adeyeye A. Echocardiographic Assessment of Cardiac Changes During Normal Pregnancy Among Nigerians. *Clinical Medicine Insights Cardiology*. 2016;10:157.
44. Kampman MA, Valente MA, van Melle JP, Balci A, Roos-Hesselink JW, Mulder BJ, van Dijk A, Oudijk M, Jongbloed M and van Veldhuisen DJ. Cardiac adaption during pregnancy in women with congenital heart disease and healthy women. *Heart*. 2016;102:1302-1308.
45. Ando T, Kaur R, Holmes AA, Brusati A, Fujikura K and Taub CC. Physiological adaptation of the left ventricle during the second and third trimesters of a healthy pregnancy: a speckle tracking echocardiography study. *Am J Cardiovasc Dis*. 2015;5:119-26.
46. Song G, Liu J, Ren W, Qiao W, Zhang J, Zhan Y and Bi W. Reversible changes of left atrial function during pregnancy assessed by two-dimensional speckle tracking echocardiography. *PloS one*. 2015;10:e0125347.
47. Tso GJ, Lee JM, Shaban NM, Lui GK, Trivedi HA, Cohen MN, Bernstein PS and Taub CC. Normal echocardiographic measurements in uncomplicated pregnancy, a single center experience. *Journal of Cardiovascular Disease Research*. 2014;5:3-8.
48. Zanati Bazan SG, Borges VM, Martin LC, Magalhães CG, Hueb JC, de Arruda Silveira LV, Peraçoli JC and Matsubara BB. Disproportionate pregnancy-induced myocardial hypertrophy in women with essential hypertension. *American journal of hypertension*. 2013;26:816-821.
49. Savu O, Jurcuţ R, Giuşcă S, Van Mieghem T, Gussi I, Popescu BA, Ginghină C, Rademakers F, Deprest J and Voigt J-U. Morphological and functional adaptation of the maternal heart during pregnancy. *Circulation: Cardiovascular Imaging*. 2012;5:289-297.
50. Yoon AJ, Song J, Megalla S, Nazari R, Akinlaja O, Pollack S and Bella JN. Left ventricular torsional mechanics in uncomplicated pregnancy. *Clinical cardiology*. 2011;34:543-548.
51. Pandey A, Das A, Srinivas C, Babu M, Himabindu Y, Kumar A and Bhawani G. Maternal myocardial performance in various stages of pregnancy and post-partum. *Research Journal of Cardiology*. 2010;3:9-16.

52. Ogueh O, Brookes C and Johnson MR. A longitudinal study of the maternal cardiovascular adaptation to spontaneous and assisted conception pregnancies. *Hypertension in pregnancy*. 2009;28:273-289.
53. Tzemos N, Silversides CK, Carasso S, Rakowski H and Siu SC. Effect of pregnancy on left ventricular motion (twist) in women with aortic stenosis. *The American journal of cardiology*. 2008;101:870-873.
54. Freire CMV, Nunes MdCP, Barbosa MM, de Oliveira Longo JR, Nogueira AI, Diniz SSA, Machado LJC and de Oliveira AR. Gestational diabetes: a condition of early diastolic abnormalities in young women. *Journal of the American Society of Echocardiography*. 2006;19:1251-1256.
55. Fok W, Chan L, Wong J, Yu C and Lau T. Left ventricular diastolic function during normal pregnancy: assessment by spectral tissue Doppler imaging. *Ultrasound in obstetrics & gynecology*. 2006;28:789-793.
56. Kametas NA, McAuliffe F, Krampl E, Chambers J and Nicolaides KH. Maternal cardiac function during pregnancy at high altitude. *BJOG: An International Journal of Obstetrics & Gynaecology*. 2004;111:1051-1058.
57. Schannwell C, Schneppenheim M, Perings S, Zimmermann T, Plehn G and Strauer B. Alterations of left ventricular function in women with insulin-dependent diabetes mellitus during pregnancy. *Diabetologia*. 2003;46:267-275.
58. Moran AM, Colan SD, Mauer MB and Geva T. Adaptive mechanisms of left ventricular diastolic function to the physiologic load of pregnancy. *Clinical cardiology*. 2002;25:124-131.
59. Del Bene R, Barletta G, Mello G, Lazzeri C, Mecacci F, Parretti E, Martini E, Vecchiarino S, Franchi F and La Villa G. Cardiovascular function in pregnancy: effects of posture. *BJOG: An International Journal of Obstetrics & Gynaecology*. 2001;108:344-352.
60. Mesa A, Jessurun C, Hernandez A, Adam K, Brown D, Vaughn WK and Wilansky S. Left ventricular diastolic function in normal human pregnancy. *Circulation*. 1999;99:511-517.
61. Wolfe L, Preston R, Burggraf G and McGrath M. Effects of pregnancy and chronic exercise on maternal cardiac structure and function. *Canadian journal of physiology and pharmacology*. 1999;77:909-917.
62. Geva T, Mauer MB, Strikera L, Kirshon B and Pivarnik JM. Effects of physiologic load of pregnancy on left ventricular contractility and remodeling. *American heart journal*. 1997;133:53-59.
63. Gilson GJ, Samaan S, Crawford MH, Quails CR and Curet LB. Changes in hemodynamics, ventricular remodeling, and ventricular contractility during normal pregnancy: a longitudinal study. *Obstetrics & Gynecology*. 1997;89:957-962.
64. Mone SM, Sanders SP and Colan SD. Control mechanisms for physiological hypertrophy of pregnancy. *Circulation*. 1996;94:667-672.
65. Mabie WC, DiSessa TG, Crocker LG, Sibai BM and Arheart KL. A longitudinal study of cardiac output in normal human pregnancy. *American journal of obstetrics and gynecology*. 1994;170:849 856.
66. Poppas A, Shroff SG, Korcarz CE, Hibbard JU, Berger DS, Lindheimer MD and Lang RM. Serial assessment of the cardiovascular system in normal pregnancy: role of arterial compliance and pulsatile arterial load. *Circulation*. 1997;95:2407-2415.
67. Nisell H, Carlström K, Ek I, Freyschuss U, Grunewald C, Lunell N and Randmaa I. The effect of pregnancy on maternal central circulation and atrial natriuretic peptide concentrations during acute plasma volume expansion. *Hypertension in pregnancy*. 1993;12:525-532.
68. Vered Z, Mark Poler S, Gibson P, Wlody D and Pérez JE. Noninvasive detection of the morphologic and hemodynamic changes during normal pregnancy. *Clinical cardiology*. 1991;14:327 334.
69. Capeless EL and Clapp JF. Cardiovascular changes in early phase of pregnancy. *American journal of obstetrics and gynecology*. 1989;161:1449-1453.
70. Krajewski A, Wróblewski T and Zachwiej E. Echocardiographic assessment of the circulatory system in healthy pregnant women in the third trimester. *Ginekologia polska*. 1983;54:477-481.

71. Larkin H, Gallery E, Hunyor SN, Gyory AZ and Boyce ES. Haemodynamics of hypertension in pregnancy assessed by M-mode echocardiography. *Clinical and experimental pharmacology & physiology*. 1980;7:463-468.
72. Laird-Meeter K, Van de Ley G, Bom T, Wladimiroff J and Roelandt J. Cardiocirculatory adjustments during pregnancy—an echocardiographic study. *Clinical cardiology*. 1979;2:328-332.
73. Katz R, Karliner JS and Resnik R. Effects of a natural volume overload state (pregnancy) on left ventricular performance in normal human subjects. *Circulation*. 1978;58:434-441.
74. Rubler S, Damani PM and Pinto ER. Cardiac size and performance during pregnancy estimated \with echocardiography. *The American journal of cardiology*. 1977;40:534-540.

SUPPLEMENTAL INFORMATION

Supplemental Table 1. Literature search strategy for PubMed (MEDLINE) and Embase (Ovid).

Component	PubMed (MEDLINE)	Embase (Ovid)
1. Pregnancy	pregnancy [Mesh] OR pregnancy [tiab] OR pregnancies [tiab] OR pregnant [tiab] OR gestation [tiab] OR gestations [tiab] OR gestational [tiab] OR gravidity [Mesh] OR gravidity [tiab] OR gravidities [tiab] OR gravid [tiab]	exp pregnancy/ or exp gravidity/ or exp gestation/ or (pregnancy or pregnancies or pregnant or gestation or gestations or gestational or gravidity or gravidities or gravid).ti,ab.
2. PIH	"hypertension, pregnancy-induced" [Mesh] OR "pregnancy induced hypertension" [tiab] OR "pregnancy associated hypertension" [tiab] OR PIH [tiab] OR "hypertensive pregnancy" [tiab] OR "pregnancy hypertension" [tiab] OR "gestational hypertension" [tiab] OR "HELLP syndrome" [Mesh] OR "HELLP" [tiab] OR "Hemolysis, Elevated Liver Enzymes, Lowered Platelets" [tiab]	exp maternal hypertension/ or exp HELLP syndrome/ or (pregnancy induced hypertension or pregnancy associated hypertension or PIH or hypertensive pregnancy or pregnancy hypertension or gestational hypertension or HELLP or Hemolysis, Elevated Liver Enzymes, Lowered Platelets).ti,ab.
3. FGR	"fetal growth retardation" [tiab] OR "fetal growth retardation" [tiab] OR "fetal growth restriction" [tiab] OR FGR [tiab] OR "intrauterine growth retardation" [tiab] OR "intrauterine growth restriction" [tiab] OR IUGR [tiab] OR "Infant, Small for Gestational Age" [Mesh] OR "small for gestational age" [tiab] OR SGA [tiab]	exp intrauterine growth retardation/ or exp small for date infant/ or (fetal growth retardation or fetal growth restriction or FGR or intrauterine growth retardation or intrauterine growth restriction or IUGR or small for gestational age or SGA).ti,ab.
4. PE	"pre-eclampsia" [Mesh] OR "pre-eclampsia" [tiab] OR preeclampsia [tiab] OR preeclamptic [tiab] OR pre-eclamptic [tiab] or PE [tiab] OR "eclampsia" [Mesh] OR eclampsia [tiab] OR eclampsias [tiab] OR eclamptic [tiab] OR toxemia [tiab] OR toxemias [tiab]	exp preeclampsia/ or exp eclampsia/ or (pre-eclampsia or preeclampsia or pre-eclamptic or preeclamptic or PE or eclampsia or eclampsias or eclamptic or toxemia or toxemias).ti,ab.
5. Gestational diabetes	"Diabetes, Gestational" [Mesh] OR "pregnancy induced diabetes" [tiab] OR "gestational diabetes" [tiab] OR "diabetes gravidarum" [tiab]	exp pregnancy diabetes mellitus/ or (pregnancy induced diabetes or gestational diabetes or diabetes gravidarum).ti,ab.
6. Cardiac ultrasound	"Echocardiography "[Mesh] OR Echocardiography [tiab]	exp echocardiography/ or echocardiography.ti,ab.
7. Geometry	"Ventricular Remodeling"[Mesh] OR "ventricular remodeling" [tiab] OR "cardiac remodeling" [tiab] OR "cardiac adaptation" [tiab] OR "LV geometry" [tiab] OR "left ventricular geometry" [tiab] OR "cardiac geometry" [tiab] OR "cardiac dimension" [tiab]	exp heart ventricle remodeling/ or (ventricular remodeling or cardiac remodeling or cardiac adaptation or LV geometry or left ventricular remodeling or cardiac geometry or cardiac dimension).ti,ab.
8. Systolic function	"Stroke volume" [Mesh] OR "Ventricular Function, Left "[Mesh] OR "Ventricular Ejection Fraction" [tiab] OR "Left ventricular function" [tiab] OR "systolic function" [tiab] OR "Ejection fraction" [tiab]	exp heart ejection fraction/ or exp heart ventricle function/ or (Ventricular Ejection Fraction or Left ventricular function or systolic function or Ejection fraction).ti,ab.
9. Diastolic function	"Diastole"[Mesh] OR "Atrial Remodeling "[Mesh] OR "diastolic function" [tiab] OR "atrial remodeling" [tiab]	exp heart left ventricle filling/ or exp diastole/ or exp heart atrium remodeling/ or (diastolic function or atrial remodeling).ti,ab.
10. Aorta	"Aortic Valve" [Mesh] OR "aortic valve" [tiab] OR "aortic heart valve" [tiab]	exp aortic valve/ or (aortic valve or aortic heart valve).ti,ab.

Conducted search: (1 OR 2 OR 3 OR 4 OR 5) AND (6 OR 7 OR 8 OR 9 OR 10)

Supplemental Table 2. Quality assessment of the included studies.

Domain	Items for consideration	Sengupta *et al.* 2017[27]	Adeyeye *et al.* 2016[43]	Kampman *et al.* 2016[44]	Melchiorre *et al.* 2016[12]	Ando *et al.* 2015[45]	Cong *et al.* 2015[21]	Song *et al.* 2015[46]	Papadopoulou *et al.* 2014[39]
Study Participation	Adequate description of parity or gravidity	+	-	+	+	-	-	-	-
	Adequate description of health or comorbidities of participants	+	+	+	+	+	+	+	+
	Clear reporting of weeks amenorrhea at measurements	+	+	+	+	+	+	+	+
	Adequate description of ethnicity in the study population	-	-	-	+	-	-	+	-
	Height of the study participants reported	-	-	-	+	-	-	+	-
	Non-pregnant weight/BMI reported of the study participants	-	-	-	-	-	-	-	-
	Adequate description of medication or supplements used by the study population	-	-	+	-	-	+	-	-
	Adequate description of participant recruitment	-	+	+	+	+	-	-	-
	Adequate description of inclusion and exclusion criteria	+	+	+	+	+	+	+	+
Study Attrition	Reasons for loss to follow-up/drop-out are provided	+	+	+	?	?	-	+	+
	Adequate description of participants lost to follow-up / differences between participants who completed the study and drop-outs	-	-	-	?	?	-	+	+
Variable Measurements	Method of measurement is adequately valid and reliable	+	+	+	+	+	+	+	+
	The methods and setting are the same for all study participants and throughout follow-up	+	+	+	+	+	+	+	+
Data Reporting	Time frame of measurements are reported as mean	-	+	+	-	+	+	+	-
Study Design	Study used a longitudinal study design	+	+	+	-	-	+	+	+
	Multiple (>2) longitudinal pregnant measurements during pregnancy of the variable	+	+	-	-	-	+	-	+
	Reference value was a pre-pregnant measurement of the variable	-	-	-	-	-	-	-	-
	Score percentage	53%	59%	65%	53%	41%	53%	65%	53%
	Score	**MQ**	**MQ**	**HQ**	**MQ**	**MQ**	**MQ**	**HQ**	**MQ**

Supplemental Table 2. Quality assessment of the included studies. *(continued)*

Ducas *et al.* 2014[30]	Tso *et al.* 2014[47]	Bazan *et al.* 2013[48]	Estensen *et al.* 2013[36]	Savu *et al.* 2012[49]	Dennis *et al.* 2012[22]	Yoon *et al.* 2011[50]	Rossi *et al.* 2011[29]	Pandey *et al.* 2010[51]	Hamad *et al.* 2009[23]	Ogueh *et al.* 2009[52]	Tzemos *et al.* 2008[53]	Freire *et al.* 2006[54]	Fok *et al.* 2006[55]	San-Frutos *et al.* 2005[24]	Kametas *et al.* 2004[56]	Schannwell *et al.* 2003[57]	Moran *et al.* 2002[58]	Simmons *et al.* 2002[25]	Del Bene *et al.* 2001[59]	Borghi *et al.* 2000[26]
+	-	-	+	-	+	-	-	+	+	+	-	-	-	+	+	+	+	+	+	+
+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+
+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+
-	-	-	+	-	+	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
-	+	+	+	-	-	-	-	+	+	-	-	-	-	-	+	-	+	+	-	+
+	-	-	-	+	-	-	-	+	-	-	-	-	-	-	-	-	-	-	-	-
-	-	+	+	+	+	-	-	-	-	-	-	+	-	+	-	-	+	+	-	+
+	+	-	+	+	+	+	-	+	+	+	-	+	+	+	+	-	+	+	+	+
+	+	+	+	+	+	+	+	+	+	-	-	+	+	+	-	+	+	+	-	+
-	?	?	+	+	?	?	?	+	+	+	?	-	+	-	?	-	-	+	+	?
-	?	?	-	-	?	?	?	-	-	-	?	-	-	-	?	-	-	-	-	?
+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
+	+	-	-	+	+	+	+	-	+	+	-	+	-	+	+	+	-	+	-	+
+	-	-	+	+	-	-	-	+	+	+	-	+	+	+	-	+	+	+	+	-
-	-	-	+	+	-	-	-	-	-	+	-	-	+	-	-	+	+	+	+	-
-	-	-	-	-	-	-	-	-	-	+	-	-	-	-	-	-	-	-	+	-
59%	47%	41%	76%	71%	59%	41%	35%	65%	65%	65%	18%	53%	53%	59%	47%	53%	65%	71%	59%	59%
MQ	**MQ**	**MQ**	**HQ**	**HQ**	**MQ**	**MQ**	**MQ**	**HQ**	**HQ**	**HQ**	**LQ**	**MQ**	**MQ**	**MQ**	**MQ**	**MQ**	**HQ**	**HQ**	**MQ**	**MQ**

Supplemental Table 2. Quality assessment of the included studies. *(continued)*

Mesa *et al.* 1999[60]	Wolfe *et al.* 1999[61]	Geva *et al.* 1997[62]	Poppas *et al.* 1997[66]	Gilson *et al.* 1997[63]	Mone *et al.* 1996[64]	Mabie *et al.* 1994[65]	Nisell *et al.* 1993[67]	Vered *et al.* 1991[68]	Capeless *et al.* 1989[69]	Escudero *et al.* 1988[19]	Sanchez *et al.* 1986[20]	Airaksinen *et al.* 1986[28]	Krajewski *et al.* 1983[70]	Kuzniar *et al.* 1983[27]	Larkin *et al.* 1980[71]	Laird-meeter *et al.* 1979[72]	Katz *et al.* 1978[73]	Rubler *et al.* 1977[74]
-	+	+	-	+	-	+	+	+	+	+	+	-	-	+	-	-	-	-
+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
-	-	-	+	+	+	+	-	-	-	-	-	-	-	-	-	-	-	-
-	+	-	-	-	-	+	-	+	-	-	-	-	-	-	-	-	-	-
-	+	-	-	+	-	-	-	-	-	-	-	-	-	-	-	-	-	-
-	+	+	+	+	+	-	+	-	-	-	-	-	-	-	-	-	-	-
-	+	+	+	+	-	+	+	-	-	-	-	+	-	-	-	-	-	-
-	+	+	-	+	-	-	-	-	+	-	-	-	-	-	-	-	-	-
+	-	-	+	+	+	-	+	+	-	?	?	+	?	?	?	-	?	?
-	-	-	-	-	-	-	-	-	-	?	?	-	?	?	?	-	?	?
+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
+	+	-	+	+	-	-	+	+	-	-	+	+	-	+	+	+	-	-
+	+	+	+	+	+	+	+	+	+	-	-	+	-	-	-	+	+	-
+	+	+	+	+	+	+	-	-	+	-	-	+	-	-	-	-	+	-
-	-	-	-	-	-	-	-	-	+	-	-	-	-	-	-	-	-	-
47%	76%	59%	65%	82%	53%	59%	59%	53%	53%	29%	35%	53%	24%	35%	29%	35%	35%	24%
MQ	**HQ**	**MQ**	**HQ**	**HQ**	**MQ**	**MQ**	**MQ**	**MQ**	**MQ**	**LQ**	**MQ**	**MQ**	**LQ**	**MQ**	**LQ**	**MQ**	**MQ**	**LQ**

Supplemental Table 3. Characteristics of the study population in the reference (Ref) and normotensive pregnancy (Preg) groups.

	Subjects (n)		Mean age (yrs)		Mean non-pregnant weight (kg)		Mean height (cm)		Parity / gravidity (n)						Reference	GA (weeks)#
									Nulli-		Primi-		Multi-			
Study	Ref	Preg	Ref	Preg	Ref	Preg	Ref	Preg	Ref	Preg	Ref	Preg	Ref	Preg		
Sengupta *et al.* 2017[37]	20	35	25	23	58	-	-	-	20	-	-	15*	-	15*	NP controls	1st-3rd trim
Adeyeye *et al.* 2016[43]	100	100	28	28	64	-	-	-	-	-	-	-	-	-	NP controls	15-35
Kampman *et al.* 2016[44]	49	49	30	30	-	-	-	-	30	30	-	-	19	19	PP (1 year)	20 & 32
Melchiorre *et al.* 2016[12]	50	559	30	32	56	-	167	165	50	559	-	-	-	-	NP controls	11-39
Ando *et al.* 2015[45]	21	74	30	29	-	-	-	-	-	-	-	-	-	-	NP controls	21 & 33
Cong *et al.* 2015[21]	30	43	31	29	-	-	-	-	-	-	-	-	-	-	NP controls	14-38
Song *et al.* 2015[46]	50	50	29	29	-	-	163	163	-	-	-	-	-	-	PP (6 months)	36
Papadopoulou *et al.* 2014[39]	11	27	30	30	-	-	-	-	-	-	-	-	-	-	NP controls	8-36
Ducas *et al.* 2014[30]	34	34	29	29	-	-	-	-	-	-	-	-	-	-	PP (16 weeks)	34
Tso *et al.* 2014[47]	24	92	30	27	73	-	162	162	-	-	-	-	-	-	NP controls	22 & 34
Bazan *et al.* 2013[48]	48	47	31	29	62	-	162	155	-	-	-	-	-	-	NP controls	35-38
Estensen *et al.* 2013[36]	63	65	32‡	32	-	-	168‡	168	-	38	-	21	-	6	PP (6 months)	14-36
Savu *et al.* 2012[49]	31	51	30‡	30	-	-	-	-	-	-	-	-	-	-	PP (4 months)	12-32
Dennis *et al.* 2012[22]	20	40	29	32	-	-	-	-	18	10	-	-	2	30	NP controls	36
Yoon *et al.* 2011[50]	23	32	28	25	-	-	-	-	-	-	-	-	-	-	NP controls	28
Rossi *et al.* 2011[29]	5	14	29	30	-	-	-	-	-	-	-	-	-	-	NP controls	20 & 32
Pandey *et al.* 2010[51]	22	46	26‡	26	54‡	54	164‡	164	-	26	-	8	-	12	PP (8-12 weeks)	15-40
Hamad *et al.* 2009[23]	30	30	31	31	73	73	167	167	30	30	-	-	-	-	PP (3-6 months)	33
Ogueh *et al.* 2009[52]	13	13	34	34	-	-	-	-	13**	13**	-	-	-	-	Prepregnant	6-36
Tzemos *et al.* 2008[53]	10	10	33	32	-	-	-	-	-	-	-	-	-	-	NP controls	2nd trimester
Freire *et al.* 2006[54]	13	13	30	30	-	-	-	-	-	-	-	-	-	-	PP (19 weeks)	34
Fok *et al.* 2006[55]	29	35	31‡	31	-	-	-	-	-	-	-	-	-	-	PP (6-8 weeks)	8-36
San-Frutos *et al.* 2005[24]	18	18	-	-	-	-	-	-	-	-	*18*	*18*	-	-	PP (6 months)	37
Kametas *et al.* 2004[56]	34	307	28	27	56	-	151	151	-	-	-	-	-	-	NP controls	27
Schannwell *et al.* 2003[57]	51	51	26	26	-	-	-	-	-	-	*26*	*26*	-	-	PP (8 weeks)	9-33
Moran *et al.* 2002[58]	30	30	32	32	-	-	165	165	0.61†	0.61†	-	-	-	-	PP (12-14 weeks)	10-38
Simmons *et al.* 2002[25]	44	44	29	29	-	-	163	163	-	-	*44*	*44*	-	-	PP (13 weeks)	1st-3rd trimester
Del Bene *et al.* 2001[59]	13	13	33	33	-	-	-	-	-	-	*7*	*7*	*9*	*9*	Prepregnant	10-34
Borghi *et al.* 2000[26]	10	35	30	31	57	-	165	162	-	-	-	1.63†	-	-	NP controls	31
Mesa *et al.*1999[60]	8	36	32‡	32	-	-	-	-	-	-	-	-	-	-	PP (7 weeks)	1st-3rd trimester
Wolfe *et al.* 1999[61]	41	41	29	29	-	-	164	164	0.7†	0.7†	-	-	-	-	PP (3-4 months)	17-37
Geva *et al.* 1997[62]	34	34	32	32	-	-	-	-	0.6†	0.6†	*1.6†*	*1.6†*	-	-	PP (12-14 weeks)	10-38
Gilson *et al.* 1997[63]	76	76	21	21			-	-	-	-	*76*	*76*	-	-	PP (6 weeks)	15-36

Supplemental Table 3. Characteristics of the study population in the reference (Ref) and normotensive pregnancy (Preg) groups. *(continued)*

	Subjects (n)		Mean age (yrs)		Mean non-pregnant weight (kg)		Mean height (cm)		Parity / gravidity (n)						Reference	GA (weeks)#
									Nulli-		Primi-		Multi-			
Study	Ref	Preg	Ref	Preg	Ref	Preg	Ref	Preg	Ref	Preg	Ref	Preg	Ref	Preg		
Mone *et al.* 1996[64]	33	33	31	31	-	-	-	-	-	-	-	-	-	-	PP (8-10 weeks)	9-38
Mabie *et al.* 1994[65]	14	18	23‡	23	-	-	163‡	163	8‡	8	-	-	-	-	PP (12 weeks)	8-39
Poppas *et al.* 1997[66]	10	14	32‡	32	-	-	-	-	-	-	-	-	6‡	6	PP (6 months)	12-31
Nisell *et al.* 1993[67]	14	14	28	28	-	-	-	-	11	11	-	-	-	-	PP (3 months)	35
Vered *et al.* 1991[68]	15	15	30	30	-	-	169	169	-	-	*11*	*11*	*4*	*4*	PP (8 weeks)	10-40
Capeless *et al.* 1989[69]	8	8	31	31	-	-	-	-	0.4†	0.4†	-	-	-	-	Prepregnant	6-24
Escudero *et al.* 1988[19]	10	10	21	27	-	-	-	-	10	10	-	-	-	-	NP controls	26-42
Sanchez *et al.* 1986[20]	10	22	25	23	-	-	-	-	-	-	-	*22*	-	-	NP controls	32
Airaksinen *et al.* 1986[28]	11	11	29	29	-	-	-	-	-	-	-	-	-	-	PP (16 weeks)	13-33
Krajewski *et al.* 1983[70]	27	20	-	27	-	-	-	-	-	-	-	-	-	-	NP controls	26-41 weeks
Kuzniar *et al* 1983[27]	25	25	24	-	-	-	-	-	-	25	-	-	-	-	NP controls	36
Larkin *et al.* 1980 [71]	12	12	27	31	-	-	-	-	-	-	-	-	-	-	NP controls	34
Laird-meeter *et al.* 1979[72]	13	13	21-29	21-29	-	-	-	-	-	-	-	-	-	-	PP (6 weeks)	1st-3rd trimester
Katz *et al.* 1978[73]	19	19	25	25	-	-	-	-	-	-	-	-	-	-	PP (6-12 weeks)	1st-3rd trimester
Rubler *et al.* 1977[74]	15	40	24	23	-	-	-	-	-	-	-	-	-	-	NP controls	13-term

Only the first author is given for each study. For subjects, each unique pregnancy is taken into account. Parity is presented in normal font; gravidity is presented in italic font.

†Mean value. ‡ (Mean) value of study group.

PP, postpartum. GA, gestational age.

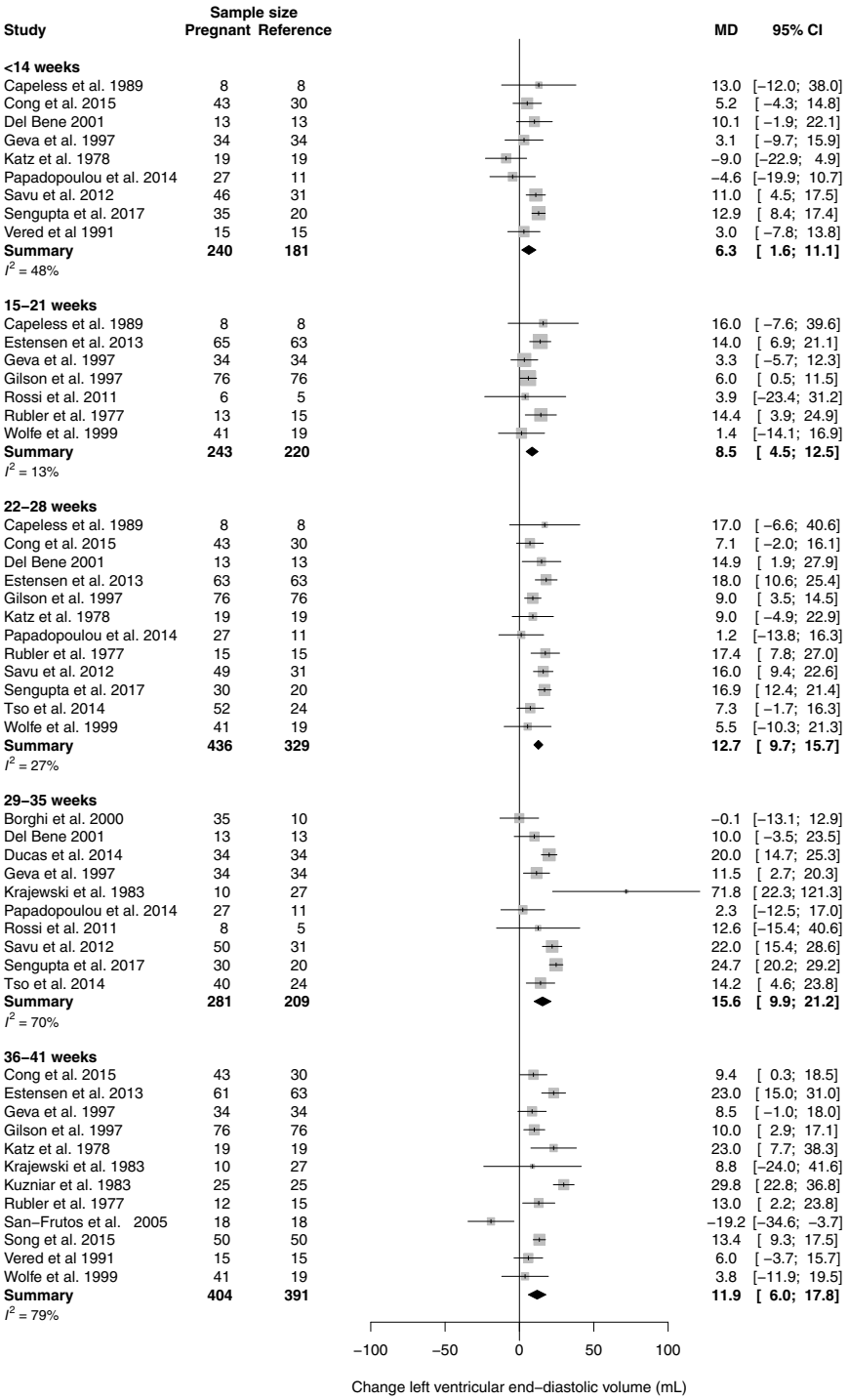
*Parity only reported for those women that completed the follow-up or parity only known for a subgroup of the study population.

** Median parity 0, with a range of 0-1. #, reported in weeks unless stated otherwise.

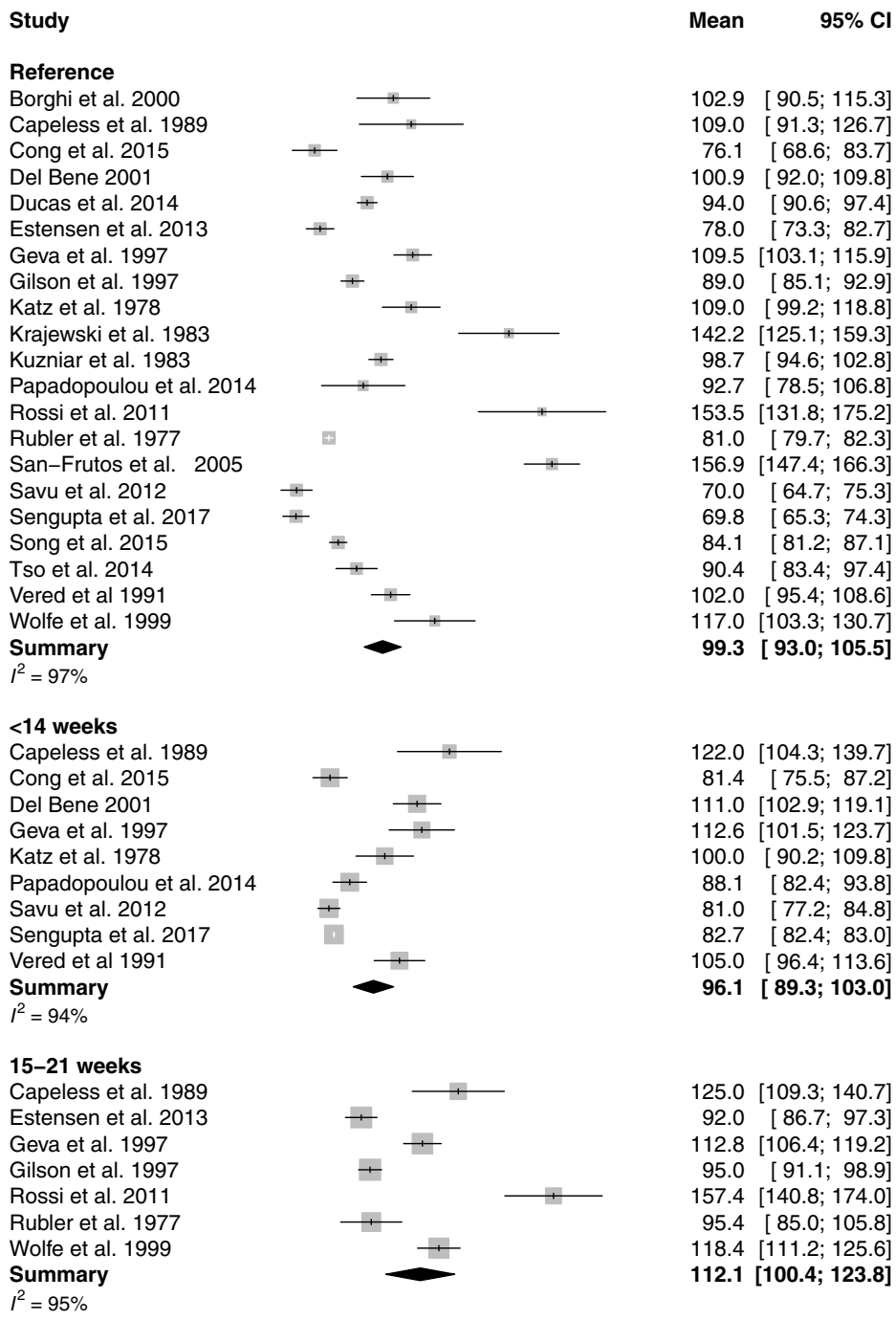
Supplemental Table 4. Characteristics of the study population in the reference (Ref) group and the group with pregnancies complicated by hypertension (CP)

	Subjects (n)		Mean age (yrs)		Mean non-pregnant weight (kg)		Mean height (cm)		Parity / gravidity (n)						Reference	GA (Weeks)#	Complication
									Nulli-		Primi-		Multi-				
Study	Ref	Preg	Ref	Preg	Ref	Preg	Ref	Preg	Ref	Preg	Ref	Preg	Ref	Preg			
Cong *et al.* 2015[21]	30	70	31	31	-	-	-	-	-	-	-	-	-	-	NP controls	29 & 36	Preeclampsia
Dennis *et al.* 2012[22]	20	40	29	31	-	-	-	-	18	26	-	-	2	14	NP controls	36	Preeclampsia
Hamad *et al.* 2009[23]	35	35	31	31	82	82	167	166	30	35	-	-	-	-	PP (3-6 months)	35	Preeclampsia
San-Frutos *et al.* 2005[24]	15	15	30	30	-	-	-	-		-	-	-	-	-	PP (6 months)	36	Preeclampsia
Simmons *et al.* 2002[22]	15	15	32	32	-	-	160	160	-	-	*15*	*15*	-	-	PP (15 weeks)	3rd trimester	Preeclampsia
Borghi *et al.* 2000[25]	10	40	30	31	57	-	165	163	-		-	1.72†	-	-	NP controls	28	Preeclampsia
Escudero *et al.* 1988[19]	10	9	21	24	-	-	-	-	10	9	-	-	-	-	NP controls	>26	PIH
Sanchez *et al.* 1986[20]	10	16	25	26	-	-	-	-	-	16	-	-	-	-	NP controls	32	PIH
Kuzniar *et al.* 1983[27]	25	42	24	17-38	-	-	-	-	-	-	--	-	-	-	NP controls	35	Preeclampsia

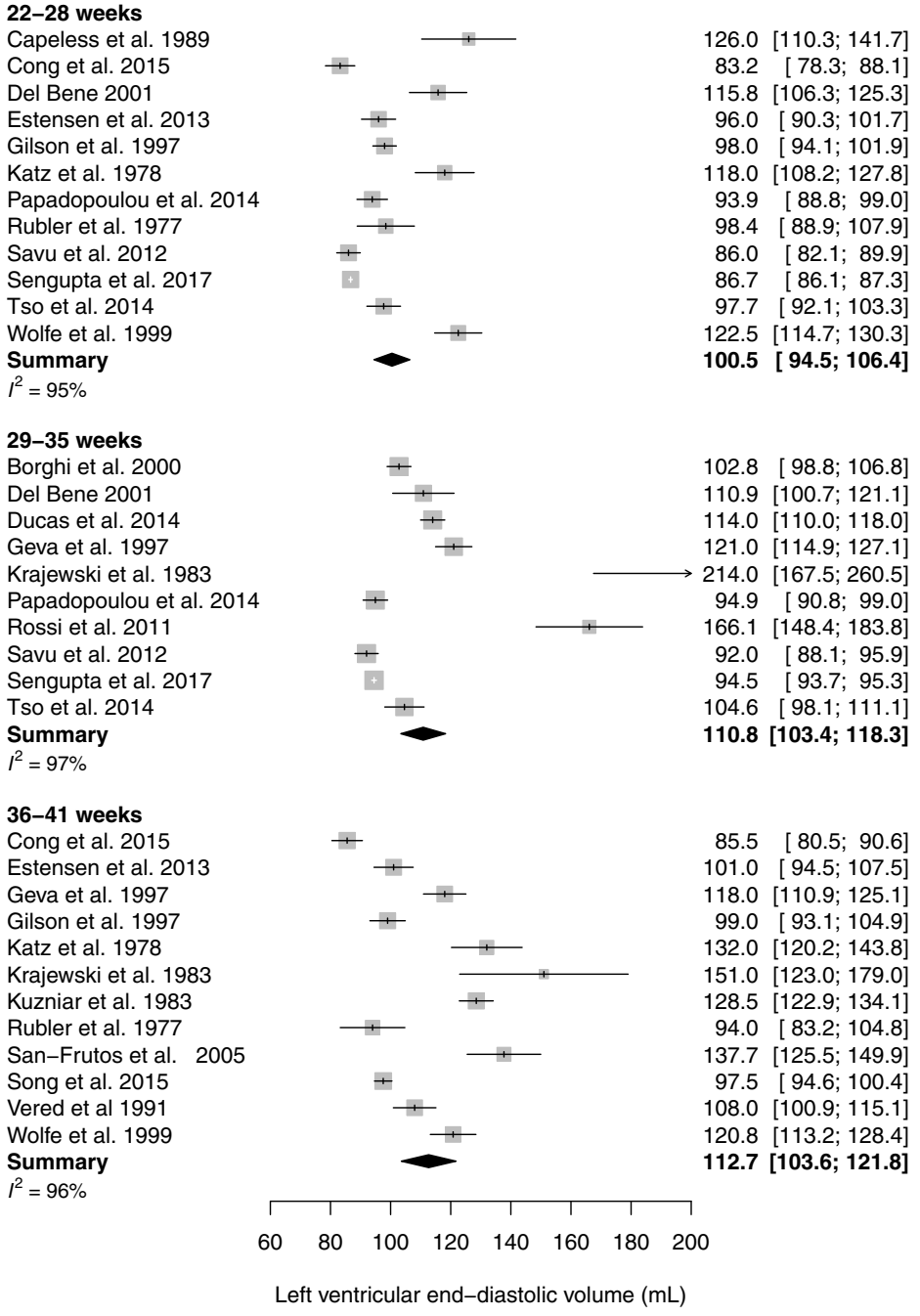
Only the first author is given for each study. Parity is presented in normal font; gravidity is presented in italic font.
PP, postpartum. GA, gestational age. PIH, pregnancy-induced hypertension.
†Mean value. #, reported in weeks unless stated otherwise.



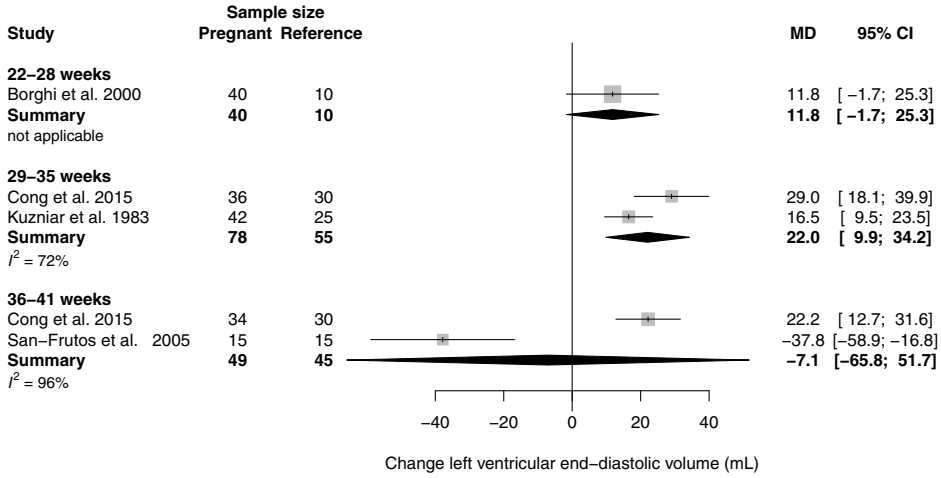
Supplemental Figure 1. Forest plot of LVEDV change during normotensive pregnancy.



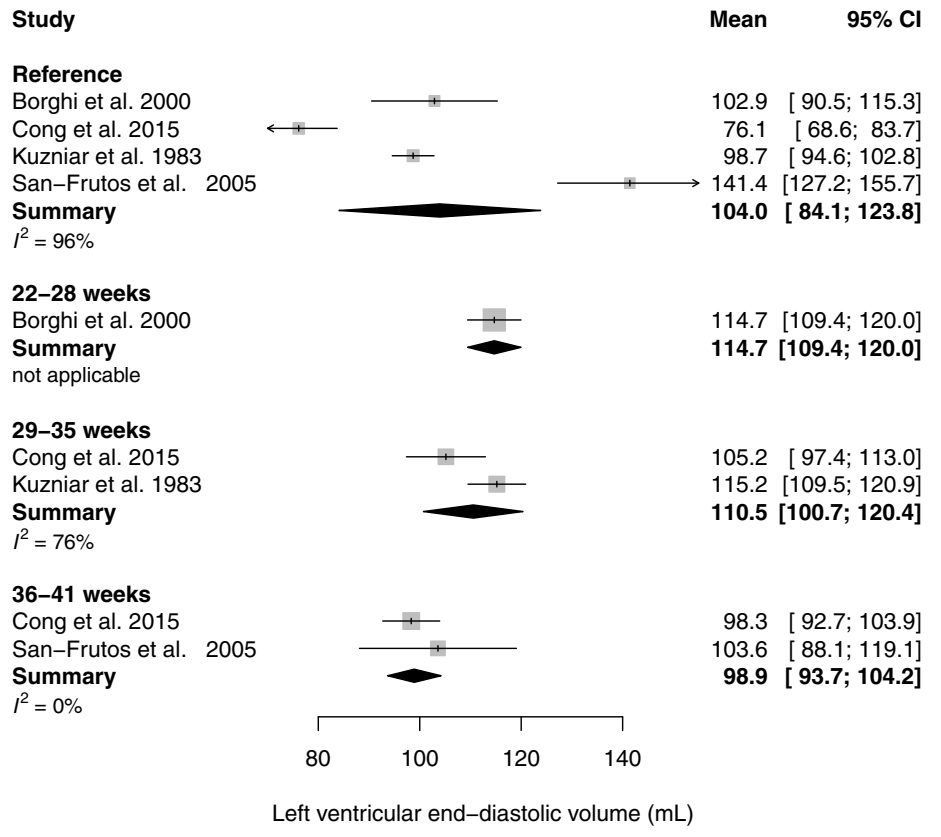
Supplemental Figure 2. Forest plot of absolute LVEDV values during normotensive pregnancy.



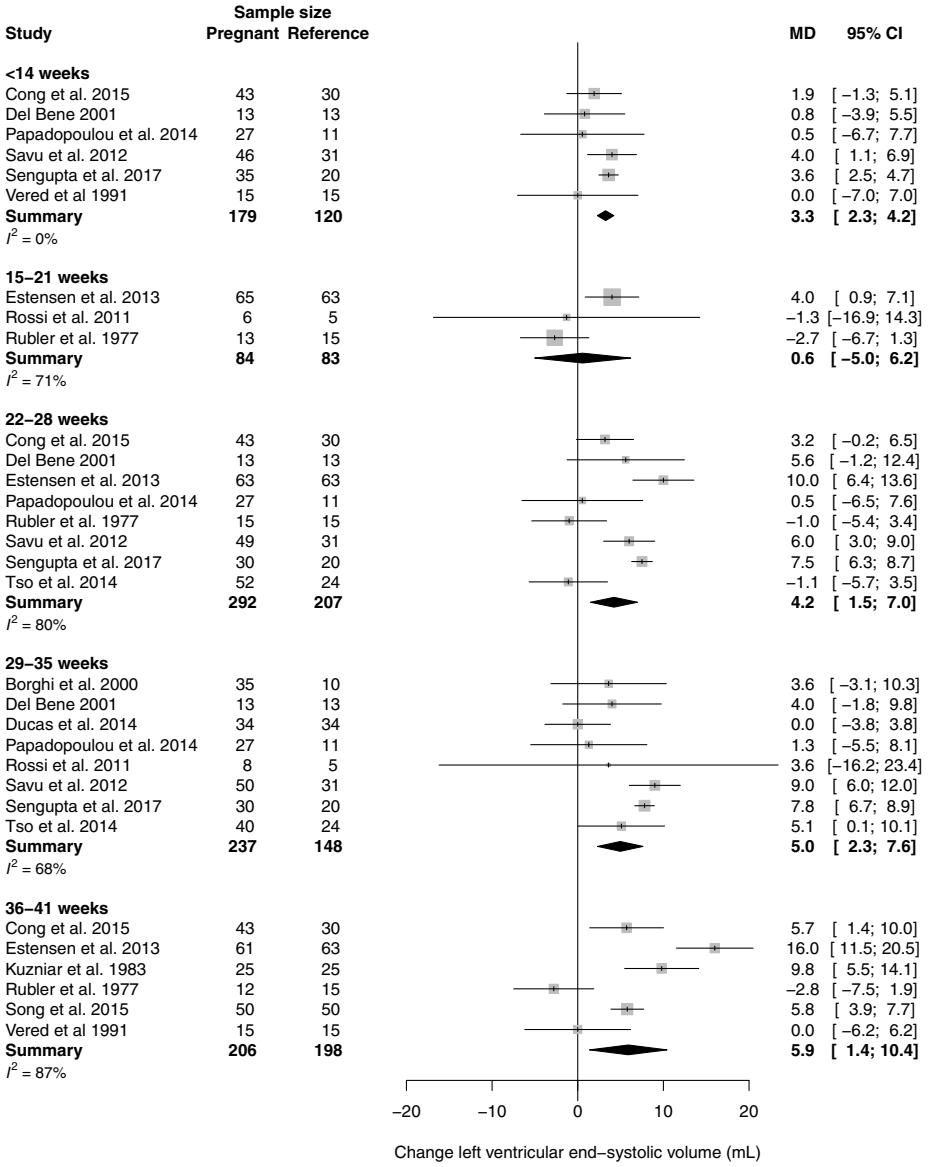
Supplemental Figure 2. Forest plot of absolute LVEDV values during normotensive pregnancy. *(continued)*



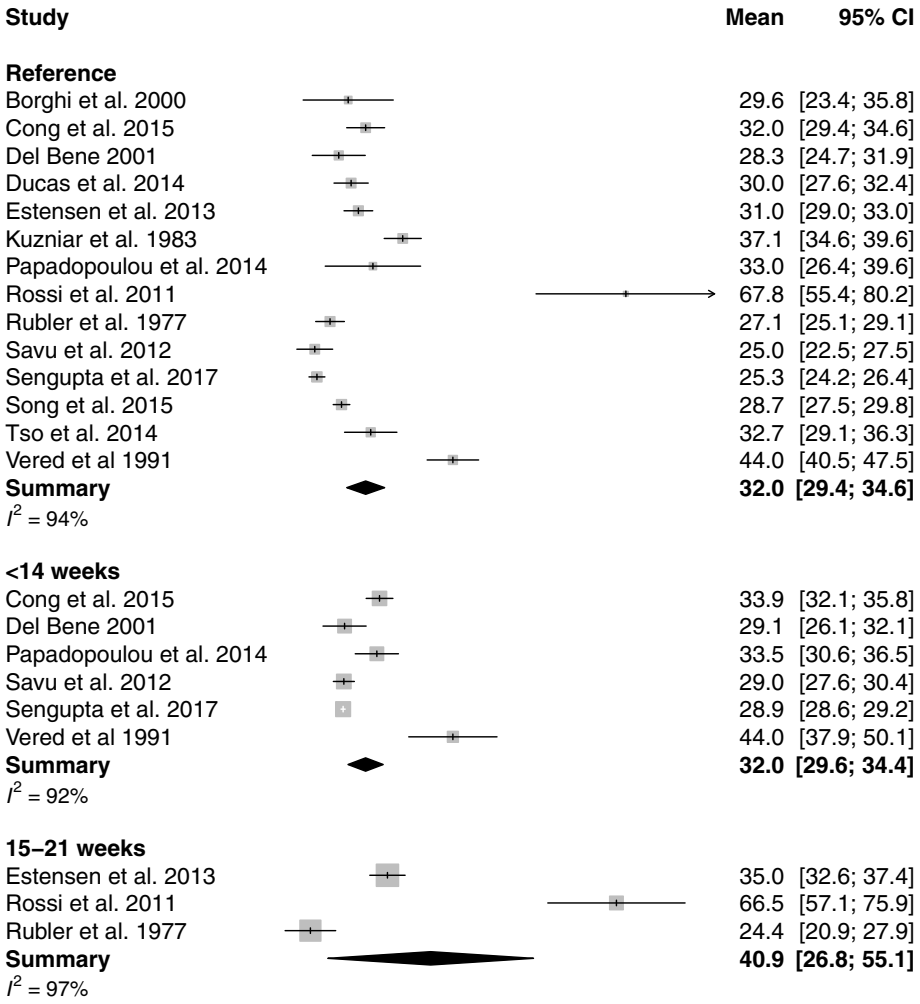
Supplemental Figure 3. Forest plot of LVEDV change during hypertensive pregnancy.



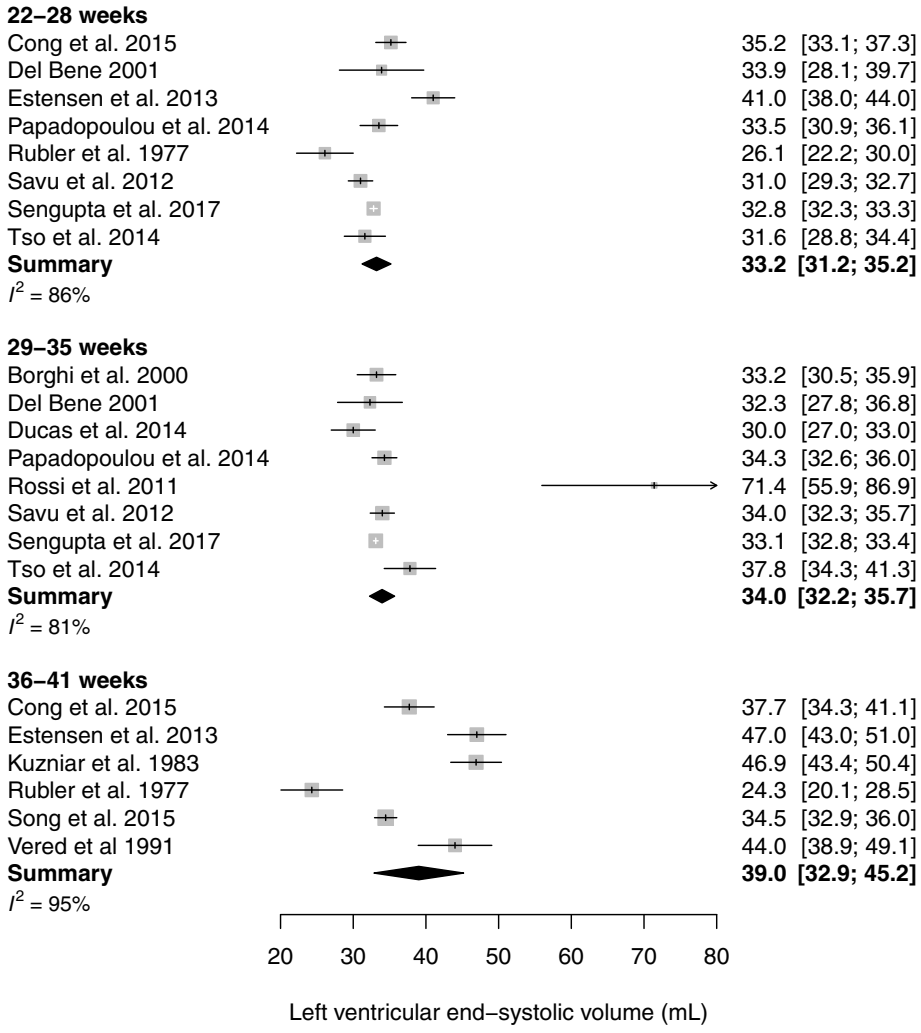
Supplemental Figure 4. Forest plot of absolute LVEDV values during hypertensive pregnancy.



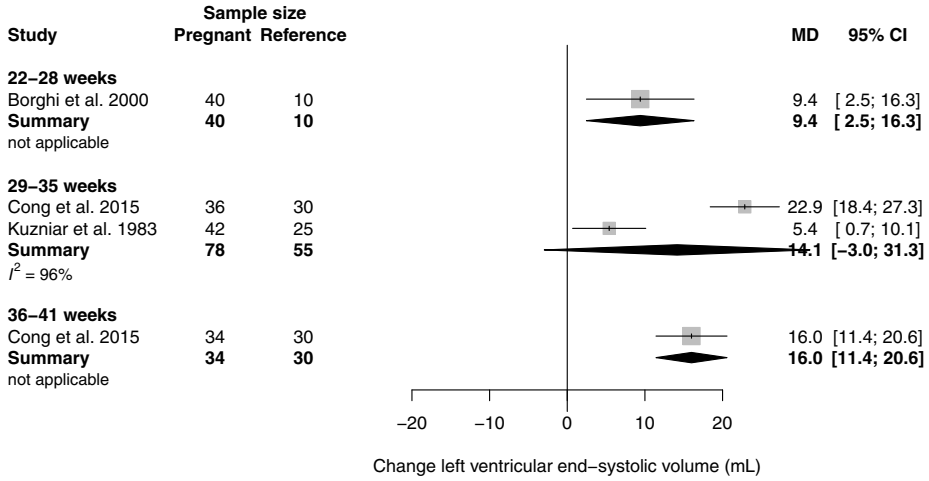
Supplemental Figure 5. Forest plot of LVESV change during normotensive pregnancy.



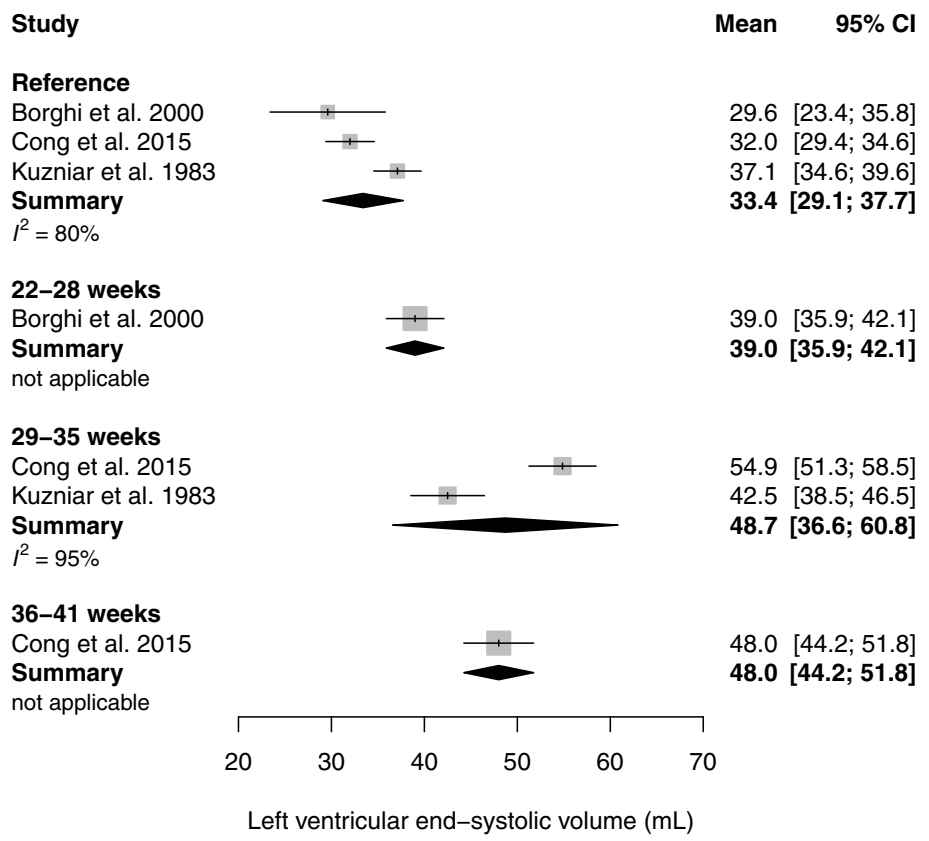
Supplemental Figure 6. Forest plot of absolute LVESV values during normotensive pregnancy.



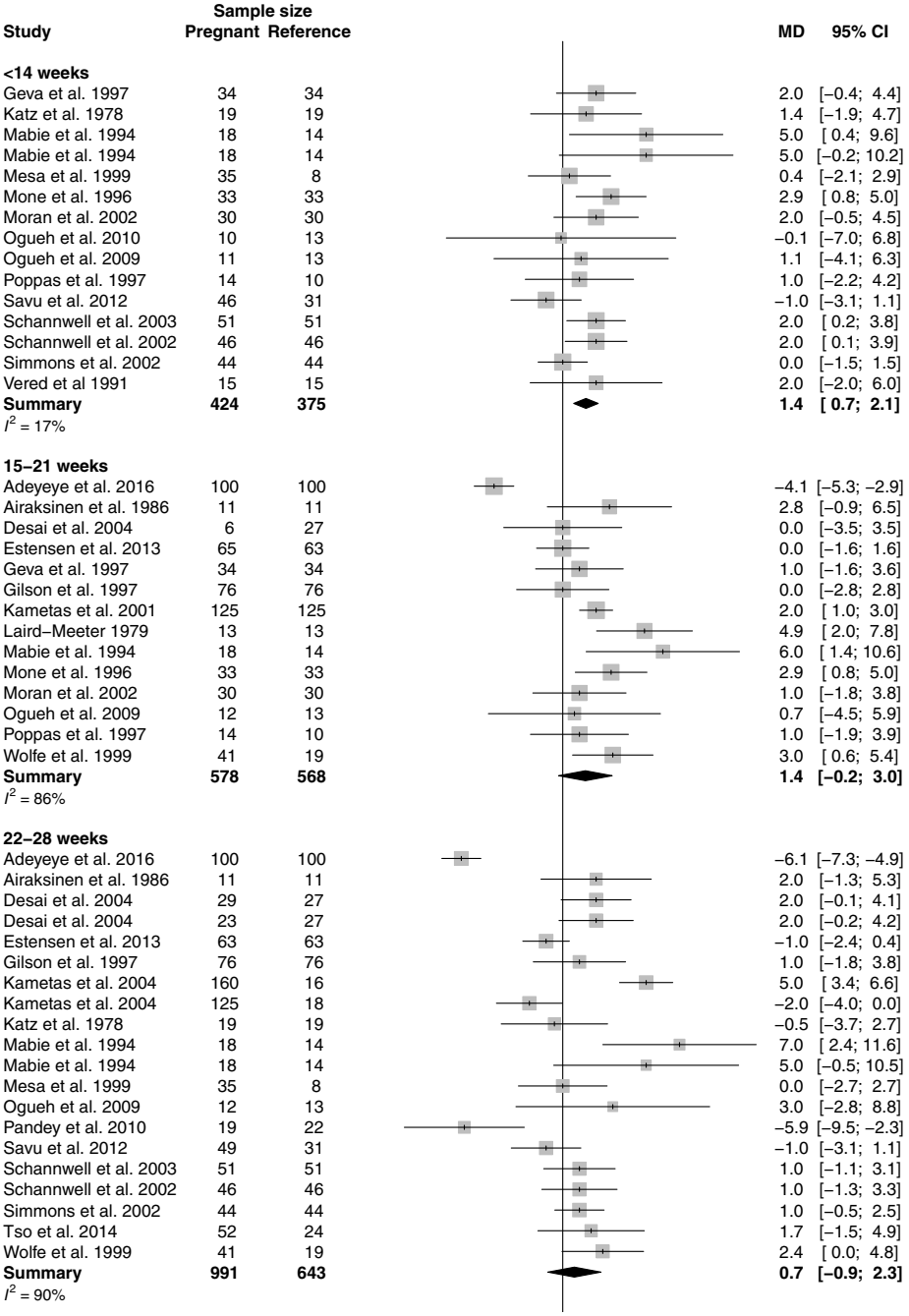
Supplemental Figure 6. Forest plot of absolute LVESV values during normotensive pregnancy. *(continued)*



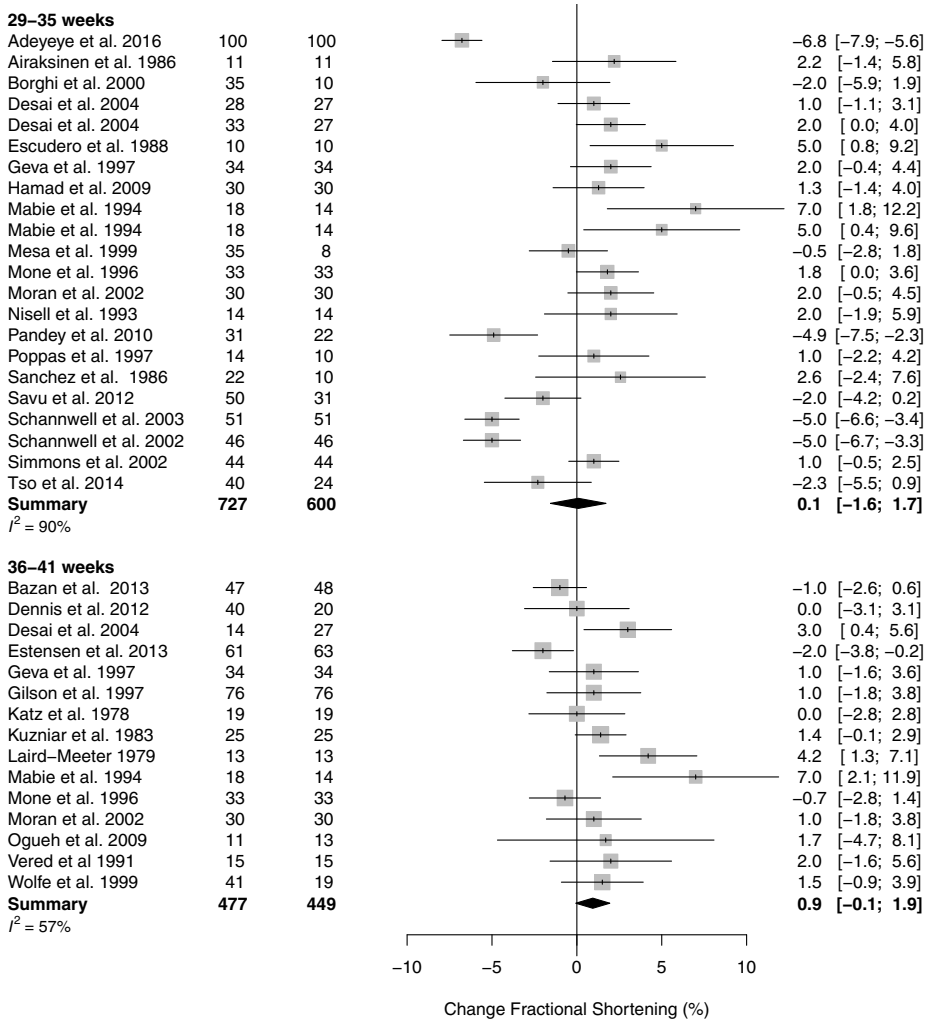
Supplemental Figure 7. Forest plot of LVESV change during hypertensive pregnancy.



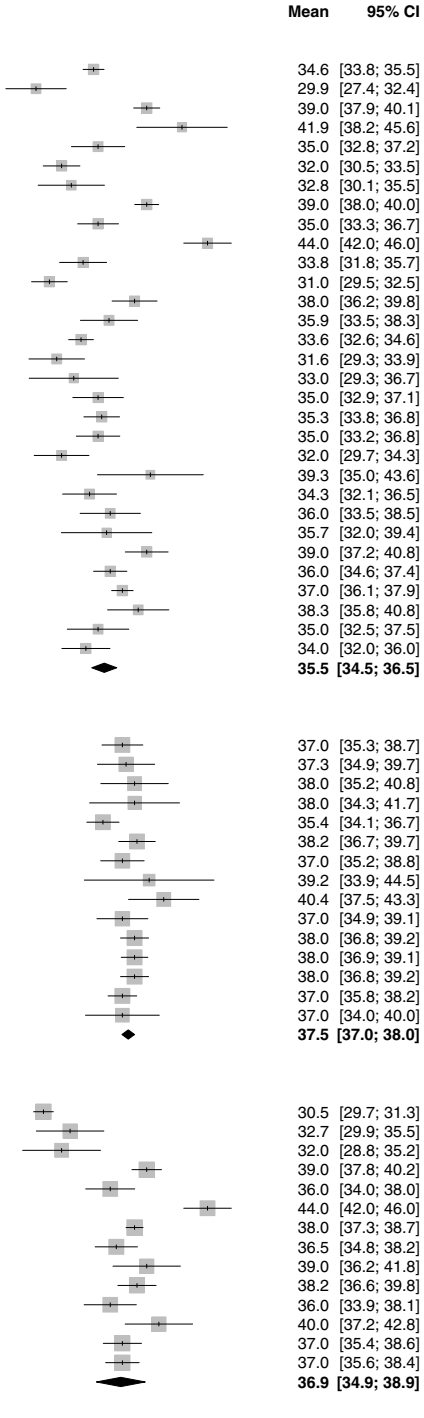
Supplemental Figure 8. Forest plot of absolute LVESV values during hypertensive pregnancy.



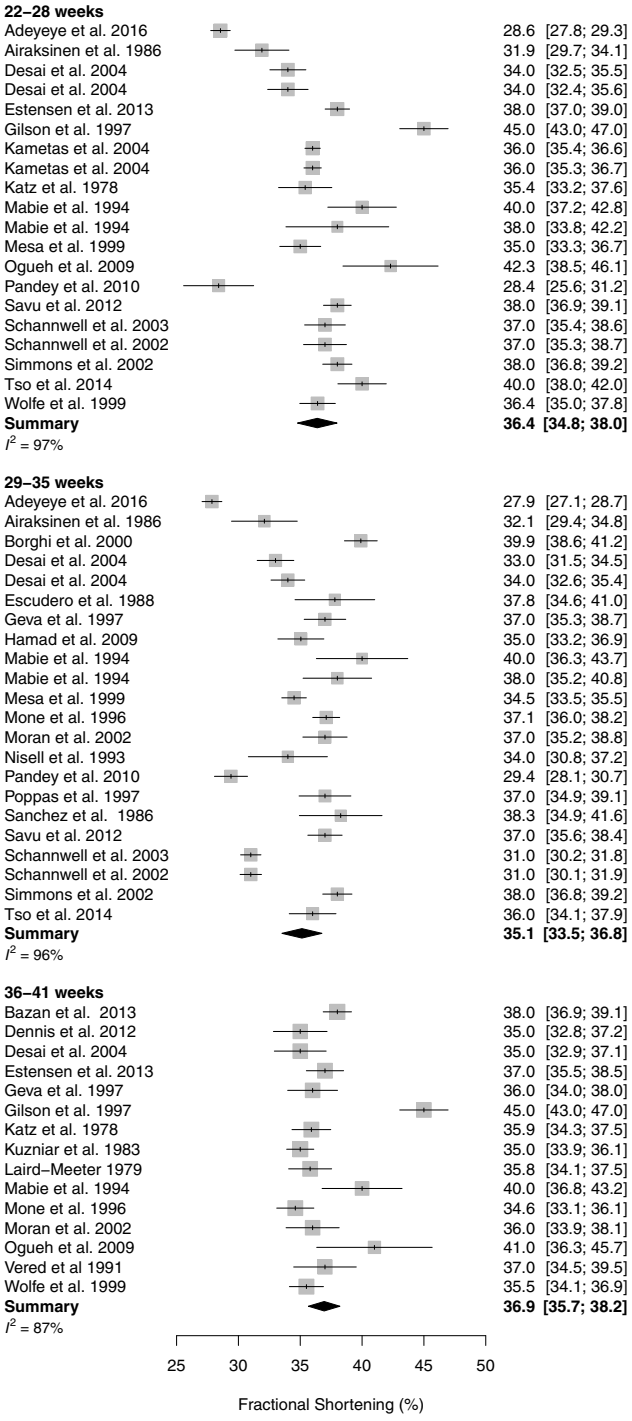
Supplemental Figure 9. Forest plot of FS change during normotensive pregnancy.



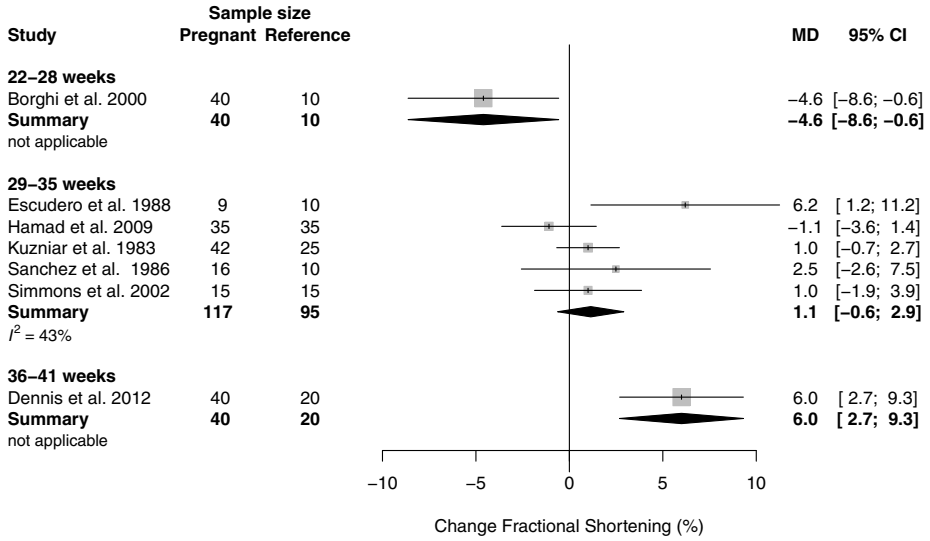
Supplemental Figure 9. Forest plot of FS change during normotensive pregnancy. *(continued)*



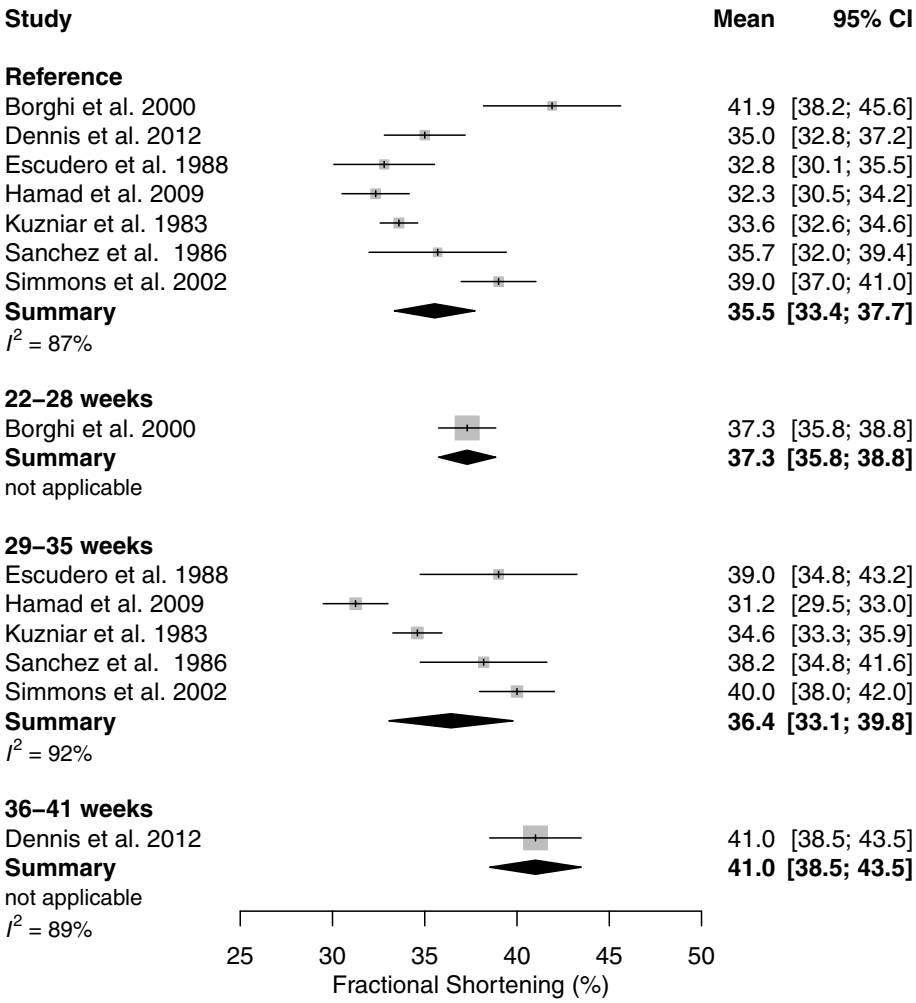
Supplemental Figure 10. Forest plot of absolute FS values during normotensive pregnancy.



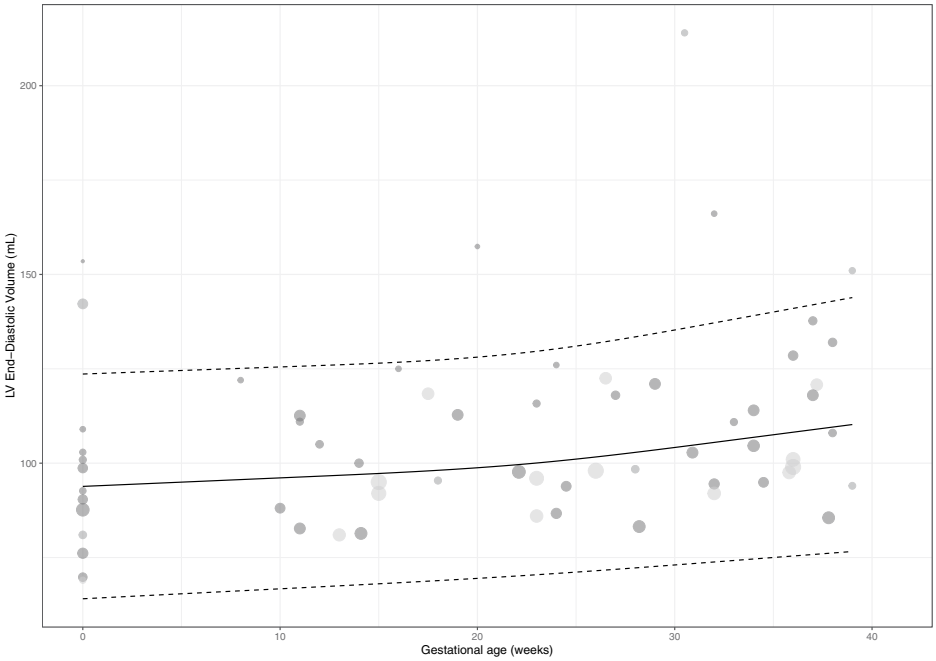
Supplemental Figure 10. Forest plot of absolute FS values during normotensive pregnancy. *(continued)*



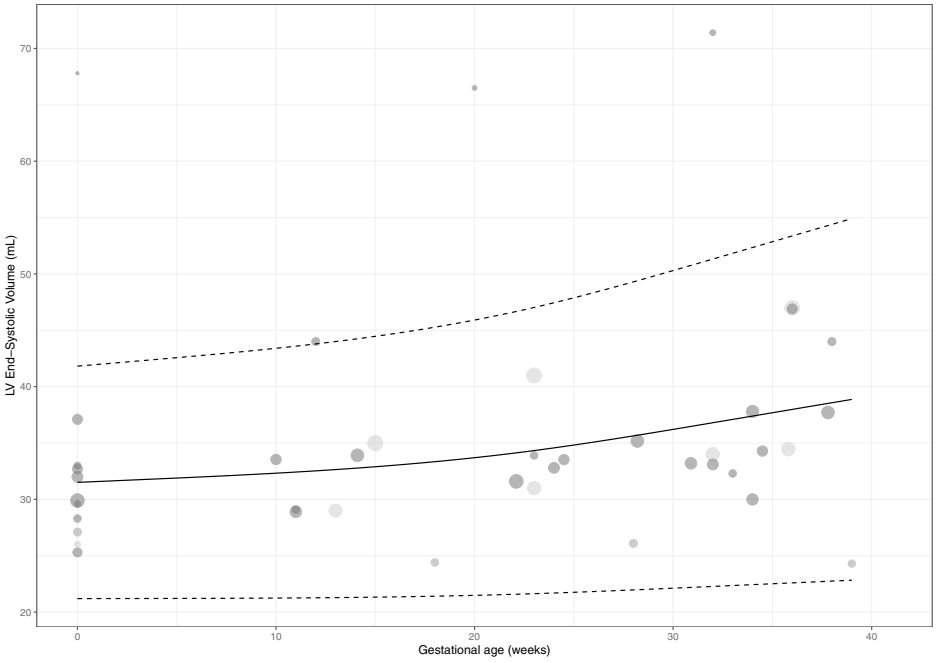
Supplemental Figure 11. Forest plot of FS change during hypertensive pregnancy.



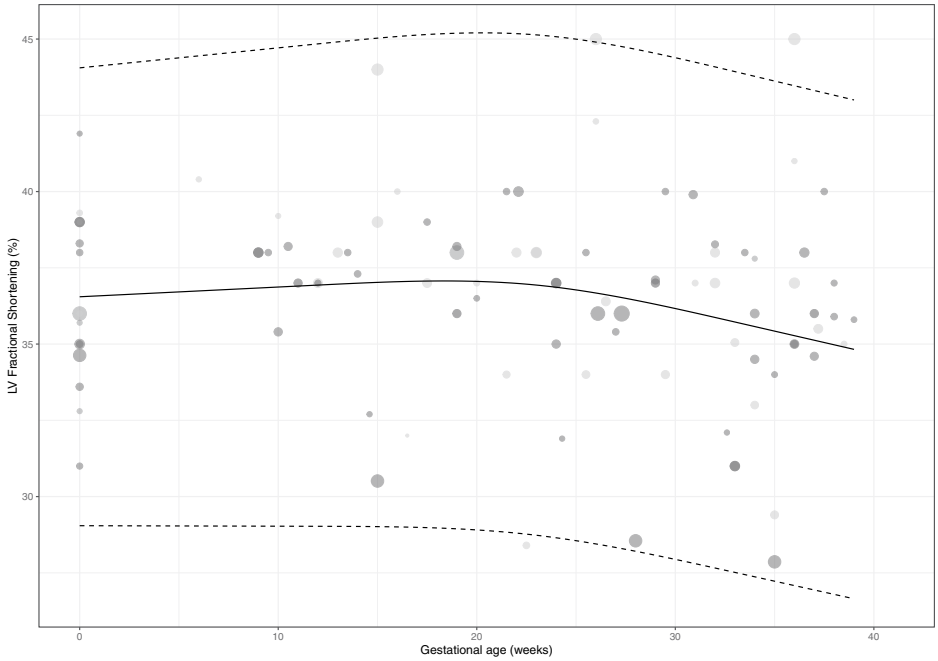
Supplemental Figure 12. Forest plot of absolute FS values during hypertensive pregnancy.



Supplemental Figure 13. Reference curve for LVEDV in normotensive pregnancy.



Supplemental Figure 14. Reference curve for LVESV in normotensive pregnancy.



Supplemental Figure 15. Reference curve for FS in normotensive pregnancy.

Cardiovascular disease risk is only elevated in hypertensive, formerly preeclamptic women

N.M. Breetveld[1], C. Ghossein-Doha[1], S.M.J. van Kuijk[2], A.P. van Dijk[3], M.J. van der Vlugt[3], W.M. Heidema[4], R.R. Scholten[4], M.E.A. Spaanderman[1]

[1] *Department of Obstetrics and Gynaecology, Research School GROW, Maastricht University Medical Centre (MUMC+), Maastricht, The Netherlands*

[2] *Department of Epidemiology, Maastricht University Medical Centre (MUMC+), Maastricht, The Netherlands*

[3] *Department of Cardiology, Radboud University Medical Centre (Radboudumc), Nijmegen, The Netherlands*

[4] *Department of Obstetrics and Gynecology, Radboud University Medical Centre (Radboudumc), Nijmegen, The Netherlands*

British Journal of Obstetrics and Gynaecology. *2015 Jul;122(8):1092-100.*

doi: 10.1111/1471-0528.13057.

ABSTRACT

Objective

To analyse the predicted 10- and 30-year risk scores for cardiovascular disease (CVD) in patients who experienced preeclampsia (PE) 5–10 years previously compared with healthy parous controls.

Design

Observational study.

Setting

Tertiary referral hospital in the Netherlands.

Population

One hundred and fifteen patients with a history of PE and 50 controls. PE patients were categorised into two groups, hypertensive ($n = 21$) and normotensive ($n = 94$), based on use of antihypertensive medication, and next categorised into subgroups based on the onset of PE: early-onset PE ($n = 39$) and late-onset PE ($n = 76$).

Methods

All participants underwent cardiovascular risk screening 5–10 years after index pregnancy. We measured body mass, height and blood pressure. Blood was analysed for fasting glucose, insulin and lipid levels. All participants completed a validated questionnaire. The 10- and 30-year Framingham risk scores were calculated and compared.

Main outcome measures

Estimated Framingham 10- and 30-year risk scores for CVD.

Results

The overall 10- and 30-year CVD median risks weighing subjects' lipids were comparable between formerly PE women and controls; 1.6 versus 1.5% ($P = 0.22$) and 9.0 versus 9.0% ($P = 0.49$), respectively. However, hypertensive formerly PE women have twice the CVD risk as normotensive formerly PE women: 10- and 30-year CVD median risks were 3.1 versus 1.5% ($P < 0.01$) and 19.0% versus 8.0% ($P < 0.01$), respectively. Risk estimates based on BMI rather than lipid profile show comparable results. Early-onset PE clustered more often in the hypertensive formerly PE group and showed significantly higher 10- and 30 year CVD risk estimates based on lipids compared with the late-onset PE group: 1.7 versus 1.3% ($P < 0.05$) and 10.0 versus 7.0% ($P < 0.05$), respectively.

Conclusions

Women who are hypertensive after preeclampsia, have a twofold risk of developing CVD in the next 10–30 years. Formerly PE women who are normotensive in the first 10 years after their preeclamptic pregnancy have a comparable future cardiovascular risk to healthy controls.

Keywords

Cardiovascular risk, Framingham risk score, hypertension, metabolic syndrome, preeclampsia.

INTRODUCTION

Preeclampsia (PE), a vascular pregnancy-related disorder complicating 5–8% of all pregnancies[1] is not only a major cause of fetal and maternal morbidity and mortality[2,3] but also increases the risk for premature cardiovascular disease (CVD) later in life[4,5]. PE is diagnosed as new-onset hypertension after 20 weeks gestational age with proteinuria (0.3 g/day)[6]. Depending on gestational age at delivery, patients with a history of PE have about a two- to – sevenfold risk of developing ischaemic cardiac disease compared with healthy controls and an approximately four-fold risk of developing chronic hypertension within 15 years after pregnancy[4]. Cardiovascular disease is the number one cause of death in women[7]. It is not known whether PE itself, as a gender-specific disorder, increases this risk independently or through risk factors known to be associated with both PE and CVD. Patients with a history of PE exhibit more often constituents of the metabolic syndrome, e.g. insulin resistance, dyslipidaemia, hypertension, micro-albuminuria and obesity compared with patients with a history of uncomplicated pregnancies[8–11]. When detected in time, these factors may be modifiable[12], emphasising the importance of cardiovascular follow-up in these patients. Quantifying the person-specific CVD risk could be useful in counselling these patients.

At present, there is no tailored risk score available to predict cardiovascular disease in this specific population (women with a history of PE). Several risk scores have been proven to be of predictive value in other different risk populations. The Framingham risk score calculator is the most widely used and a well validated strategy to estimate personalised risk[13–15]. Although a few studies have analysed the Framingham risk score in a population of former PE women, these studies did not differentiate between the risk calculator modelled on lipids or on BMI[16–18]. Moreover, these studies did not differentiate between the subgroups of former PE patients, either by onset of disease or later postgestation chronic hypertension[16–18]. The aim of this study was to compare the predicted risk of cardiovascular disease in the next 10 and 30 years as computed with the Framingham risk score calculator, between patients with a history of PE and women who had a normotensive pregnancy in the past (5–10 years after index pregnancy) and subsequently compare subgroups within the former PE group based on onset of disease and/or whether hypertension has developed. We hypothesise that (1) patients with a history of PE have higher predicted Framingham CVD risk scores compared with patients with a history of only uncomplicated pregnancies and that (2) the risk estimates vary among the different subgroups of former PE patients.

METHODS

The study protocol of this observational study was approved by the Medical Ethics Committee of the Radboud University Medical Centre (CMO: 2010/245). For this study, women were included between 2010 and 2012.

Study population

Formerly preeclamptic women were recruited from a database of women who had preeclampsia and volunteered to participate in a cardiovascular follow-up study program. PE in index-pregnancy was diagnosed according to criteria set the International Society of Hypertension in Pregnancy: new-onset hypertension, systolic blood pressure (SBP) ≥ 140 mmHg and/or diastolic blood pressure (DBP) ≥ 90 mmHg, after 20 weeks' gestation and proteinuria exceeding 0.3 g/day[6,19]. Early-onset PE was defined as PE developing before 34 weeks' gestation. [Correction added on 5 December 2014, after first online publication: the number of weeks of gestation has been changed from '35 weeks' to '34 weeks' in the preceding sentence.] Women who had completed the 5- to 10-year postpartum cardiovascular risk screening were eligible for analysis in the current study. Formerly preeclamptic women who participated in a previous study were invited to participate in this study by mail. Initially, former PE women were recruited at the 6 week postpartum screening by a clinician, and were seen at 1 year postpartum, and invited to participate in this study approximately 5 years later. The catchment area of this study population was in the east side of the Netherlands in which the socioeconomic status is reported to be average with a low prevalence of immigrants. Controls were recruited by advertisement in local newspapers, schools and childcare centres in the same area. Women in the control group had to be between 25 and 45 years old, and to have had their first pregnancy 5–10 years earlier.

Pregnancy charts were checked to ensure an uncomplicated pregnancy. Uncomplicated pregnancies were defined as pregnancies not complicated by gestational hypertension, PE, HELLP syndrome or fetal growth restriction, placental abruption or intrauterine fetal demise. Patients and controls underwent the same cardiovascular risk screening according to standardised protocol. At the time of cardiovascular risk screening, all women were nonpregnant and had stopped breastfeeding, women who had pregnancies after the index pregnancy had to be at least 6 months postpartum.

Exclusion criteria used in this study were known diabetes mellitus, auto-immune diseases and pre-existent hypertension prior to index-pregnancy, as these diseases could lead to bias. Finally, participants who did not wish to be informed about the outcome of the screening were excluded.

Measurements

The cardiovascular risk screening started at 08:00 hours in a temperature-controlled room (22°C), after an overnight fast. Body weight (kg, Seca 888 scale, Hamburg, Germany) and height (m) were measured. After 15 minutes' rest, blood pressure (BP) was determined for 30 minutes (at a 3-minute interval) in upright sitting position, using a semiautomatic oscillometric device (Dinamap Vital Signs Monitor 1846; Critikon, Tampa, FL, USA) with a cuff-size appropriate for arm circumference. Participants were instructed not to talk during measurements. The median blood pressure was used for analysis. As the Framingham risk model both weighs the use of antihypertensive medication and actual blood pressure, women were assigned to the hypertensive group when using anti-hypertensive medication. A venous blood sample was taken at the level of the antecubital vein and analysed for fasting glucose (mmol/l), insulin (mmol/l) and lipids (mg/dl): low-density lipoprotein (LDL), high density lipoprotein (HDL), triglycerides and total cholesterol. Body mass index (BMI) was calculated by dividing body weight (kg) by squared height (m). Participants filled out a questionnaire regarding general history, current medication intake, intoxications, lifestyle factors and family history for CVD (in first line relatives < 60 years old). The cardiovascular risk screening was performed following a standardised study protocol by one experienced physician.

Framingham risk scores

Framingham risk scores were calculated with a gender-specific multivariable risk factor algorithm[20]. Variables included sex, age, systolic blood pressure (SBP), hypertension treatment, current smoking and de novo diabetes mellitus plus lipid spectrum (HDL and total cholesterol) or body mass index (BMI)[20–23]. The 10-year risk for CVD was calculated with the 'Cardiovascular disease (10-year risk)' calculator using BMI or lipids in the age range of 30– 74 years[21]. Due to the young age of a few participants, the risk score for 10 years could not be estimated for nine participants. The 30-year risk for CVD was calculated with the 'Cardiovascular disease (30-year risk)' calculator using BMI or lipids in the age range of 20–59 years[22]. Likewise, for the 30-year risk, the 'full CVD' risk score was used which included coronary death, myocardial infarction, fatal or non-fatal stroke, coronary insufficiency, angina pectoris, transient ischaemic attack, intermittent claudication or congestive heart failure[22].

Data analysis

We performed all statistical analyses using SPSS version 20.0 (version 20, IBM SPSS Statistics, Armonk, NY, USA). We reported normally distributed continuous variables as mean (standard deviation) and otherwise as median (range). Binary variables were reported as absolute value (percentage). Formerly preeclamptic patients were subdivided into two groups: a group with hypertension (HTPE) at the time of the cardiovascular evaluation

and women without hypertension (NTPE). In addition, we subdivided the PE group into a group with a history of early-onset of PE and a group with a history of late PE. We used the independent t-test for evaluating differences between groups in continuous variables that were normally distributed. Dichotomous data were analysed using the chi-square test. Differences between variables that were not normally distributed were analysed using the nonparametric Kruskal–Wallis test or the nonparametric Mann–Whitney U-test where appropriate. Differences between the Framingham risk score based on BMI versus lipids were analysed with the Wilcoxon Signed Rank test. A two-sided P-value of < 0.05 was considered statistically significant. We used the difference in risk of developing CVD within 30 years after gestation between the PE and control group to estimate the sample size needed. We determined this sample size on the basis of a clinically relevant proportional difference of 25% in an average 30-year Framingham Risk score (in healthy women estimated to be 10–3.5%) between the PE and the control group. A minimum of 42 patients per group was needed for power of 80%, using an alpha of 5% for determining statistical significance. To compensate for possible heterogeneity among formerly PE patients, we included at least two formerly PE patients for each included control.

RESULTS

In this observational study we included 115 patients with a history of PE and 50 controls with an uncomplicated pregnancy. The characteristics of patients and controls are shown in Table 1. Most women belonged to the European continental ancestry group, two women were of Turkish origin, and one was of Moroccan origin. Patients with previous PE, were on average, 3 years younger, had higher weight and BMI and were using less alcohol compared with controls. The interval between delivery at index pregnancy and cardiovascular risk screening was approximately 2 years longer ($P < 0.01$) and gestational age at delivery was approximately 6 weeks shorter in the PE group compared with controls ($P < 0.01$).

In the former PE group, 21 women had been diagnosed with hypertension and 94 women had not been. In the control group, none of the women was diagnosed with chronic hypertension. The variables of the Framingham risk calculator are presented in Table 2. Patients in the hypertensive formerly PE group have a higher age, SBP and BMI ($P < 0.01$). Moreover, early-onset PE clustered more often in the hypertensive former PE group than in the normotensive former PE group, 90 and 61%, respectively ($P < 0.01$). The results of the 10- and 30-year Framingham risk scores are presented in Table 3. The 10-year predicted risk score weighing subjects' lipids did not differ between formerly PE patients and controls (1.6 and 1.5%, respectively; $P = 0.22$), nor did the 30-year predicted risk score using lipids (9.0 and 9.0%, respectively; $P = 0.49$). The 10-year predicted risk

Table 1. Characteristics of PE and CO group.

	Controls (*n* = 50)	Formerly PE (*n* = 115)	*P*-value
Patient characteristics			
Age, years	39 ± 4.0	36 ± 4.0	**<0.01**
Height, m	1.71 ± 0.1	1.69 ± 0.1	0.09
Weight, kg	69 ± 12	74 ± 18	**<0.05**
BMI, kg/m^2	23.3 ± 3.0	25.6 ± 6.2	**<0.01**
Obesity, (BMI>30kg/m^2), *n* (%)	2/50 (4)	21/115 (18)	**<0.05**
Smoking, *n* (%)	5/50 (10)	9/115 (8)	0.76
Alcohol, *n* (%)	36/50 (72)	26/115 (23)	**<0.01**
Family history of CVD, *n* (%)	22/50 (44)	49/115 (43)	0.87
Obstetric variables			
Primiparous, *n* (%)	5/50 (10)	41/115 (36)	**<0.01**
Postpartum, years	8.0 ± 2.7	5.4 ± 2.6	**<0.01**
Recurrent PE, *n* (%)	-	27/82 (33)	-
Index pregnancy			
GA at birth, weeks	39.6 ± 2.3	33.3 ± 4.3	**<0.01**
Birth weight, g	3367 ± 574	1800 ± 939	**<0.01**
SGA, *n* (%)	-	61/115 (53)	-
IUFD, *n* (%)	-	8/115 (7)	-
Early-onset PE, *n* (%)	-	76/115 (66)	-
Biochemical markers			
Triglycerides, mmol/l	0.9 ± 0.4	1.0 ± 0.5	0.15
Total cholesterol, mg/dl	187.0 ± 29.7	180.1 ± 28.6	0.16
LDL, mg/dl	110.6 ± 25.9	112.7 ± 24.5	0.62
HDL, mg/dl	61.6 ± 13.0	51.8 ± 9.9	**<0.01**
Glucose, mmol/l	4.7 ± 0.4	4.8 ± 0.6	0.27
Insulin, mmol/l	6.3 ± 3.6	8.8 ± 4.7	**<0.01**
HOMA, IR	1.3 ± 0.8	1.9 ± 1.1	**<0.01**
Blood pressure			
Systolic blood pressure, mmHg	110 ± 10	117 ± 13	**<0.01**
Diastolic blood pressure, mmHg	71 ± 7	74 ± 10	0.07
Mean arterial pressure, mmHg	82 ± 8	86 ± 11	**<0.01**

Significant values are written in bold.

BMI, body mass index; CVD, cardiovascular disease; GA, gestational age; HDL, high density lipoprotein; HOMA, homeostatic model assessment; IUFD, intrauterine fetal death; LDL, low density lipoprotein; PE, preeclampsia; SGA, small for gestational age.

Table 2. Demographic characteristics of CO, NTPE and HTPE groups.

	CO (*n* = 50)	NTPE (*n* = 94)	HTPE (*n* = 21)	*P*-value
Age, years	39 ± 4.0	35 ± 3.9	37 ± 3.8	**<0.01**
Early-onset PE, *n* (%)	0 (0)	57/94 (61)	19/21 (90)	**<0.01**
Systolic blood pressure, mmHg	110 ± 10	115 ± 12	125 ± 12	**<0.01**
Antihypertensive treatment, *n* (%)	0 (0)	0 (0)	21/21 (100%)	**<0.01**
Smoking, *n* (%)	5/50 (10)	8/94 (9)	1/21 (5)	0.85
Diabetes, *n* (%)	0 (0)	0 (0)	1/21 (5)	0.13
BMI, kg/m^2	23.3 ± 3.0	25.1 ± 6.2	28.0 ± 5.9	**<0.01**
HDL, mg/dl	61.6 ± 13.0	52.2 ± 10.3	50.0 ± 7.8	**<0.01**
Total cholesterol, mg/dl	187.0 ± 29.7	178.0 ± 28.8	189.9 ± 26.5	0.11

score for the hypertensive formerly PE was higher than in normotensive formerly PE women and controls (respectively, 3.1, 1.5 and 1.5%; $P < 0.01$). The 30-year predicted risk was also higher in the hypertensive formerly PE than in the other groups (respectively, 19.0, 8.0 and 9.0%; $P < 0.01$). The 10-year predicted risk score using BMI instead of lipid profile did not differ between formerly PE patients and controls (1.5 and 1.5% respectively; $P = 0.60$), nor did the 30-year predicted risk score (9.0 and 9.0% respectively; $P = 0.86$). In contrast, the 10-year predicted risk score for the hypertensive formerly PE was higher than that in normotensive formerly PE and controls (respectively, 3.4, 1.5 and 1.5%; $P < 0.01$). Also, the 30-year predicted risk was higher in the hypertensive formerly PE compared with the other groups (respectively, 19.0, 8.0 and 9.0%; $P < 0.01$). The differences we observed were irrespective of the model used, either with or without the use of observed lipid profile (Table 3). Despite comparable estimated median risk, comparing both risk models, the 10-year risk weighing BMI or lipid profile, we observed significant

Table 3. Predicted Framingham CVD risk scores based on lipids or BMI in formerly PE women and healthy parous controls.

	CO (*n* = 50)	PE (*n* = 115)	NTPE (*n* = 94)	HTPE (*n* = 21)
10 year CVD risk				
Lipids	1.5 (1.0;1.9)	1.6 (1.1;2.4)	1.5 (1.1;2.0)	3.1 (2.2;4.3)*,**
BMI	1.5 (1.2;2.3)***	1.7 (1.2;2.4)***	1.5 (1.1;2.0)	3.4 (2.2;5.0)*,**
30 year CVD risk				
Lipids	9.0 (7.0;12.0)	9.0 (7.0;14.0)	8.0 (6.0;11.0)	19.0 (15.0;26.0)*,**
BMI	9.0 (8.0;14.0)***	9.0 (7.0;14.0)	8.0 (6.8;11.0)	19.0 (14.0;28.5)*,**

$^{*}P < 0.01$ relative to CO.

$^{**}P < 0.01$ relative to NTPE.

***Significantly higher than the calculator using lipids.

differences for the CO group and PE group. The 30-year risk models using BMI versus lipid profile indicated significant differences for the CO group, but comparable results for PE, NTPE and HTPE.

Table 4 present the results of the analysis after subdividing the PE group into a subgroup consisting of women who had early-onset PE and a group of women who had late-onset PE. The 10- and 30-year predicted risk score weighing subjects' lipids or BMI did not differ between late-onset PE and controls. However, the 10- and 30-year predicted risk score for early-onset PE based on lipids was higher than in the late-onset PE group (respectively, 1.7 versus 1.3%; $P < 0.05$ and 10.0 versus 7.0%; $P < 0.05$). The 10-year predicted risk score based on the lipids was higher in the early-onset PE than the controls (1.7 and 1.5%, respectively; $P < 0.05$) but only differed from the CO. When weighing BMI, the 10-year predicted risk score did not differ between early-onset PE and both other groups. However, the 30-year predicted risk score for early-onset PE was higher than in the late-onset PE group (10.0 and 8.0%, respectively $P < 0.05$) but did not differ from the control group.

When comparing both risk models (Table 4) we observed a significantly higher score for the risk model weighing BMI compared with the model weighing lipids in the 10-year risk assessment for the late-onset PE group and the CO group and for the 30-year risk assessment in the CO group.

Table 4. Predicted Framingham CVD risk scores based on early- and late-onset PE in formerly PE women and healthy parous controls.

	CO ($n = 50$)	Late-onset PE ($n = 39$)	Early-onset PE ($n = 76$)
10 year CVD risk			
Lipids	1.5 (1.0;1.9)	1.3 (0.9;2.2)	1.7 (1.3;2.5) *,**
BMI	1.5 (1.2;2.3) ***	1.5 (1.1;2.2) ***	1.7 (1.3;2.6)
30 year CVD risk			
Lipids	9.0 (7.0;12.0)	7.0 (6.0;12.0)	10.0 (7.0;14.8)**
BMI	9.0 (8.0;14.0)***	8.0 (6.0;11.0)	10.0 (8.0;14.8) **

*$P < 0.05$ relative to CO.

**$P < 0.05$ relative to late-onset PE.

***Significantly higher than the calculator using lipids.

Next, we subdivided the former PE group into four subgroups based on onset and whether they had hypertension. In the late-onset PE group, 37/39 (95%) were normotensive and 2/39 (5%) were HT. In the early-onset PE group, 57/76 (75%) were NT and 19/76 (25%) were hypertensive. The 10- and 30-year predicted risk score based on the lipids was higher in the early PE-HT compared with the early PE-NT and controls (3.0 versus 1.6 versus 1.5%, $P < 0.01$; 17 versus 9 versus 9%, $P < 0.01$, respectively). The 10- and 30-year

predicted risk score based on the BMI was also higher in early PE-HT compared to early PE-NT and controls (3.1% versus 1.5% versus 1.5% $P < 0.01$; 19% versus 8% versus 9% $P < 0.01$, respectively). However, the modelled cardiovascular disease risk of early PE-NT did not differ in any way from that observed in controls.

DISCUSSION

Main findings

Despite the fact that formerly PE patients have elevated risk of CVD and death compared to healthy parous controls, still the largest fraction will not suffer from these remote vascular complications. In order to differentiate between those with low and elevated risk, we modelled remote cardiovascular risk using Framingham risk scores in formerly PE patients and controls 5 to 10 years after birth, and analysed the predicted 10- and 30-year risk scores. In contrast to our expectations, as group, formerly PE patients had comparable risk estimates compared to healthy parous controls. In contrast to hypertension, other risk factors that are known to be increased after PE (e.g. cholesterol, BMI) did not contribute substantially to the modelled increased risk for CVD in our studied population. Nonetheless, treated hypertensive formerly PE patients had twofold risk on CVD—compared to both normotensive formerly PE patients and controls. The increased risk of CVD after PE appears to be primarily related to blood pressure control and not subclinical biochemical classical cardiovascular risk factors. This study is a translation of the increased risk after PE to a predicting risk score to the patient.

Strengths and limitations

This study compares both formerly PE patients and healthy parous controls at a time interval after birth sufficient to be fully recovered. As such, both the effect of pregnancy course and underlying risk factors could be weighted reliably. Until now, studies that analysed the Framingham risk score in a population did not make a distinction between hypertensive and normotensive former preeclamptic women[16–18]. In fact, normotensive former PE women and women with a history of late-onset PE had comparable modelled cardiovascular event risk with that observed in controls. Women on antihypertensive medication showed a significant increased risk score. This study has some limitations that need to be addressed. First, most women that participated in this study belonged to the European continental ancestry group. Therefore our findings may not fully be translational to other populations. Second, on average, healthy parous controls were older than formerly PE. This difference might have affected calculated risk scores, but can be expected in higher rather than lower risk estimates. Third, the control group was recruited by advertisement in contrast to the former PE group which was a hospital

based recruitment. The women responding to advertisement on cardiovascular check, may somehow have a predisposition for CVD or may have subtle signs making them question their CV risk. If the latest is true, the scores of the control group may give an overestimation of the CV risk. Fourth, it would be an interesting analysis to study in the control group a normotensive and hypertensive group. Unfortunately, our set of included controls does not give us the opportunity to answer this. However, the prevalence of chronic hypertension amongst young women with a history of normotensive pregnancies is extremely low and underscores the suggestion that the increased risk of cardiovascular disease in formerly preeclamptic women primarily originates from high blood pressure. Fifth, the Framingham risk score has not been validated in former PE patients. It may be that the Framingham risk score is not fully applicable for patients with previous PE. Even though we were unable to substantiate an intrinsic detrimental effect of PE itself on remote cardiovascular health, we cannot completely rule out PE to be an independent risk factor for CVD that should be included in the risk prediction independent of other conventional risk factors.

The Framingham risk CV scoring system is originally developed using older populations of men and women[20], and may not be directly applicable in our study population with an average age of 37 years. Thus the scorings system may underestimate the risk score in our population. It would require a very long-term follow-up of a large cohort of postpartum women to determine alternate cut-offs for the 10-year and 30-year risk estimates for cardiovascular events. Further, by weighing traditional cardiovascular risk factors in patients without vascular gestational problems, differences in risk scores primarily seem to originate from chronic hypertension despite treatment, unless BP is really substantially lowered. As the prevalence chronic hypertension rises up to approximately fourfold within 15 years after giving birth[4], our data suggest that the excess in CVD confines to those developing chronic hypertension.

Interpretation

The Framingham risk score is the most compared risk calculator and widely used in North American countries[16]. Other risk models for ischaemic heart disease (IHD) and stroke are SCORE, CUORE and the Reynolds risk score[16,24]. In comparison, the Framingham risk score is the only model which is able to model both 10- and 30-year risk[23]. Despite similarities in estimated outcome, results are conflicting in precision and accuracy. Although some claim the Framingham 10-year risk calculator to estimate close to the actual observed risk[25], others state that the Framingham risk model overestimates the risk of CVD[26,27], or underestimate it in young women. Previous studies claimed the calculated 10- and 30-years CV risk, based on the Framingham risk calculator to be raised in former PE patients compared to controls[16–18]. However, these studies did not report on the differ-

ences between BMI and lipid risk model calculators. In our study, the BMI based model seems to present higher risk estimates on the CVD risk in the next 10–30 years.

Nowadays it is not known which postpartum interval needs to be taken into account to rule out the pregnancy induced alterations in the CV system. It is important to wait a certain period to assure that most PE changes have returned to a steady state. When it is likely that this state is reached, the Framingham risk calculator may be applicable to calculate patients individual risk score. The outcome of the risk calculator may be considered a surrogate marker for CV outcome. We expected, considering the reported elevated chance on cardiovascular disease in these women, a higher cardiovascular risk in formerly preeclamptic women as a whole, especially when also taking lipid profile into account. To our surprise, we did not see this. Only after taking hypertension into account did a higher risk estimate become visible. Therefore we think that, even though we detailed group differences, our analysis underscores the use of the risk calculator in individual care. Follow-up of this population is necessary to validate expectation with observation.

Hypertension strongly affects CVD risk[28]. Moreover, hypertension relates to significant chronic disability[29] and increases the risk of progression to chronic kidney disease and obvious cardiovascular morbidity and mortality[30,31]. Coronary heart disease is three times more frequent in hypertensive than in normotensive individuals[29] and even an SBP ≥ 115 mmHg accounts for two-thirds of cerebrovascular diseases and almost half of ischaemic heart disease cases[32]. As such, there is no single factor except elevated BP that plays a more important role in increasing cardiovascular morbidity, mortality and overall mortality[29].

Functionally, antihypertensive medication has the ability to reverse or correct high blood pressure-induced structural and functional alterations in large and small arteries[33]. Clinically, the detrimental effects on cardiovascular health can be reversed by antihypertensives[34]. In young patients (30–54 years), hypertension treatment resulted in a 41% reduction of cerebrovascular events and 27% risk reduction of fatal and non-fatal cardiovascular events[35]. Meta-analysis of 1 million participants demonstrated a linear association between SBP and DBP and the risk of CVD mortality (down to 115 mmHg and 75 mmHg)[36]. Every 10 mmHg and 5 mmHg decrease of the usual (long-term average) SBP and DBP, respectively, results in a 40% reduction of risk of death from stroke and a 30% reduction in the risk of IHD[36]. Even a small reduction of 2 mmHg from the usual SBP results in a 10% lower stroke mortality and about a 7% lower mortality from IHD or other vascular causes throughout middle age[36]. Consequently, antihypertensives are one of the more cost-effective methods of reducing premature cardiovascular morbidity and mortality[37]. It should be noted that lifestyle interventions could already be sufficient in patients with mildly elevated BP, and should always be suggested when patients receive medication, as these may lower the necessary dosage[38]. However, compliance with long-term healthy lifestyle adjustments is extremely low[34]. Based on average achieved

reduction in traditional cardiovascular risk factors imputed in the several cardiovascular risk models, lifestyle adjustment may lead to a 4–13% reduction in CVD in patients with a history of PE[24].

We found in our study the highest prevalence of hypertension after early-onset PE, which is in line with previous findings[39,40]. The different subclassifications in our study allowed us to conclude that chronic hypertension is a key factor in predicting CVD risk later in life, even in the highest risk subgroup of women with early-onset PE. Moreover, those women with a history of early-onset PE who were normotensive, had comparable risk estimates as controls. Nevertheless, our results suggest that early-onset PE is also associated with the highest risk for hypertension, in contrast to late-onset PE, and there should be greater awareness of the necessity of cardiovascular follow-up.

In contrast to hypertension, other risk factors that are known to be increased after PE (e.g. cholesterol, BMI) did not contribute substantially to the modelled increased risk for CVD in our studied population, either after early-onset or after late-onset disease. Therefore, the observations in this study, together with the available reported evidence, indicate that the PE-related increased risk for CVD is probably increased by chronic hypertension. Nevertheless, it is still unclear whether (1) PE in the absence of other risk factors also predisposes independently to chronic HT and CVD and (2) PE magnifies the negative effects of other subclinical risk factors on cardiovascular health, thus expediting the development of premature CVD. Preventive strategies, early detection and corrective BP treatment towards healthy reference values reduces the risk of coronary heart failure (CHF)[41] and may prevent or delay the onset of costly CVD or renal disease[37]. It is important to manage a careful follow-up, as more than half of known and treated hypertensive subjects still end up with uncontrolled BP despite antihypertensive medicines[42]. The follow-up of former PE patients is also incomplete, as more than one-third of these women do not have their blood pressure followed-up after gestation or opportunistic blood pressure measurements taken when a former PE patient visits the GP for other reasons[43]. Apparently, pregnancies complicated by a vascular disorder are still not being fully recognised as a potential risk factor for developing chronic hypertension and CVD. Besides, there is as yet no tailored risk score model available to assess a patient's individual risk for CVD after PE. Clinicians often perform CV risk assessment on different ways. Most studies have shown group differences for CV risk with an increased risk in former PE women compared with controls. In our study, we used the Framingham risk assessment to calculate the individual CV risk of patients. It is possible to communicate the increased risk to the patient, and make them more aware of the importance of blood pressure measurements and control during follow-up. More importantly, the cardiovascular risk assessment does not stop after one follow-up screening. A woman with no current hypertension has an increased risk of becoming hypertensive in the following

years. We stress the importance of ongoing surveillance which at present we do not think is practised consistently.

CONCLUSIONS

In this study, patients with a history of PE without chronic hypertension have a comparable estimated future risk to develop CVD events compared with patients with uncomplicated pregnancies. In contrast, patients with previous PE who develop chronic hypertension in the first decade after pregnancy have an approximately twofold higher risk of developing CVD in the next 10–30 years. One of five former PE patients who are currently hypertensive seem to be destined for a cardiovascular event. Only former PE women with chronic hypertension and/or early-onset PE have an increased risk score. Apparently, hypertension is a very important and useful risk factor in this specific population. Our findings stress again the importance of CVD screening and follow-up in former PE patients with a special focus on blood pressure measurement and treatment.

DISCLOSURE OF INTERESTS

We have no conflict of interests to report.

CONTRIBUTION TO AUTHORSHIP

MJV, RRS, APD, WMH and MEAS led this study in Nijmegen (The Netherlands). MEAS and CGH suggested looking at the predicted Framingham risk score for developing cardiovascular disease in the next 10–30 years in this specific population (PE and CO). NMB performed the analysis and wrote the manuscript, under the supervision of CGH, SMJK and MEAS. The manuscript was revised and approved by each author.

DETAILS OF ETHICS APPROVAL

The study protocol was approved by the Nijmegen Medical Centre Medical Ethics Committee before patient enrolment (NL32718.091.10). All subjects gave written informed consent before participation. The followed procedures were in conformity with institutional guidelines and adhered to the principles of the Declaration of Helsinki and Title

45, U.S. Code of Federal Regulation, Part 46, Protection of Human Subjects, Revised 13 November 2001, effective 13 December 2001.

FUNDING

None.

REFERENCES

1. Evans CS, Gooch L, Flotta D, Lykins D, Powers RW, Landsittel D, *et al*. Cardiovascular system during the postpartum state in women with a history of preeclampsia. *Hypertension* 2011;58:57–62.
2. Zhang J, Meikle S, Trumble A. Severe maternal morbidity associated with hypertensive disorders in pregnancy in the United States. *Hypertens Pregnancy* 2003;22:203–12.
3. ACOG practice bulletin. ACOG Committee on Practice Bulletins – Obstetrics: Diagnosis and management of preeclampsia and eclampsia. *Obstet Gynecol* 2002;99:159–67.
4. Bellamy L, Casas JP, Hingorani AD, Williams DJ. Pre eclampsia and risk for cardiovascular disease and cancer in later life: systematic review and meta analysis. *BMJ* 2007;335:974–7.
5. Melchiorre K, Sutherland GR, Liberati M, Thilaganathan G. Preeclampsia is associated with persistent postpartum cardiovascular impairment. *Hypertension* 2011;58:709–15.
6. Gifford RW, August PA, Cunningham G, Green LA, Lindheimer MD, McNellis D, *et al*. National high blood pressure education program working group on high blood pressure in pregnancy. Report of the national high blood pressure education program working group on high blood pressure in pregnancy. *Am J Obstet Gynecol* 2000;183: S1–22.
7. Roger VL, Go AS, Lloyd-Jones DM, Benjamin EJ, Berry JD, Borden WB, *et al*. Heart disease and stroke statistics – 2012 update: a report from the American Heart Association. *Circulation* 2012;125: e2–220.
8. Van Rijn BB, Nijdam ME, Bruinse HW, Roest M, Uiterwaal CS, Grobbee DE, *et al*. Cardiovascular disease risk factors in women with a history of early-onset preeclampsia. *Obstet Gynecol* 2013;121:1040–8.
9. Smith GN, Walker MC, Liu A, Wen SW, Swansburg M, Ramshaw H, *et al*. A history of preeclampsia identifies women who have underlying cardiovascular risk factors. *Am J Obstet Gynecol* 2008;200:58. e1–8.
10. Manten GTR, Sikkema MJ, Voorbij HAM, Visser GHA, Bruinse HW, Franx A. Risk factors for cardiovascular disease in women with a history of pregnancy complicated by preeclampsia or intrauterine growth restriction. *Hypertens Pregnancy* 2007;26:39–50.
11. Hermes W, Franx A, van Pampus MG, Bloemenkamp KWM, Bots ML, van dPJ, *et al*. Cardiovascular risk factors in women who had hypertensive disorders late in pregnancy: a cohort study. *Am J Obstet Gynecol* 2013;208:474.e1–e8.
12. Brown MC, Best KE, Pearce MS, Waugh J, Robson SC, Bell R. Cardiovascular disease risk in women with pre eclampsia: systematic review and meta analysis. *Eur J Epidemiol* 2013;28:1–19.
13. Wilson PWF, D'Agostino RB, Levy D, Belanger AM, Silbershatz H, Kannel WB. Prediction of coronary heart disease using risk factor categories. *Circulation* 1998;97:1837–47.
14. National Health and Medical Research Council (NHMRC). Guidelines for the assessment of absolute cardiovascular disease risk. 2009. Available from: www.heartfoundation.org.au/SiteCollectionDocuments/guidelines-Absolute-risk.pdf. Accessed 2 January 2014.
15. Greenland P, Alpert J, Beller GA, Benjamin EF, Budoff MJ, Fayad ZA, *et al*. 2010 ACCF/AHA Guideline for Assessment of Cardiovascular Risk in Asymptomatic Adults: A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J *Am Coll Cardiol* 2010;56:e50–103.
16. Hermes W, Tamsma JT, Grootendorst DC, Franx A, van der Post J, van Pampus MG, *et al*. Cardiovascular risk estimation in women with a history of hypertensive pregnancy disorders at term: a longitudinal follow-up study. *BMC Pregnancy Childbirth* 2013;13:126.
17. Fraser A, Nelson SM, Macdonald-Wallis C, Cherry L, Butler E, Sattar N, *et al*. 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;125:1367–80.

18. Smith GN, Pudwell J, Walker M, Wen S. Ten-year, thirty-year, and lifetime cardiovascular disease risk estimates following a pregnancy complicated by preeclampsia. *J Obstet Gynaecol Can* 2012;34:830– 5.
19. Brown MA, Lindheimer MD, de Swiet M, van Assche A, Moutquin JM. The classification and diagnosis of the hypertensive disorders of pregnancy: statement from the international society for the study of hypertension in pregnancy (ISSHP). *Hypertens Pregnancy* 2001;20:9– 14.
20. D'Agostino RB Sr, Vasan RS, Pencina MJ, Wolf PA, Cobain M, Massaro JM, *et al*. General cardiovascular risk profile for use in primary care: the Framingham Heart Study. *Circulation* 2008;117:743–53.
21. Framingham Heart Study. General Cardiovascular Disease (10-year risk) (based on D'Agostino RB, Vasan RS, Pencina MJ, Wolf PA, Cobain M, Massaro JM, *et al*. General cardiovascular risk profile for use in primary care: The Framingham Heart Study. *Circulation* 2008;117:743–53.) 2014 Available from: www.framinghamheartstudy.org/risk-functions/cardiovascular-disease/10-year-risk.php. Accessed 19 May 2014.
22. Framingham Heart Study. Cardiovascular Disease (30-year risk) (based on Pencina MJ, D'Agostino RB, Larson MG, Massaro JM, Vasan RS. Predicting the 30-year risk of cardiovascular disease. The Framingham Heart Study. *Circulation* 2009;119:3078–3084.) 2014 Available from: www.framinghamheartstudy.org/riskfunctions/cardiovascular-disease/30-year-risk.php. Accessed 19 May 2014
23. Pencina MJ, D'Agostino RB Sr, Larson MG, Massaro JM, Vasan RS. Predicting the 30-year risk of cardiovascular disease: The Framingham Heart Study. *Circulation* 2009;119:3078–84.
24. Berks D, Hoedjes M, Raat H, Duvekot JJ, Steegers EAP, Habbema JDF. Risk of cardiovascular disease after pre-eclampsia and the effect of lifestyle interventions: a literature – based study. *BJOG* 2013;120:924–31.
25. Sayin MR, Cetiner MA, Karabag T, Akpinar I, Sayin E, Kurcer MA, *et al*. Framingham risk score and severity of coronary artery disease. *Herz* 2013;1–6.
26. Barroso LC, Muro EC, Herrera ND, Ochoa GF, Hueros JIC, Buitrago F. Performance of the framingham and SCORE cardiovascular risk prediction functions in a non-diabetic population of a Spanish health care centre: a validation study. *Scand J Prim Health Care* 2010;28:242–8.
27. Giavarina D, Barzon E, Cigolini M, Mezzena G, Soffiati G. Comparison of methods to identify individuals at increased risk of cardiovascular disease in Italian cohorts. *Nutr Metab Cardiovasc Dis* 2007;17:311–18.
28. Mancia G, Fagard R, Narkiewicz K, Redón J, Zanchetti A, Böhm M, *et al*. 2013 Practice guidelines for the management of arterial hypertension of the European Society of Hypertension (ESH) and the European Society of Cardiology. *J Hypertens* 2013;31:1925–38.
29. Mancia G, Grassi G. Management of essential hypertension. *Br Med Bull* 2010;94:189–99.
30. Lim S. Recent update in the management of hypertension. *Acta Med Indones* 2007;39:186–91.
31. Israili ZH, Hernández-Hernández R, Valasco M. The future of antihypertensive treatment. *Am J Ther* 2007;14:121–34.
32. World Health Organization. The World Health Report 2002: Reducing Risks, Promoting Healthy Life. Geneva: *WHO*, 2002.
33. Rehman A, Schiffrin EL. Vascular effects of antihypertensive drug therapy. *Curr Hypertens Rep* 2010;12:226–32.
34. Mancia G, De Backer G, Dominiczak A, Cifkova R, Fagard R, Germano G, *et al*. 2007 Guidelines for the management of arterial hypertension. *J Hypertens* 2007;25:1105–87.
35. Quan A, Kerlikowske K, Gueyffier F, Boissel JP. Efficacy of treating hypertension in women. *J Gen Intern Med* 1999;14:718–29.
36. Lewington S, Clarke R, Qizilbash N, Peto R, Collins R; Prospective Studies Collaboration. Age specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. *Lancet* 2002;360: 1903–13.
37. Elliott WJ. The economic impact of hypertension. *J Clin Hypertens (Greenwich)* 2003;5(3 suppl 2):3–13.

38. Perk J, de Backer G, Gohlke H, Graham I, Reiner Z, Verschuren WMM, *et al*. European Guidelines on cardiovascular disease prevention in clinical practice (version 2012). *Eur Heart J* 2012;33: 635 1701.
39. Melchiorre K, Thilaganathan B. Maternal cardiac function in preeclampsia. *Curr Opin Obstet Gynecol* 2010;23:440–7.
40. Ghossein-Doha C, Peeters L, van Heijster S, van Kuijk S, Spaan J, Delhaas T, *et al*. Hypertension after preeclampsia is preceded by changes in cardiac structure and function. *Hypertension* 2013;62:382 90.
41. Levy D, Larson MG, Vasan RS, Kannel WB, Ho KK. The progression from hypertension to congestive heart failure. *JAMA* 1996;275: 1557–62.
42. Schelleman H, Klungel OH, Kromhout D, de Boer A, Stricker B. Prevalence and determinants of undertreatment of hypertension in the Netherlands. *J Hum Hypertens* 2004;18:317–24.
43. Nijdam ME, Timmerman MR, Franx A, Bruinse HW, Numans ME, Grobbee DE, *et al*. Cardiovascular risk factor assessment after pre-eclampsia in primary care. *BMJ Fam Pract* 2009; 10:77.

Prevalence of asymptomatic heart failure in formerly pre-eclamptic women: a cohort study

N. M. Breetveld[1], C. Ghossein-Doha[1], S. M. J. van Kuijk[2], A. P. van Dijk[3], M. J. van der Vlugt[3], W. M. Heidema[4], J. van Neer[1], V. van Empel[5], H.P. Brunner-La Rocca[5], R. R. Scholten[4], M. E. A. Spaanderman[1]

[1] *Department of Obstetrics and Gynecology, Research School GROW, Maastricht University Medical Centre (MUMC+), Maastricht, The Netherlands*

[2] *Department of Epidemiology, Maastricht University Medical Centre (MUMC+), Maastricht, The Netherlands*

[3] *Department of Cardiology, Radboud University Medical Centre (RadboudUMC), Nijmegen, The Netherlands*

[4] *Department of Obstetrics and Gynecology, Radboud University Medical Centre (RadboudUMC), Nijmegen, The Netherlands*

[5] *Department of Cardiology, Maastricht University Medical Centre (MUMC+), Maastricht, The Netherlands*

Ultrasound in Obstetrics & Gynecology. *2017 Jan; 49(1):134-142.*

doi: 10.1002/uog.16014.

ABSTRACT

Objectives

After pre-eclampsia (PE), the prevalence of structural heart disease without symptoms, i.e. heart failure Stage B (HF-B), may be as high as one in four women in the first year postpartum. We hypothesize that a significant number of formerly pre-eclamptic women with HF-B postpartum are still in their resolving period and will not have HF-B during follow-up.

Methods

In this prospective longitudinal cohort study, we included 69 formerly pre-eclamptic women who underwent serial echocardiographic measurements at 1 and 4 years postpartum. HF-B was diagnosed as left ventricular hypertrophy (left ventricular mass index (LVMi) > 95g/m^2), concentric remodeling (relative wall thickness > 0.42 and LVMi ≤ 95g/m^2), mild systolic dysfunction (left ventricular ejection fraction > 40% and < 55%) or asymptomatic valvular disease. Women were subdivided and analyzed according to HF-B outcome: no HF-B at either visit; HF-B at first visit only; HF-B at second visit only; HF-B at both visits.

Results

The prevalence of HF-B in formerly pre-eclamptic women was 23% in the first year postpartum and 23% after 4 years. At the second visit, HF-B had resolved in 62.5% of affected women but was newly developed in 19% of initially unaffected women. At the first visit, 56% of women diagnosed with HF-B had reduced systolic function whereas at the second visit 69% of women with HF-B had concentric remodeling with mostly normal ejection fraction, consistent with diastolic dysfunction.

Conclusions

The prevalence of HF-B can be considered consistently high (1 in 4) amongst formerly pre-eclamptic women at follow-up. Nonetheless, at an individual level, more than 60% of women found initially to be affected by HF-B will recover, whilst about 20% of formerly pre-eclamptic women with normal echocardiography in the first year postpartum will develop HF-B over the following years.

Keywords

Cardiovascular disease, echocardiography, heart failure, HFpEF, pre-eclampsia.

INTRODUCTION

Cardiovascular disease (CVD) is the leading cause of death worldwide [1–3]. Although more men are affected by CVD than women, more women die of the disease[4]. Aside from the classical risk factors that contribute to the development of CVD[2], women also have gender-specific risk factors such as pre-eclampsia (PE), a hypertensive pregnancy syndrome[5], which increases the risk for CVD developing within 15 years after pregnancy by two- to seven-fold[6]. In contrast to healthy pregnancies in which left ventricular (LV) eccentric hypertrophy occurs, during a pre-eclamptic pregnancy the left ventricle undergoes remodeling and concentric hypertrophy occurs, resembling that seen in heart failure (HF)[7,8]. The additional PE-induced increase in left ventricular mass (LVM) does not always resolve completely postpartum[9]. In fact, the incidence of preclinical HF Stage B (HF-B) is 24% at 1 year postpartum in formerly pre-eclamptic patients[9].

HF is becoming a major health problem as life expectancy and prevalence of risk factors rise globally, leading to high healthcare costs, exceeding even those of cancer[10]. The progression of preclinical HF-B to the clinical stage C is associated with a five-fold increase in cardiovascular-related morbidity, mortality and decrease in quality of life[11,12]. This highlights the importance of identifying patients early in Stage B, which is potentially reversible when treated appropriately.

More women are affected by HF than are men[4], and therefore sex differences in this condition should be evaluated. Currently, it is not known whether HF-B persists in formerly pre-eclamptic women. On the one hand, if HF-B persists, secondary prevention programs could be implemented. On the other hand, if HF-B resolves spontaneously over time, expectant management seems a reasonable option. In our study, we hypothesize that a significant number of women with HF-B at 1 year postpartum are still in their resolving period and will no longer have HF-B 4 years later. To this end, we performed serial cardiac ultrasound examinations in women with a history of PE at 1 and 4 years postpartum.

METHODS

This longitudinal cohort study was approved by the medical ethics committee of the Radboud University Medical Center (NL32718.091.10) before patient enrollment and all subjects provided written informed consent before participation. The procedures we followed conformed with institutional guidelines and adhered to the principles of the Declaration of Helsinki and Title 45, U.S. Code of Federal Regulation, Part 46, Protection of Human Subjects, Revised 13 November 2001, effective 13 December 2001. We included women who had a 1-year postpartum clinical cardiovascular risk assessment

following a pregnancy complicated by PE and invited them for a second postpartum follow-up screening between 2009 and 2011.

Study Population

Formerly pre-eclamptic women were recruited by an obstetric clinician at the 6-week-postpartum visit to participate in a 1-year postpartum cardiovascular screening assessment. At 4 years postpartum, women were invited by mail to participate in the cardiovascular follow-up study. The catchment area of this study population was in the east side of the Netherlands in which the socioeconomic status is reported to be average, with a low prevalence of immigrants. For the second visit, we included 69 women without any pre-existing comorbidity (diabetes mellitus, autoimmune disease, or pre-existing hypertension) and with a complete workup at both visits that allowed us to diagnose HF-B at two separate time points following a pregnancy complicated by PE.

PE in the index pregnancy was diagnosed according to the criteria set by the International Society of Hypertension in Pregnancy: new-onset hypertension, systolic blood pressure (SBP) ≥ 140mmHg and/or diastolic blood pressure (DBP) ≥ 90mmHg, after 20 weeks' gestation and proteinuria exceeding 0.3g/day[13]. Early-onset PE was diagnosed as PE developing before 34 weeks' gestation. Preterm PE was defined as PE requiring delivery before 37 weeks' gestation. Four women in the study population gave birth to twins. All birth weights were included in our analysis. A birth weight ≤ 10th percentile was defined as small-for-gestational age. Patients underwent cardiovascular screening and echocardiographic measurements according to a standardized protocol at both postpartum intervals. Most women were of continental European ancestry; two women were of Turkish descent and one was of Moroccan descent. At the time of the first set of measurements, no woman was pregnant, all had stopped breastfeeding and none was using oral contraceptives. Women who had become pregnant again after their index pregnancy had to be at least 6 months postpartum for their second measurement.

Cardiovascular screening

Each cardiovascular screening examination started at 8:00am in a temperature-controlled room (22 °C), after an overnight fast and was performed following a standardized study protocol by an experienced physician. The cardiovascular screening consisted of determination of body mass index (BMI) by measuring body weight (Seca 888 scale, Hamburg, Germany) and height. After 15min of rest, SBP, DBP and mean arterial pressure (MAP) were measured for 30min (at 3-min intervals) with the patient in an upright sitting position, using a semi-automatic oscillometric device (Dinamap Vital Signs Monitor 1846; Critikon, Tampa, FL, USA) with a cuff size appropriate for arm circumference. We used the median of each patient's measurements for statistical analysis. During the measurements, the participants were not allowed to talk and external disturbances were kept to

a minimum. Hypertension was defined as SBP ≥ 140mmHg and/or DBP ≥ 90mmHg and/or if taking antihypertensive medication. Prehypertension was defined as SBP of 120–139mmHg and/or DBP of 80–89mmHg. Blood samples were taken by venepuncture at the level of the antecubital vein and analyzed for fasting glucose (mmol/L), fasting insulin (mU/L) and lipids (mmol/L; low-density lipoprotein (LDL), high density lipoprotein (HDL), total cholesterol and triglycerides). The homeostasis model assessment index for insulin resistance (HOMAIR) was calculated by insulin (mU/L)×glucose (mmol/L)/22.5[14]. All participants collected their urine 24h preceding the measurements. The 24-h urine sample was assayed for albumin and creatinine to determine the (micro)albuminuria corrected for creatinine output (g/mol creatinine) (Aeroset, Abbot Laboratories, Chicago, IL, USA). Participants completed a questionnaire consisting of general history, current medication intake, intoxications (smoking was defined as ≥ one cigarette per day), lifestyle factors and family history of CVD (in first-degree relatives < 60 years old), occurrence of PE in first-degree relatives and gestational age at which participants themselves were born and their birth weight. Preterm birth was defined as a birth before 37 weeks' gestation.

Echocardiographic measurements

Echocardiographic measurements were performed with a phased-array echocardiographic Doppler system. We performed two-dimensional, M-mode and Doppler echocardiography according to the guidelines of the American Society of Echocardiography (ASE)[15]. We measured LV end-diastolic (LVEDd) and LV end-systolic (LVESd) diameters as well as end-diastolic interventricular septum thickness (IVST) and posterior wall thickness (PWT) using M-mode in the parasternal long-axis view. LVM was calculated using the formula $0.8\times (1.04 ((LVEDd+PWT+IVST)^3 - LVEDd^3)) + 0.6$ and indexed for body surface area (BSA; Dubois formula), as recommended by the ASE[16]. The relative wall thickness (RWT) was calculated using the formula $(2\times PWT)/LVEDd$[16]. LV end-diastolic volume (LVEDV) and LV end-systolic volume (LVESV) were estimated using the Teicholz formula[16]. Left ventricular ejection fraction (LVEF) was calculated by $[(LVEDV - LVESV)/LVEDV]\times 100$. In all cardiac assessments, heart rate (HR) was obtained by taking the reciprocal of the mean of five consecutive R–R intervals on the electrocardiogram multiplied by 60. Stroke volume and cardiac output were indexed for BSA.

Definition of heart failure stage B

HF was diagnosed according to the guidelines of the American Heart Association[12]. HF-B was defined as the presence of previous myocardial infarction, LV hypertrophy (left ventricular mass index (LVMi) > 95g/m^2), concentric remodeling (RWT > 0.42 and LVMi ≤ 95g/m^2), mildly impaired LVEF (> 40% and < 55%) or asymptomatic valvular disease[16]. We defined asymptomatic valvular disease as mild aortic valve insufficiency or central aortic valve insufficiency. HF with preserved ejection fraction (HFpEF) in this

subclinical stage was defined as LVEF ≥ 55% but with the occurrence of one of the other criteria for HF-B[16].

Statistical analysis

We performed all statistical analyses using SPSS Statistics version 21.0 (IBM Corp., Armonk, NY, USA). We subdivided the PE group into four subgroups based on the HF-B outcome: (1) formerly pre-eclamptic women with no HF-B at either visit were categorized as HF-$B^{-/-}$; (2) formerly pre-eclamptic women with HF-B at both visits were categorized as HF-$B^{+/+}$; (3) formerly pre-eclamptic women with HF-B at the first visit but no HF-B at the second visit were categorized as HF-$B^{+/-}$; (4) formerly pre-eclamptic women who developed de-novo HF-B between the two visits were categorized as HF-$B^{-/+}$. We analyzed our data non-parametrically and reported continuous data as median (interquartile range) due to the modest sample size after subdividing the study population. We analyzed the continuous data with Wilcoxon's signed-rank test for intragroup differences and the Mann–Whitney U-test for intergroup differences. Dichotomous data were analyzed using McNemar's test for intragroup differences and Fisher's exact test for intergroup differences and were reported as number (percentage). A P-value of < 0.05 was considered statistically significant. We determined the sample size needed for our study based on previous findings by Melchiorre *et al.* on the prevalence of altered geometry at 1 year postpartum in formerly preterm and term pre-eclamptic women (30%) compared with controls (6%)[9]. The required sample size was calculated with a desired power of 0.95 and a two-sided α of 0.05. A minimum of 64 patients at 1 year and at 4 years postpartum was necessary for determining statistical significance.

RESULTS

Of the 69 formerly pre-eclamptic women included, 16 (23%) had HF-B at the first visit, 1 year postpartum, and 16 (23%) had HF-B at the second visit, 4 years postpartum (Figure 1). Six (37.5%) of the 16 women with HF-B at the first visit sustained this condition, which was observed at the second visit (HF-$B^{+/+}$), and in 10 (62.5%) of the 16 women HF-B resolved before the second visit (HF-$B^{+/-}$). Of the 53 patients with no HF-B at the first visit, 43 (81%) preserved normal cardiac function and had a normal echocardiography scan at the second visit (HF-$B^{-/-}$); however, 10 (19%) developed de-novo HF-B within the subsequent 4 years (HF-$B^{-/+}$).

Characteristics of the formerly pre-eclamptic women are shown in Table 1. Body weight was comparable between the two visits. The index pregnancy was complicated by early-onset PE in 68% of cases and by preterm PE in 75%. Of the 69 women included, 44 (64%) had a subsequent pregnancy at the time of the second visit of which nine (20%)

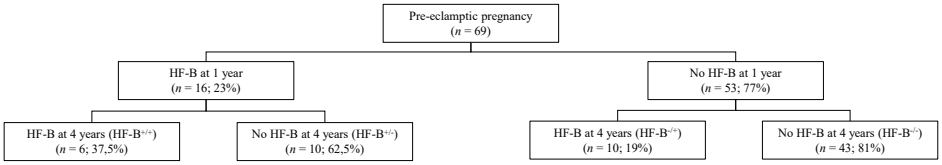


Figure 1. Flowchart of formerly pre-eclamptic women who were screened for heart failure Stage B (HF-B) at 1 year and 4 years postpartum. + and – indicate presence or absence, respectively, of HF-B at 1 year/4 years.

Table 1. Characteristics of 69 formerly pre-eclamptic women at 1 and 4 years postpartum.

Characteristics	1 year (*n* = 69)	4 years (*n* = 69)	*P*
Age (years)	32 (29-35)	35 (33-39)	**<0.01**
Weight (kg)	66 (60-75)	67 (61-77)	0.07
BMI (kg/m^2)	23.2 (21.3-27.2)	23.9 (21.3-26.3)	0.06
Obese (BMI ≥ 30 kg/m^2)	9/69 (13)	11/69 (16)	0.63
Smoker	6/69 (9)	6/69 (9)	1.00
Family history of CVD	21/69 (30)	26/69 (38)	0.41
Family history of PE in first-degree relative	20/69 (29)	-	NA
Antihypertensive treatment	16/69 (23)	13/69 (19)	0.38
Number of years postpartum	0.6 (0.3-2.5)	4.4 (2.6-7.3)	**<0.01**
Heart failure Stage B	16/69 (23)	16/69 (23)	1.00
Heart failure with preserved LVEF	7/69 (10)	12/69 (17)	0.30
Index pregnancy			
Early-onset PE*	46/68 (68)	-	NA
Preterm PE	52/69 (75)	-	NA
Primiparous, *n* (%)	57/69 (83)	18/69 (26)	**<0.01**
GA at birth (weeks)	33.4 (30.1-36.9)	-	NA
Birth weight (g)	1572 (963-2573)	-	NA
SGA neonate	28/69 (41)	-	NA
IUFD	7/69 (10)	-	NA
Subsequent pregnancy†	-	44/69 (64)	NA
Recurrent PE	-	9/44 (20)	NA
Maternal offspring pregnancy‡			
GA at birth (weeks)	40 (37-40)	-	NA
Preterm birth	10/52 (19)	-	NA
Birth weight (g)	3050 (2500-3500)	-	NA

Data are given as median (interquartile range), median [range] or *n*/N (%).
*Time of onset of pre-eclampsia (PE) unknown in one case.
†Pregnancy between index pregnancy and second visit.
‡Pregnancy of which woman in this study was offspring.
BMI, body mass index; CVD, cardiovascular disease; GA, gestational age; IUFD, intrauterine fetal death; LVEF, left ventricular ejection fraction; NA, not applicable; SGA, small-for-gestational age.

had recurrent PE. Of the study population, 29% had a first-degree relative who had a pregnancy complicated by PE. Characteristics of the cohort after excluding women with twin pregnancy are shown in Table S1.

Inter- and intragroup differences in HF-B vs no-HF-B

Table 2 shows the cardiac and metabolic characteristics in women with and without HF-B at each follow-up visit. Data excluding women with a twin pregnancy are shown in Table S2. The phenotype of the group of women with HF-B at the first visit differed in some aspects from the phenotype of the group of women with HF-B at the second

Table 2. Cardiac and metabolic characteristics of heart failure Stage B (HF-B) in 69 formerly pre-eclamptic women categorized according to presence or absence of HF-B at 1 and 4 years postpartum.

	1 year			4 years		
Parameter	**HF-B (*n* = 16)**	**No-HF-B (*n* = 53)**	***P***	**HF-B (*n* = 16)**	**No-HF-B (*n* = 53)**	***P***
Myocardial infarction	0 (0)	-	NA	0 (0)	-	NA
LV hypertrophy	3 (19)	-	NA	1 (6)	-	NA
Concentric remodeling	5 (31)	-	NA	11 (69)*	-	NA
Mildly impaired LVEF	9 (56)	-	NA	4 (25)	-	NA
Asymptomatic valvular disease	1 (6)	-	NA	1 (6)	-	NA
Heart failure with preserved LVEF	7 (44)	-	NA	12 (75)	-	NA
Metabolic syndrome						
Fasting glucose (mmol/L)	4.9 (4.4-5.1)	4.8 (4.6-5.1)	0.54	4.8 (4.5-5.0)	4.7 (4.4-5.0)	0.37
Fasting insulin (mU/L)	11.5 (8.3-14.0)	8.0 (6.0-10.0)	**<0.05**	8.5 (6.3- 11.9)	7.7 (5.4-10.0)	0.22
$HOMA_{IR}$	2.5 (1.7-3.2)	1.9 (1.3-2.2)	**<0.05**	1.8 (1.4-2.8)	1.5 (1.1-2.1)	0.22
Triglyceride (mmol/L)	1.0 (0.7-1.5)	0.9 (0.7-1.1)	0.32	0.8 (0.7-1.2)	0.9 (0.7-1.1)	0.60
Total cholesterol (mmol/L)	4.8 (4.3-5.3)	4.6 (4.1-5.2)	0.31	4.5 (4.1-5.1)	4.6 (4.2-5.0)	0.65
LDL (mmol/L)	3.0 (2.6-3.6)	2.8 (2.4-3.4)	0.25	2.9 (2.4-3.5)	2.9 (2.5-3.2)	0.72
HDL (mmol/L)	1.2 (1.1-1.3)	1.3 (1.2-1.5)	0.10	1.2 (1.1-1.4)	1.4 (1.1-1.5)	0.09
Albumin/creatinine ratio (g/mol)	0.5 (0.1-1.9)	1.0 (0.3-2.1)	0.14	0.8 (0.6-1.2)	0.5 (0.2-1.6)	0.30
SBP (mmHg)	124 (116-144)	115 (107-123)	**<0.01**	116 (110-129)	115 (106-123)	0.37
DBP (mmHg)	76 (68-83)	68 (64-73)	**<0.01**	74 (71-82)	72 (66-77)	0.11
MAP (mmHg)	91 (84-104)	82 (79-92)	**<0.01**	86 (82-94)	83 (77-94)	0.20
Heart rate (bpm)	70 (65-80)	66 (60-75)	0.13	69 (64-79)	62 (59-76)	0.08
BMI (kg/m^2)	27.8 (22.8-33.0)	22.8 (20.9-25.0)	**<0.01**	25.2 (22.5-30.6)	23.6 (21.1-25.7)	0.17
Antihypertensive treatment	5 (31)	11 (21)	0.50	4 (25)	9 (17)	0.48

Data are given as *n* (%) or median (interquartile range).

*$P < 0.05$ compared with HF-B at 1 year postpartum.

BMI, body mass index; DBP, diastolic blood pressure; HDL, high density lipoprotein; HOMAIR, homeostatic model assessment for insulin resistance; LDL, low density lipoprotein; LV, left ventricular; LVEF, left ventricular ejection fraction; MAP, mean arterial pressure; NA, not applicable; SBP, systolic blood pressure.

visit. Concentric remodeling was present in 31% of women at visit 1 compared with 69% at visit 2 ($P < 0.05$). On the other hand, systolic dysfunction, as indicated by mildly impaired LVEF, was present in 56% at visit 1 compared with 25% at visit 2 ($P = 0.15$). The prevalence of LV hypertrophy and asymptomatic valvular disease did not differ when comparing data from both visits.

At visit 1, the HF-B group had comparable fasting glucose, triglycerides, total cholesterol, LDL, HDL and albumin/creatinine ratio levels compared with the no-HF-B group (Table 2). Fasting insulin and HOMA levels were higher in the HF-B group compared with the no-HF-B group, along with higher SBP, DBP, MAP and BMI. At visit 2, no significant differences were seen between the groups with and without HF-B.

Inter- and intragroup differences in HF-B$^{-/-}$ vs HF-B$^{-/+}$

We first compared HF-B$^{-/-}$ and HF-B$^{-/+}$ subgroups (Table 3; data excluding women with twin pregnancy are given in Table S3). Baseline characteristics, obstetric characteristics of index pregnancy complicated by PE and offspring pregnancy were comparable between the two groups except for a higher prevalence of primiparous women in the HF-B$^{-/-}$ group compared with the HF-B$^{-/+}$ group at visit 1 (93% vs 60%). LVMi did not differ between subgroups at visit 1 or 2. RWT did not differ between subgroups at visit 1, but it was higher in the HF-B$^{-/+}$ group compared with HF-B$^{-/-}$ at visit 2. LVEF did not differ between subgroups at visit 1 or 2. However, in the HF-B$^{-/+}$ group, LVEF had decreased significantly at visit 2 when compared with visit 1. Stroke volume (SV) and SV index did not differ between groups at visit 1 or 2. However, in the HF-B$^{-/-}$ group, both SV and SV index had increased at visit 2 compared with visit 1, whereas they did not change over time in the HF-B$^{-/+}$ group. The ratio of early to late ventricular filling velocity (EA ratio) did not differ between the two groups at visit 1 or 2, whereas cardiac output (CO) and CO index were higher in the HF-B$^{-/+}$ group compared with the HF-B$^{-/-}$ group at visit 1, but this difference was no longer present at visit 2. Moreover, in the HF-B$^{-/-}$ group, CO and CO index had increased at visit 2 compared with visit 1, whereas they did not change over time in the HF-B$^{-/+}$ group. HR was significantly higher in the HF-B$^{-/+}$ group compared with the HF-B$^{-/-}$ group at visit 1, but this intergroup difference was not present at visit 2. LVEDV did not differ between groups at visit 1 or 2. However, in the HF-B$^{-/-}$ group, LVEDV was increased at visit 2 compared with visit 1, while in the HF-B$^{-/+}$ it remained unchanged.

Table 4 presents the cardiometabolic variables at visits 1 and 2 in each subgroup of women (Table S4 shows data after excluding women with a twin pregnancy). No metabolic variable differed between the HF-B$^{-/-}$ and HF-B$^{-/+}$ subgroups at either visit. Moreover, in the HF-B$^{-/-}$ group, fasting glucose had decreased between visits 1 and 2 (4.8 vs 4.7mmol/L, $P < 0.05$), DBP had increased (68 vs 72mmHg, $P < 0.05$) and BMI had increased (22.5 vs 23.5kg/m^2, $P < 0.05$). In the HF-B$^{-/+}$ group, all metabolic variables remained unchanged over time.

Table 3. Pregnancy characteristics and cardiac indices in 69 formerly pre-eclamptic women, categorized according to absence of heart failure Stage B (HF-B) at 1 year and 4 years postpartum (HF-$B^{-/-}$), absence of HF-B at 1 year but presence at 4 years (HF-$B^{-/+}$), presence of HF-B at both 1 and 4 years (HF-$B^{+/+}$) and presence of HF-B at 1 year but absence at 4 years (HF-$B^{+/-}$).

Characteristic	HF-$B^{-/-}$ (n = 43)	HF-$B^{-/+}$ (n = 10)	P	HF-$B^{+/+}$ (n = 6)	HF-$B^{+/-}$ (n = 10)	P
Postpartuminterval (years)						
1 year	0.6 (0.3-2.4)	0.6 (0.3-2.4)	0.91	0.9 (0.4-2.1)	0.6 (0.3-2.5)	0.64
4 years	4.3 (2.7-7.3)*	4.3 (3.7-6.7)*	0.94	5.8 (2.6-6.8)†	4.7 (3.3-6.0)*	0.09
Index pregnancy						
Early-onset PE	26/43 (60)	8/10 (80)	0.30	4/5 (80)	8/10 (80)	1.00
Preterm PE	32/43 (74)	8/10 (80)	1.00	4/6 (67)	8/10 (80)	0.60
Primiparous at 1 year	40/43 (93)	6/10 (60)	**<0.05**	3/6 (50)	8/10 (80)	0.30
Primiparous at 4 years	14/43 (33)*	1/10 (10)	0.25	1/6 (17)	2/10 (20)†	1.00
GA at birth (weeks)	34.9 (30.6-37.0)	32.6 (27.6-35.2)	0.26	30.2 (27.4-37.4)	31.8 (28.5-35.9)	0.64
Birth weight (g)	1817 (1098-2695)	1350 (667-2013)	0.20	955 (480-2615)	1457 (941-2540)	0.48
SGA neonate	16/43 (37)	7/10 (70)	0.08	2/6 (33)	3/10 (30)	1.00
IUFD	3/43 (7)	2/10 (20)	0.24	2/6 (33)	0/10 (0)	0.13
Subsequent pregnancy‡	27/43 (63)	7/10 (70)	1.00	3/6 (50)	7/10 (70)	0.61
Recurrent PE	3/27 (11)	0/7 (0)	1.00	3/3 (100)	3/7 (43)	0.20
Maternal offspring pregnancy						
GA at birth (weeks)	40.0 (37.3-40.0)	40.0 (33.5-40.5)	0.85	40.0 (37.0-40.0)	39.0 (34.3-41.3)	1.00
Preterm birth	6/36 (17)	2/6 (33)	0.32	0/4 (0)	2/6 (33)	0.50
Birth weight (g)	3200 (2550-3550)	2875 (2500-3500)	0.57	2000(1990-2000)	3000 (2500-3500)	0.07
Family history of PE in first degree relative	12/43 (28)	3/10 (30)	1.00	4/6 (67)	1/10 (10)	**<0.05**
Cardiac measurements						
LVM index (g/m^2)						
1 year	63 (53-69)	60 (57-64)	0.62	76 (51-95)	65 (59-79)	0.79
4 years	59 (51-64)†	63 (40-66)	0.98	58 (50-81)	62 (49-74)	0.79
RWT						
1 year	0.31 (0.26-0.35)	0.32 (0.29-0.35)	0.63	0.43 (0.37-0.47)	0.33 (0.30-0.42)	0.18
4 years	0.33 (0.29-0.36)	0.44 (0.31- 0.46)†	**<0.05**	0.44 (0.41-0.45)	0.32 (0.28-0.37)	**<0.01**
LVEF (%)						
1 year	65 (61-69)	68 (61-72)	0.38	55 (51-63)	53 (50-59)	0.71
4 years	64 (61-67)	62 (54-66) †	0.09	57 (55-59)	65 (61-67)*	**<0.01**
SV (mL)						
1 year	73 (60-85)	83 (73-88)	0.11	62 (59-82)	78 (63-85)	0.43
4 years	78 (72-89)*	85 (73-88)	0.65	74 (63-108)	83 (70-91)	0.69

Table 3. Pregnancy characteristics and cardiac indices in 69 formerly pre-eclamptic women, categorized according to absence of heart failure Stage B (HF-B) at 1 year and 4 years postpartum (HF-B$^{-/-}$), absence of HF-B at 1 year but presence at 4 years (HF-B$^{-/+}$), presence of HF-B at both 1 and 4 years (HF-B$^{+/+}$) and presence of HF-B at 1 year but absence at 4 years (HF-B$^{+/-}$). *(continued)*

Characteristic	HF-B$^{-/-}$ (n = 43)	HF-B$^{-/+}$ (n = 10)	P	HF-B$^{+/+}$ (n = 6)	HF-B$^{+/-}$ (n = 10)	P
SV index (mL/m^2)						
1 year	40 (35-49)	48 (40-53)	0.15	33 (29-47)	40 (32-46)	0.64
4 years	45 (41-51)†	47 (42-51)	0.65	39 (37-52)	42 (37-48)	1.00
E/A ratio						
1 year	1.57 (1.31-2.04)	1.35 (1.19-1.68)	0.16	1.46 (1.24-1.68)	1.56 (1.16-1.91)	1.00
4 years	1.61 (1.44-1.95)	1.66 (1.43-1.83)	0.85	1.58 (1.25-1.80)	1.60 (1.19-1.88)	0.79
CO (L/min)						
1 year	4.5 (3.8-5.2)	5.6 (5.3-6.3)	**<0.01**	4.2 (4.0-6.2)	5.3 (4.1-5.6)	0.79
4 years	4.8 (4.2-6.0)*	5.3 (4.8-6.2)	0.18	5.6 (4.4-7.7)	5.0 (4.5-5.4)	0.39
CO index (L/min/m^2)						
1 year	2.5 (2.1-3.0)	3.2 (3.0-3.8)	**<0.01**	2.3 (1.9-3.6)	2.8 (2.2-3.2)	0.88
4 years	2.7 (2.4-3.2)†	2.9 (2.6-3.4)	0.25	3.0 (2.6-3.8)	2.6 (2.2-2.9)	0.15
Heart rate (bpm)						
1 year	60 (56-65)	73 (65-77)	**<0.01**	70 (66-74)	69 (60-78)	0.79
4 years	62 (57-69)	64 (58-74)	0.34	73 (61-78)	64 (59-70)	0.26
LVEDV (mL)						
1 year	81 (68-94)	90 (77-102)	0.12	85 (57-108)	95 (80-141)	0.26
4 years	89 (76-103)*	90 (78-103)	0.93	88 (68-140)	101 (72-111)	0.79

Data are given as median [range], n/N (%) or median (interquartile range).

Comparison with 1 year postpartum: $^{*}P < 0.01$; $^{\dagger}P < 0.05$.

‡Pregnancy between index pregnancy and second visit.

CO, cardiac output; EA ratio, ratio of early-to-late ventricular filling velocity; GA, gestational age; IUFD, intrauterine fetal death; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; LVMi, left ventricular mass index; PE, pre-eclampsia; RWT, relative wall thickness; SGA, small-for-gestational age; SV, stroke volume.

Table 4. Metabolic variables in 69 formerly pre-eclamptic women categorized according to absence of heart failure Stage B (HF-B) at 1 year and 4 years postpartum (HF-$B^{-/-}$), absence of HF-B at 1 year but presence at 4 years (HF-$B^{-/+}$), presence of HF-B at both 1 and 4 years (HF-$B^{+/+}$) and presence of HF-B at 1 year but absence at 4 years (HF-$B^{+/-}$).

Variable	HF-$B^{-/-}$ (n = 43)	HF-$B^{-/+}$ (n = 10)	P	HF-$B^{+/+}$ (n = 6)	HF-$B^{+/-}$ (n = 10)	P
Fasting glucose (mmol/L)						
1 year	4.8 (4.5-5.1)	4.9 (4.7-5.4)	0.39	4.9 (4.6-5.0)	4.7 (4.2-5.2)	0.71
4 years	4.7 (4.4-4.9)[†]	4.8 (4.4-5.0)	0.82	4.8 (4.7-5.3)	4.8 (4.3-5.4)	0.64
Fasting insulin (mU/L)						
1 year	8.0 (6.0-10.0)	9.0 (7.5-12.5)	0.36	13.0 (9.8-15.5)	10.0 (7.8-14.0)	0.49
4 years	7.2 (5.4-10.0)	8.0 (6.6-11.9)	0.31	11.2 (4.5-12.8)	8.3 (4.3-13.6)	0.88
$HOMA_{IR}$						
1 year	1.7 (1.3-2.2)	1.9 (1.6-3.0)	0.35	2.7 (2.1-3.5)	2.1 (1.6-3.1)	0.43
4 years	1.5 (1.1-2.0)	1.7 (1.5-2.5)	0.31	2.6 (1.0-2.9)	1.7 (0.8-3.1)	0.88
Triglyceride (mmol/L)						
1 year	0.9 (0.7-1.0)	0.9 (0.6-1.3)	0.69	1.0 (0.8-1.3)	1.2 (0.5-1.7)	0.71
4 years	0.9 (0.7-1.1)	0.8 (0.6-0.9)	0.23	1.2 (0.7-1.3)	0.9 (0.7-1.4)	0.88
Total cholesterol (mmol/L)						
1 year	4.6 (4.1-5.2)	4.5 (4.2-4.9)	0.84	4.8 (4.5-5.2)	4.7 (4.2-5.3)	0.56
4 years	4.6 (4.2-4.9)	4.6 (4.2-5.1)	0.91	4.5 (4.1-5.5)	4.8 (4.3-5.5)	0.43
LDL (mmol/L)						
1 year	2.8 (2.4-3.4)	2.8 (2.4-3.3)	0.94	3.0 (2.8-3.6)	3.0 (2.6-3.4)	0.59
4 years	2.8 (2.4-3.2)	3.0 (2.2-3.4)	0.51	2.7 (2.5-3.7)	2.9 (2.7-3.6)	0.37
HDL (mmol/L)						
1 year	1.3 (1.2-1.5)	1.3 (1.1-1.5)	0.45	1.2 (1.1-1.4)	1.2 (1.1-1.3)	1.00
4 years	1.4 (1.1-1.5)	1.2 (1.1-1.4)	0.12	1.2 (1.1-1.5)	1.4 (1.1-1.5)	0.64
Albumin/creatinine ratio (g/mol)						
1 year	1.0 (0.3-2.1)	0.8 (0.3-1.7)	0.64	0.2 (0.0-0.7)	0.9 (0.3-2.3)	0.12
4 years	0.5 (0.2-1.7)	0.6 (0.1-1.0)	0.96	1.1 (0.7-3.9)	0.5 (0.4-1.3)	0.07
SBP (mmHg)						
1 year	115 (107-123)	117 (105-122)	0.79	146 (116-155)	123 (114-126)	0.15
4 years	114 (104-122)	112 (107-122)	0.80	129 (117-135)	119 (109-130)	0.18
DBP (mmHg)						
1 year	68 (63-74)	66 (64-71)	0.69	82 (77-89)	70 (68-78)	**<0.05**
4 years	72 (66-76)[†]	72 (69-75)	0.86	84 (78-91)	75 (66-78)	**<0.05**
MAP (mmHg)						
1 year	83 (79-92)	82 (79-89)	0.72	104 (88-109)	87 (83-97)	0.07
4 years	82 (77-93)	83 (80-86)	0.93	96 (89-105)	86 (80-95)	0.06
Heart rate (bpm)						
1 year	66 (60-74)	74 (62-76)	0.29	71 (66-80)	70 (63-82)	0.88
4 years	62 (59-72)	69 (64-80)	0.17	70 (63-80)	62 (59-82)	0.37

Table 4. Metabolic variables in 69 formerly pre-eclamptic women categorized according to absence of heart failure Stage B (HF-B) at 1 year and 4 years postpartum (HF-$B^{-/-}$), absence of HF-B at 1 year but presence at 4 years (HF-$B^{-/+}$), presence of HF-B at both 1 and 4 years (HF-$B^{+/+}$) and presence of HF-B at 1 year but absence at 4 years (HF-$B^{+/-}$). *(continued)*

Variable	HF-$B^{-/-}$ (*n* = 43)	HF-$B^{-/+}$ (*n* = 10)	*P*	HF-$B^{+/+}$ (*n* = 6)	HF-$B^{+/-}$ (*n* = 10)	*P*
BMI (kg/m^2)						
1 year	22.5 (20.8-24.1)	24.3 (22.2-27.2)	0.15	28.3 (23.6-33.2)	27.6 (22.2-34.4)	0.79
4 years	23.5 (20.8-25.0)†	24.4 (22.4-27.2)	0.30	29.9 (21.9-33.8)	25.2 (22.7-35.0)	0.88
1 year	10/43 (23)	1/10 (10)	0.67	4/6 (67)	1/10 (10)	**<0.05**
4 years	7/43 (16)	1/10 (10)	1.00	3/6 (50)	2/10 (20)	0.30
Prehypertension						
1 year	7/43 (16)	4/10 (40)	0.19	0/6 (0)	4/10 (40)	0.23
4 years	5/43 (12)	2/10 (20)	0.60	3/6 (50)	3/10 (30)	0.61
Hypertension						
1 year	10/43 (23)	1/10 (10)	0.67	5/6 (83)	2/10 (20)	**<0.05**
4 years	9/43 (21)	1/10 (10)	0.67	3/6 (50)	2/10 (20)	0.30

Data are given as median (interquartile range) or *n*/N (%).

Comparison with 1 year postpartum: **P* < 0.01; †*P* < 0.05.

BMI, body mass index; DBP, diastolic blood pressure; HDL, high density lipoprotein; $HOMA_{IR}$, homeostatic model assessment for insulin resistance; LDL, low density lipoprotein; MAP, mean arterial pressure; SBP, systolic blood pressure.

Inter- and intragroup differences in HF-B$^{+/+}$ vs HF-B$^{+/-}$

We subsequently compared HF-B$^{+/+}$ and HF-B$^{+/-}$ subgroups (Table 3; data excluding women with twin pregnancy are given in Table S3). Baseline characteristics, obstetric characteristics of index pregnancy and offspring pregnancy were comparable between the two groups. However, among the HF-B$^{+/+}$ group there was a significantly greater proportion of women with a family history of PE compared with the HF-B$^{+/-}$ group (67% vs 10%). LVMi did not differ between subgroups at either visit. RWT did not differ between subgroups at visit 1 but was higher in the HF-B$^{+/+}$ group compared with the HF-B$^{+/-}$ group at visit 2. LVEF did not differ between subgroups at visit 1. LVEF was significantly higher in the HF-B$^{+/-}$ group compared with the HF-B$^{+/+}$ group at visit 2, and was increased in this subgroup compared to the first visit. SV, SV index, EA ratio, CO, CO index, HR and LVEDV did not differ between subgroups at visit 1 or 2. When analyzing metabolic risk factors (Table 4), no variable differed between the two subgroups at either visit (Table S4 shows data after excluding women with a twin pregnancy). DBP was significantly higher in the HF-B$^{+/+}$ group at visits 1 and 2 compared with the HF-B$^{+/-}$ group. Moreover, at visit 1, hypertension was significantly more prevalent in the HF-B$^{+/+}$ group compared with the HF-B$^{+/-}$ group (83% vs 20%). However, at visit 2, this significant difference in hypertension prevalence was no longer present between the two subgroups.

DISCUSSION

To the best of our knowledge, this is the first presentation of a longitudinal cohort study on the prevalence of asymptomatic HF in formerly pre-eclamptic women. The prevalence of preclinical HF-B is similar at 1 and 4 years postpartum (23%) suggesting a persistent cardiac condition. However, HF-B resolved in two-thirds of originally affected women, and one in five initially unaffected women developed HF-B in the years thereafter.

The cardiovascular implications of PE do not end with delivery[17]. In fact, in contrast to the physiological LV remodeling in normal pregnancy, which resolves in the first weeks postpartum, the PE-induced cardiac adaptation may persist for at least several months postpartum[8,18]. To date, it is unknown whether (and when) PE-induced cardiac remodeling resolves completely. Traditional cardiovascular risk factors may affect the resolving process after PE and could be responsible for the differences in postpartum recovery between healthy and PE pregnancies.

The observed 23% prevalence of HF-B in the first year postpartum is in line with previous findings[9]. Our data show that although the prevalence of HF-B at both visits is comparable, the underlying components are different. More than half of the women diagnosed with HF-B at visit 1 recovered, while about one in five formerly pre-eclamptic women without prior subclinical HF-B developed HF-B in the years thereafter, mostly as

a result of concentric remodeling. Considering diastolic dysfunction is the most prevalent form of cardiac dysfunction in women, it may be hypothesized that the development towards concentric remodeling could be a more persistent condition in these women than the initial HF-B variant with mostly reduced systolic function.

HF can occur with a reduced EF (HFrEF) or with a preserved EF (HFpEF), the latter occurring more often in women than in men with a noteworthy 2:1 ratio[19]. Despite significant uncertainty and conflicting results, the pathophysiological problem in patients with HFpEF has been related to impaired diastolic reserve[20]. HFpEF is thought to develop from a 'systemic pro-inflammatory state' induced by comorbidities and with the involvement of microvascular endothelial inflammation[21], all of which are thought to be involved in the etiology of PE[22]. Although this terminology is applied to symptomatic HF, specifying different subclinical phenotypes within the HF spectrum may theoretically allow stratification for potential early diagnosis and care to prevent progression. The prevalence of subclinical HFpEF in our population increased more than two-fold between both visits. Although borderline significant, in combination with the shift in concentric remodeling between both visits it is tempting to speculate that this shift may indicate a mechanistic response to the persistently high blood pressure that results in increased concentric remodeling[23].

Recent evidence suggests that chronic volume and pressure overload determine the resulting phenotype of hypertrophic remodeling[24]. Untreated chronic high blood pressure is a well-known cause of structural cardiovascular alterations[25] and cardiovascular morbidity[26]. In the development of actual CVD, chronically elevated blood pressure is considered to be an important intermediate risk condition, which is easily identifiable and modifiable, enabling the timely institution of measures to prevent the premature development of a more debilitating CVD in women[2,27]. Besides the mechanical strain and risks, HF risk may also originate from all or a subset of biochemical stressors consistent with metabolic syndrome[28]. This is reflected in our findings, as some of the metabolic syndrome constituents seem to play a role in the prevalence of HF-B at visit 1. However, no association was found between the metabolic syndrome constituents and HF-B at visit 2, suggesting that different mechanisms contribute to the high prevalence at both time points. As most HF-B women have a phenotypical profile of consistent diastolic dysfunction, these findings may indicate a difference in either pressure or volume load, common in formerly pre-eclamptic women[29,30].

In women, HF is often detected at a late and clinically overt stage. Formerly pre-eclamptic women should be aware of the increased risk for potentially reversible HF-B before it develops to the much less reversible symptomatic Stages C and D. Therefore, patients and clinicians should be aware of the importance of regular postpartum cardiovascular follow-up after a pre-eclamptic pregnancy. The patient may benefit from secondary prevention if CVD is diagnosed at an early stage. However, before specific

treatment can be implemented in daily clinical practice, intervention trials are necessary, in order to prevent CVD in formerly pre-eclamptic women. Follow-up studies with a longer postpartum interval are necessary to provide more information on the prevalence of HF-B. Whether PE induces HF or whether PE and HF are a common result of the same susceptibility is yet to be determined.

This prospective longitudinal cohort study has some limitations. First, most women had ancestry originating from Europe. Therefore, our results may not be fully applicable to women of other ethnic origins. Second, after subdividing the cohort according to HF outcome, the number of women per subgroup became modest thus increasing the risk of Type I error. However, we did detect clinically relevant significant differences between subgroups. Therefore, considering the sample size, prevalence of abnormalities, and potential importance of the observations, additional studies confirming our findings are required.

In conclusion, the prevalence of subclinical HF-B is persistently high in the years after a PE pregnancy. Nonetheless, there is a noteable shift in individuals and phenotypes contributing to HF-B in the years after PE. From a clinical perspective, these findings may imply that cardiovascular risk screening at approximately 1 year postpartum is important, and that an additional assessment a few years later is necessary. Whether lifestyle change and pharmacological therapy are effective at preventing progression or development towards clinical HF in these women needs to be investigated.

REFERENCES

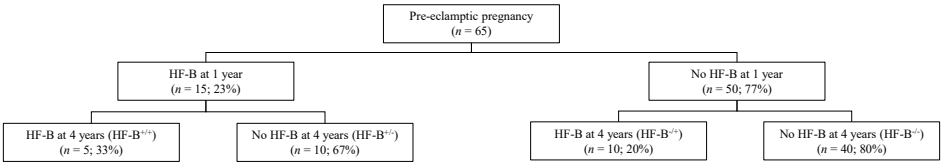
1. Yusuf S, Reddy S, Ounpuu S, Anand S. Global burden of cardiovascular diseases: part I: general considerations, the epidemiologic transition, risk factors, and impact of urbanization. *Circulation* 2001; 104: 2746–2753.
2. Go AS, Mozaffarian D, Roger VL, Benjamin EJ, Berry JD, Blaha MJ, Dai S, Ford ES, Fox CS, Franco S, Fullerton HJ, Gillespie C, Hailpern SM, Heit JA, Howard VJ, Huffman MD, Judd SE, Kissela BM, Kittner SJ, Lackland DT, Lichtman JH, Lisabeth LD, Mackey RH, Magid DJ, Marcus GM, Marelli A, Matchar DB, McGuire DK, Mohler ER 3rd, Moy CS, Mussolino ME, Neumar RW, Nichol G, Pandey DK, Paynter NP, Reeves MJ, Sorlie PD, Stein J, Towfighi A, Turan TN, Virani SS, Wong ND, Woo D, Turner MB; American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Heart disease and stroke statistics—2014 update: a report from the American Heart Association. *Circulation* 2014; 129: e28–e292.
3. World Health Organization. Media Centre. Cardiovascular diseases (CVDs). Fact sheet. Reviewed September 2016. http://www.who.int/mediacentre/factsheets/ fs317/en.
4. Mosca L, Barrett-Connor E, Wenger NK. Sex/gender differences in cardiovascular disease prevention: what a difference a decade makes. *Circulation* 2011; 124: 2145–2154.
5. Roberts JM, Cooper DW. Pathogenesis and genetics of pre-eclampsia. *Lancet* 2001; 357: 53–56.
6. Bellamy L, Casas JP, Hingorani AD, Williams DJ. Pre-eclampsia and risk of cardiovascular disease and cancer in later life: systematic review and meta-analysis. *BMJ* 2007; 335: 974.
7. Lang RM, Pridjian G, Feldman T, Neumann A, Lindheimer M, Borow KM. Left ventricular mechanics in preeclampsia. *Am Heart J* 1991; 121: 1768–1775.
8. Simmons LA, Gillin AG, Jeremy RW. Structural and functional changes in left ventricle during normotensive and preeclamptic pregnancy. *Am J Physiol Heart Circ Physiol* 2002; 283: H1627–H1633.
9. Melchiorre K, Sutherland GR, Liberati M, Thilaganathan B. Preeclampsia is associated with persistent postpartum cardiovascular impairment. *Hypertension* 2011; 58: 709–715.
10. Kuznetsova T, Herbots L, Jin Y, Stolarz-Skrzypek K, Staessen JA. Systolic and diastolic left ventricular dysfunction: from risk factors to overt heart failure. *Expert Rev Cardiovasc Ther* 2010; 8: 251–258.
11. Ammar KA, Jacobsen SJ, Mahoney DW, Kors JA, Redfield MM, Burnett JC Jr, Rodeheffer RJ. Prevalence and prognostic significance of heart failure stages: application of the American College of Cardiology/American Heart Association heart failure staging criteria in the community. *Circulation* 2007; 115: 1563–1570.
12. Jessup M, Abraham WT, Casey DE, Feldman AM, Francis GS, Ganiats TG, Konstam MA, Mancini DM, Rahko PS, Silver MA, Stevenson LW, Yancy CW. 2009 focused update: ACCF/AHA Guidelines for the Diagnosis and Management of Heart Failure in Adults: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines: developed in collaboration with the International Society for Heart and Lung Transplantation. *Circulation* 2009; 119: 1977–2016.
13. Brown MA, Lindheimer MD, de Swiet M, Van Assche A, Moutquin JM. The classification and diagnosis of the hypertensive disorders of pregnancy: statement from the International Society for the Study of Hypertension in Pregnancy (ISSHP). *Hypertens Pregnancy* 2001; 20: IX–XIV.
14. Bonora E, Targher G, Alberiche M, Bonadonna RC, Saggiani F, Zenere MB, Monauni T, Muggeo M. Homeostasis model assessment closely mirrors the glucose clamp technique in the assessment of insulin sensitivity: studies in subjects with various degrees of glucose tolerance and insulin sensitivity. *Diabetes Care* 2000; 23: 57–63.
15. Sahn DJ, DeMaria A, Kisslo J, Weyman A. Recommendations regarding quantitation in M-mode echocardiography: results of a survey of echocardiographic measurements. *Circulation* 1978; 58: 1072 1083.
16. Lang RM, Bierig M, Devereux RB, Flachskampf FA, Foster E, Pellikka PA, Picard MH, Roman MJ, Seward J, Shanewise JS, Solomon SD, Spencer KT, Sutton MS, Stewart WJ. Recommendations for chamber

quantification: a report from the American Society of Echocardiography's Guidelines and Standards Committee and the Chamber Quantification Writing Group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology. *J Am Soc Echocardiogr* 2005; 18: 1440–1463.

17. 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.
18. Melchiorre K, Thilaganathan B. Maternal cardiac function in preeclampsia. *Curr Opin Obstet Gynecol* 2011; 23: 440–447.
19. Scantlebury DC, Borlaug BA. Why are women more likely than men to develop heart failure with preserved ejection fraction? *Curr Opin Cardiol* 2011; 26: 562–568.
20. Abudiab MM, Redfield MM, Melenovsky V, Olson TP, Kass DA, Johnson BD, Borlaug BA. Cardiac output response to exercise in relation to metabolic demand in heart failure with preserved ejection fraction. *Eur J Heart Fail* 2013; 15: 776–785.
21. Paulus WJ, Tschope C. A novel paradigm for heart failure with preserved ejection fraction: comorbidities drive myocardial dysfunction and remodeling through coronary microvascular endothelial inflammation. *J Am Coll Cardiol* 2013; 62: 263–271.
22. Powe CE, Levine RJ, Karumanchi SA. Preeclampsia, a disease of the maternal endothelium: the role of antiangiogenic factors and implications for later cardiovascular disease. *Circulation* 2011; 123: 2856 2869.
23. Ghossein-Doha C, Spaanderman M, van Kuijk SM, Kroon AA, Delhaas T, Peeters L. Long-term risk to develop hypertension in women with former preeclampsia: a longitudinal pilot study. *Reprod Sci 2014*; 21: 846–853.
24. Calderone A, Takahashi N, Izzo NJ Jr, Thaik CM, Colucci WS. Pressure- and volume-induced left ventricular hypertrophies are associated with distinct myocyte phenotypes and differential induction of peptide growth factor mRNAs. *Circulation* 1995; 92: 2385–2390.
25. Davila DF, Donis JH, Odreman R, Gonzalez M, Landaeta A. Patterns of left ventricular hypertrophy in essential hypertension: should echocardiography guide the pharmacological treatment? *Int J Cardiol* 2008; 124: 134–138.
26. Israili ZH, Hernandez-Hernandez R, Valasco M. The future of antihypertensive treatment. *Am J Ther* 2007; 14: 121–134.
27. Mancia G, De Backer G, Dominiczak A, Cifkova R, Fagard R, Germano G, Grassi G, Heagerty AM, Kjeldsen SE, Laurent S, Narkiewicz K, Ruilope L, Rynkiewicz A, Schmieder RE, Boudier HA, Zanchetti A, Vahanian A, Camm J, De Caterina R, Dean V, Dickstein K, Filippatos G, Funck-Brentano C, Hellemans I, Kristensen SD, McGregor K, Sechtem U, Silber S, Tendera M, Widimsky P, Zamorano JL, Erdine S, Kiowski W, Agabiti-Rosei E, Ambrosioni E, Lindholm LH, Viigimaa M, Adamopoulos S, Agabiti-Rosei E, Ambrosioni E, Bertomeu V, Clement D, Erdine S, Farsang C, Gaita D, Lip G, Mallion JM, Manolis AJ, Nilsson PM, O'Brien E, Ponikowski P, Redon J, Ruschitzka F, Tamargo J, van Zwieten P, Waeber B, Williams B. 2007 Guidelines for the Management of Arterial Hypertension: The Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). *J Hypertens* 2007; 25: 1105–1187.
28. Horwich TB, Fonarow GC. Glucose, obesity, metabolic syndrome, and diabetes relevance to incidence of heart failure. *J Am Coll Cardiol* 2010; 55: 283–293.
29. Aardenburg R, Spaanderman ME, van Eijndhoven HW, de Leeuw PW, Peeters LL. A low plasma volume in formerly preeclamptic women predisposes to the recurrence of hypertensive complications in the next pregnancy. *J Soc Gynecol Investig* 2006; 13: 598–603.

30. Ghossein-Doha C, Peeters L, van Heijster S, van Kuijk S, Spaan J, Delhaas T, Spaanderman M. Hypertension after preeclampsia is preceded by changes in cardiac structure and function. *Hypertension* 2013; 62: 382–390.

SUPPLEMENTAL INFORMATION



Supplemental Figure 1. Flowchart of formerly pre-eclamptic women who were screened for heart failure Stage B (HF-B) at 1 year and 4 years postpartum. + and – indicate presence or absence, respectively, of HF-B at 1 year/4 years, after excluding twin pregnancies.

Supplemental Table 1. Characteristics of 65 formerly pre-eclamptic women at 1 and 4 years postpartum, after excluding those with twin pregnancy.

Characteristic	1 year (*n* = 65)	4 years (*n* = 65)	*P*
Age (years)	32 (29-35)	35 (33-39)	**< 0.01**
Weight (kg)	66 (60-75)	67 (61-77)	0.09
BMI (kg/m^2)	23.2 (21.3-27.2)	23.9 (21.3-26.3)	0.09
Obese (BMI ≥ 30 kg/m^2)	8/65(12)	10/65 (15)	0.63
Smoker	5/65 (8)	6/65 (9)	1.00
Family history of CVD	20/65 (31)	24/65 (37)	0.52
Family history of PE in first-degree relative	19/65 (29)		NA
Antihypertensive treatment	14/65 (22)	13/65 (20)	1.00
Number of years postpartum	0.6 [0.3-2.5]	4.5 [2.6–7.3]	**< 0.01**
Heart failure Stage B	15/65 (23)	15/65 (23)	1.00
Heart failure with preserved LVEF	7/65 (11)	11/65 (17)	0.42
Index pregnancy			
Early-onset PE*	43/64 (67)		NA
Preterm PE	48/65 (74)		NA
Primiparous	54/65 (83)	15/65 (23)	**< 0.01**
GA at birth (weeks)	33.4 (30.1-37.0)		NA
Birth weight (g)	1603 (1006-2665)		NA
SGA neonate	27/65 (42)		NA
IUFD	7/65 (11)		NA
Subsequent pregnancy†	—	44/65 (68)	NA
Recurrent PE	—	9/44 (20)	NA
Maternal offspring pregnancy‡			
GA at birth (weeks)	40 (37-40)		NA
Preterm birth	10/48 (21)		NA
Birth weight (g)	3000 (2500-3500)		NA

Data are given as median (interquartile range), median [range] or *n*/N (%). * Time of onset of pre-eclampsia (PE) unknown in one case.

† Pregnancy between index pregnancy and second visit.

‡ Pregnancy of which woman in this study was offspring.

BMI, body mass index; CVD, cardiovascular disease; GA, gestational age; IUFD, intrauterine fetal death; LVEF, left ventricular ejection fraction; NA, not applicable; PE, pre-eclampsia; SGA, small for gestational age.

Supplemental Table 2. Cardiac and metabolic characteristics of heart failure Stage B (HF-B) in 65 formerly pre-eclamptic women, excluding those with a twin pregnancy, categorized according to presence and absence of HF-B at 1 and 4 years postpartum.

	1 year			4 years		
Parameter	**HF-B (*n* = 15)**	**No-HF-B (*n* = 50)**	***P***	**HF-B (*n* = 15)**	**No-HF-B (*n* = 50)**	***P***
Myocardial infarction	0 (0)	—	NA	0 (0)	—	NA
LV hypertrophy	3 (20)	—	NA	0 (0)	—	NA
Concentric remodeling	5 (33)	—	NA	11 (73)	—	NA
Mildly impaired LVEF	8 (53)	—	NA	4 (27)	—	NA
Asymptomatic valve disease	1 (7)	—	NA	1 (7)	—	NA
Heart failure with preserved LVEF	7 (47)	—	NA	11 (73)	—	NA
Metabolic syndrome						
Fasting glucose (mmol/L)	4.8 (4.3-5.1)	4.8 (4.6-5.1)	0.42	4.8 (4.5-5.0)	4.7 (4.4-4.9)	0.41
Fasting insulin (mU/L)	12.0 (8.0-14.0)	8.0 (6.0-10.0)	**< 0.05**	8.0 (6.1-11.4)	7.8 (5.4-10.0)	0.34
$HOMA_{IR}$	2.5 (1.6-3.2)	1.9 (1.4-2.3)	0.07	1.8 (1.3-2.9)	1.6 (1.1-2.1)	0.34
Triglyceride (mmol/L)	1.0 (0.6-1.6)	0.9 (0.7-1.0)	0.43	0.8 (0.7-1.2)	0.9 (0.7-1.1)	0.49
Total cholesterol (mmol/L)	4.9 (4.2-5.3)	4.6 (4.1-5.1)	0.22	4.4 (4.1-5.1)	4.6 (4.2-5.0)	0.70
LDL (mmol/L)	3.1(2.6-3.6)	2.8 (2.4-3.3)	0.17	2.9 (2.4-3.6)	2.8 (2.5-3.2)	0.64
HDL (mmol/L)	1.2 (1.1-1.3)	1.3 (1.2-1.5)	0.13	1.2 (1.1-1.5)	1.4 (1.1-1.5)	0.11
Albumin/creatinine ratio (g/mol)	0.7 (0.1-2.1)	1.0 (0.3-2.1)	0.18	0.8 (0.5-1.7)	0.5 (0.2-1.7)	0.42
SBP (mmHg)	124 (117-144)	115 (107-123)	**< 0.01**	118 (109-129)	116 (106-123)	0.41
DBP (mmHg)	75 (68-83)	68 (64-74)	**< 0.05**	74 (71-82)	72 (66-77)	0.21
MAP (mmHg)	91 (84-104)	82 (79-92)	**< 0.01**	85 (82-95)	84 (77-94)	0.33
Heart rate (bpm)	70 (64-80)	67 (60-75)	0.14	68 (63-79)	62 (59-75)	0.09
BMI (kg/m^2)	27.3 (22.3-32.8)	22.9 (20.7-24.9)	**< 0.01**	24.7 (22.4-30.4)	23.7 (21.1-25.8)	0.30
Antihypertensive treatment	4 (27)	10 (20)	0.72	4 (27)	9 (18)	0.48

Data are given as *n* (%) or median (interquartile range).

*$P < 0.05$ compared to HF-B at 1 year postpartum.

BMI, body mass index; DBP, diastolic blood pressure; HDL, high density lipoprotein; $HOMA_{IR}$, homeostatic model assessment for insulin resistance; LDL, low density lipoprotein; LV, left ventricular; LVEF, left ventricular ejection fraction; MAP, mean arterial pressure; NA, not applicable; SBP, systolic blood pressure.

Supplemental Table 3. Pregnancy characteristics and cardiac indices in 65 formerly pre-eclamptic women, excluding those with twin pregnancy, categorized according to absence of heart failure Stage B (HF-B) at 1 year and 4 years postpartum (HF-B$^{-/-}$), absence of HF-B at 1 year but present at 4 years (HF-B$^{-/+}$), presence of HF-B at both 1 and 4 years (HF-B$^{+/+}$) and presence of HF-B at 1 year but absence at 4 years (HF-B$^{+/-}$).

Characteristic	HF-B$^{-/-}$ (n = 40)	HF-B$^{-/+}$ (n = 10)	P	HF-B$^{+/+}$ (n = 5)	HF-B$^{+/-}$ (n = 10)	P
Postpartum interval (years)						
1 year	0.6 [0.3-2.4]	0.6 [0.3-2.4]	0.77	0.5 [0.4-2.1]	0.6 (0.3-2.5)	0.86
4 years	4.4 [2.7-7.3]*	4.3 [3.7-6.7]*	0.86	5.8 [2.6-6.8]†	4.7 (3.3-6.0)*	0.17
Index pregnancy						
Early-onset PE	24/40 (60)	8/10 (80)	0.30	3/4(75)	8/10 (80)	1.00
Preterm PE	29/40 (73)	8/10 (80)	1.00	3/5 (60)	8/10 (80)	0.56
Primiparous at 1 year	37/40 (93)	6/10 (60)	**< 0.05**	3/5 (60)	8/10 (80)	0.56
Primiparous at 4 years	11/40 (28)*	1/10 (10)	0.42	1/5 (20)	2/10 (20)†	1.00
GA at birth (weeks)	34.9 (30.8–37.2)	32.6 (27.6-35.2)	0.22	31.9 (26.9-37.9)	31.8 (28.5-35.9)	0.86
Birth weight (g)	1880 (1073-2770)	1350 (667-2013)	0.19	1603 (455-3018)	1457 (941-2540)	0.86
SGA neonate	15/40 (38)	7/10 (70)	0.08	2/5 (40)	3/10 (30)	1.00
IUFD	3/40 (8)	2/10 (20)	0.26	2/5 (40)	0/10 (0)	0.10
Subsequent pregnancy‡	27/40 (68)	7/10 (70)	1.00	3/5 (60)	7/10 (70)	1.00
Recurrent PE	3/27 (11)	0/7 (0)	1.00	3/3 (100)	3/7 (43)	0.20
Maternal offspring pregnancy						
GA at birth (weeks)	39.0 (37.0-40.0)	40.0 (33.5-40.5)	0.78	40.0 (36.0-40.0)	39.0 (34.3-41.3)	1.00
Preterm birth	6/33 (18)	2/6 (33)	0.58	0/3 (0)	2/6 (33)	0.50
Birth weight (g)	3150 (2500-3525)	2875 (2500;3500)	0.65	2000 (1990-2000)	3000 (2500-3500)	0.07
Family history of PE in first-degree relative	11/40 (28)	3/10 (30)	1.00	4/5 (80)	1/10 (10)	**<0.05**
Cardiac measurements						
LVMi (g/m^2)						
1 year	62 (52-69)	60 (57-64)	0.69	70 (48-96)	65 (59-79)	1.00
4 years	57 (49-64)†	63 (40-66)	0.80	53 (49-70)	62 (49-74)	0.86
RWT						
1 year	0.31 (0.27;0.35)	0.32 (0.29-0.35)	0.61	0.43 (0.41-0.48)	0.33 (0.30-0.42)	0.05
4 years	0.33 (0.29;0.36)	0.44 (0.31-0.46)†	**< 0.05**	0.44 (0.38-0.45)	0.32 (0.28-0.37)	**<0.05**
LVEF (%)						
1 year	65 (61;68)	68 (61-72)	0.38	56 (53-65)	53 (50-59)	0.31
4 years	65 (63;68)	62 (54-66)†	0.06	57 (55-59)	65 (61-67)*	**<0.01**
SV (mL)						
1 year	72 (60-84)	83 (73-88)	0.06	63 (58-88)	78 (63-85)	0.59
4 years	77 (72-87)*	85 (73-88)	0.59	77 (62-121)	83 (70-91)	0.90

Supplemental Table 3. Pregnancy characteristics and cardiac indices in 65 formerly pre-eclamptic women, excluding those with twin pregnancy, categorized according to absence of heart failure Stage B (HF-B) at 1 year and 4 years postpartum (HF-$B^{-/-}$), absence of HF-B at 1 year but present at 4 years (HF-$B^{-/+}$), presence of HF-B at both 1 and 4 years (HF-$B^{+/+}$) and presence of HF-B at 1 year but absence at 4 years (HF-$B^{+/-}$). *(continued)*

Characteristic	HF-$B^{-/-}$ (*n* = 40)	HF-$B^{-/+}$ (*n* = 10)	*P*	HF-$B^{+/+}$ (*n* = 5)	HF-$B^{+/-}$ (*n* = 10)	*P*
SV index (mL/m^2)						
1 year	39 (34-48)	48 (40-53)	0.07	35 (28-51)	40 (32-46)	0.86
4 years	44 (41-49)†	47 (42-51)	0.56	42 (37-58)	42 (37-48)	0.90
E/A ratio						
1 year	1.62 (1.31-2.03)	1.35 (1.19-1.68)	0.15	1.42 (1.20-1.50)	1.56 (1.16-1.91)	0.52
4 years	1.62 (1.44-1.94)	1.66 (1.43-1.83	0.84	1.39 (1.19-1.82)	1.60 (1.19;1.88)	0.68
CO (L/min)						
1 year	4.4 (3.8-5.1)	5.6 (5.3-6.3)	**< 0.01**	4.3 (4.0-6.4)	5.3 (4.1-5.6)	1.00
4 years	4.8 (4.2-5.7)*	5.3 (4.8-6.2)	0.15	6.1 (4.3-8.2)	5.0 (4.5-5.4)	0.44
CO index (L/min/m^2)						
1 year	2.4 (2.1-3.0)	3.2 (3.0-3.8)	**< 0.01**	2.5 (1.9-3.7)	2.8 (2.2-3.2)	0.95
4 years	2.7 (2.4-3.0)†	2.9 (2.6-3.4)	0.22	3.2 (2.5-4.0)	2.6 (2.2-2.9)	0.11
Heart rate (bpm)						
1 year	60 (55-66)	73 (65-77)	**< 0.01**	71 (66-75)	69 (60-78)	0.68
4 years	62 (57-68)	64 (58-74)	0.34	74 (61-78)	64 (59-70)	0.37
LVEDV (mL)						
1 year	80 (69-86)	90 (77-102)	0.10	74 (57-101)	95 (80-141)	0.13
4 years	87 (76-101)*	90 (78-103)	0.77	94 (66-145)	101 (72-111)	1.00

Data are given as median [range], *n*/N (%) or median (interquartile range).
Comparison with 1 year postpartum: *$P < 0.01$; †$P < 0.05$.
‡Pregnancy between index pregnancy and second visit.
CO, cardiac output; EA ratio, ratio of early-to-late ventricular filling velocity; GA, gestational age; IUFD, intrauterine fetal death; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; LVMi, left ventricular mass index; PE, pre-eclampsia; RWT, relative wall thickness; SGA, small-for-gestational age; SV, stroke volume.

Supplemental Table 4. Metabolic variables in 65 formerly pre-eclamptic women, excluding those with twin pregnancy, categorized according to absence of heart failure Stage B (HF-B) at 1 year and 4 years postpartum (HF-$B^{-/-}$), absence of HF-B at 1 year but present at 4 years (HF-$B^{-/+}$), presence of HF-B at both 1 and 4 years (HF-$B^{+/+}$) and presence of HF-B at 1 year but absence at 4 years (HF-$B^{+/-}$).

Variable	HF-$B^{-/-}$ (*n* = 40)	HF-$B^{-/+}$ (*n* = 10)	*P*	HF-$B^{+/+}$ (*n* = 5)	HF-$B^{+/-}$ (*n* = 10)	*P*
Fasting glucose (mmol/L)						
1 year	4.8 (4.6-5.1)	4.9 (4.7-5.4)	0.46	4.8 (4.5-5.1)	4.7 (4.2-5.2)	0.86
4 years	4.7 (4.4-4.9)†	4.8 (4.4-5.0)	0.86	4.8 (4.7-5.5)	4.8 (4.3-5.4)	0.59
Fasting insulin (mU/L)						
1 year	8.0 (6.0-10.0)	9.0 (7.5-12.5)	0.42	14.0 (9.0-17.0)	10.0 (7.8-14.0)	0.51
4 years	7.5 (5.4-10.0)	8.0 (6.6-11.9)	0.34	11.0 (4.4-13.2)	8.3 (4.3-13.6)	0.95
$HOMA_{IR}$						
1 year	1.7(1.4-2.3)	1.9 (1.6-3.0)	0.38	3.0 (1.8-3.8)	2.1 (1.6-3.1)	0.44
4 years	1.6 (1.1-2.0)	1.7 (1.5-2.5)	0.36	2.5 (0.9-3.0)	1.7 (0.8-3.1)	0.95
Triglyceride (mmol/L)						
1 year	0.8 (0.7-1.0)	0.9 (0.6-1.3)	0.64	0.9 (0.7-1.2)	1.2 (0.5-1.7)	0.68
4 years	0.9 (0.7-1.1)	0.8 (0.6-0.9)	0.30	1.2 (0.7-1.3)	0.9 (0.7-1.4)	1.00
Total cholesterol (mmol/L)						
1 year	4.6 (4.0-5.2)	4.5 (4.2-4.9)	0.99	4.9 (4.5-5.3)	4.7 (4.2-5.3)	0.51
4 years	4.5 (4.1-4.9)	4.6 (4.2-5.1)	1.00	4.3 (4.1-5.6)	4.8 (4.3-5.5)	0.44
LDL (mmol/L)						
1 year	2.8 (2.3-3.3)	2.8 (2.4-3.3)	0.78	3.3(2.7-3.7)	3.0 (2.6-3.4)	0.54
4 years	2.8 (2.3-3.1)	3.0 (2.2-3.4)	0.44	2.6 (2.4-3.8)	2.9 (2.7-3.6)	0.37
HDL (mmol/L)						
1 year	1.3 (1.2-1.5)	1.3 (1.1-1.5)	0.50	1.2 (1.1-1.4)	1.2 (1.1-1.3)	1.00
4 years	1.4 (1.1-1.5)	1.2 (1.1-1.4)	0.11	1.2 (1.0-1.5)	1.4 (1.1-1.5)	0.77
Albumin/creatinine ratio (g/mol)						
1 year	1.0 (0.4-2.1)	0.8 (0.3-1.7)	0.56	0.1(0.0-0.7)	0.9 (0.3-2.3)	0.17
4 years	0.5 (0.2-1.8)	0.6 (0.1-1.0)	0.89	0.9 (0.7-4.4)	0.5 (0.4-1.3)	0.10
SBP (mmHg)						
1 year	115 (107-123)	117 (105-122)	0.80	149 (130-157)	123 (114-126)	**<0.05**
4 years	116 (104-123)	112 (107-122)	0.75	130 (123-137)	119 (109-130)	0.10
DBP (mmHg)						
1 year	68 (63-74)	66 (64-71)	0.68	83 (78-94)	70 (68-78)	**<0.05**
4 years	72 (66-77)†	72 (69-75)	0.97	87 (77-93)	75 (66-78)	0.06
MAP (mmHg)						
1 year	83 (79-92)	82 (79-89)	0.69	104 (95-114)	87 (83-97)	**<0.05**
4 years	83 (77-95)	83 (80-86)	0.91	99 (89-106)	86 (80-95)	0.06
Heart rate (bpm)						
1 year	66 (60-74)	74 (62-76)	0.30	70 (66-80)	70 (63-82)	0.95
4 years	62 (59-71)	69 (64-80)	0.15	65 (62-82)	62 (59-82)	0.37

Supplemental Table 4. Metabolic variables in 65 formerly pre-eclamptic women, excluding those with twin pregnancy, categorized according to absence of heart failure Stage B (HF-B) at 1 year and 4 years postpartum (HF-$B^{-/-}$), absence of HF-B at 1 year but present at 4 years (HF-$B^{-/+}$), presence of HF-B at both 1 and 4 years (HF-$B^{+/+}$) and presence of HF-B at 1 year but absence at 4 years (HF-$B^{+/-}$). *(continued)*

Variable	HF-$B^{-/-}$ (n = 40)	HF-$B^{-/+}$ (n = 10)	*P*	HF-$B^{+/+}$ (n = 5)	HF-$B^{+/-}$ (n = 10)	*P*
BMI (kg/m^2)						
1 year	22.6 (20.5-24.1)	24.3 (22.2-27.2)	0.15	27.3(23.0-31.2)	27.6 (22.2-34.4)	1.00
4 years	23.3 (20.8-25.0)†	24.4 (22.4-27.2)	0.32	27.0 (21.5-33.1)	25.2 (22.7-35.0)	1.00
Antihypertensive treatment						
1 year	9/40 (23)	1/10 (10)	0.66	3/5 (60)	1/10 (10)	0.08
4 years	7/40 (18)	1/10 (10)	1.00	3/5 (60)	2/10 (20)	0.25
Prehypertension						
1 year	7/40 (18)	4/10 (40)	0.20	0/5 (0)	4/10 (40)	0.23
4 years	5/40 (13)	2/10 (20)	0.62	2/5 (40)	3/10 (30)	1.00
Hypertension						
1 year	9/40 (23)	1/10 (10)	0.66	4/5 (80)	2/10 (20)	0.09
4 years	9/40 (23)	1/10 (10)	0.66	3/5 (60)	2/10 (20)	0.25

Data are given as median (interquartile range) or *n*/N (%).
Comparison with 1 year postpartum: **P* < 0.01; †*P* < 0.05.
BMI, body mass index; DBP, diastolic blood pressure; HDL, high density lipoprotein; $HOMA_{IR}$, homeostatic model assessment for insulin resistance; LDL, low density lipoprotein; MAP, mean arterial pressure; SBP, systolic blood pressure.

Decreased endothelial function and increased subclinical heart failure in women several years after pre-eclampsia

N.M. Breetveld[1], C. Ghossein-Doha[1], J. van Neer[1], M.J.J.M Sengers[1], L. Geerts[1], S.M.J van Kuijk[2], A.P. van Dijk[3], M.J. van der Vlugt[3], W.M. Heidema[4], H.P. Brunner-La Rocca[5], R.R. Scholten[4], M.E.A. Spaanderman[1]

[1] *Department of Obstetrics and Gynecology, Research School GROW, Maastricht University Medical Centre (MUMC+), Maastricht, The Netherlands*

[2] *Department of Clinical Epidemiology and Medical Technology Assessment (KEMTA), Maastricht University Medical Centre (MUMC+), Maastricht, The Netherlands*

[3] *Department of Cardiology, Radboud University Medical Centre (RadboudUMC), Nijmegen, The Netherlands*

[4] *Department of Obstetrics and Gynecology, Radboud University Medical Centre (RadboudUMC), Nijmegen, The Netherlands*

[5] *Department of Cardiology, Maastricht University Medical Centre (MUMC+), Maastricht, The Netherlands*

Ultrasound in Obstetrics & Gynecology. *2018 Aug; 52(2):196-204.*

doi: 10.1002/uog.17534.

ABSTRACT

Objectives

Pre-eclampsia (PE) is associated with both postpartum endothelial dysfunction and asymptomatic structural heart alterations consistent with heart failure Stage B (HF-B). In this study, we assessed the relationship between endothelial function, measured by flow-mediated dilation (FMD), and HF-B in women with a history of PE.

Methods

This was an observational study in which 67 formerly pre-eclamptic women (≥ 4 years postpartum) and 37 healthy parous controls were assessed ultrasonographically for cardiac function and geometry, as well as for endothelial function by means of brachial artery FMD. HF-B was diagnosed as left ventricular hypertrophy (left ventricular mass index (LVMi) > 95g/m^2), concentric remodeling (relative wall thickness > 0.42 and LVMi ≤ 95g/m^2), mild systolic dysfunction (left ventricular ejection fraction > 40% and < 55%) or asymptomatic valvular disease. Cardiovascular and metabolic syndrome variables were compared between women with history of PE and controls, as well as between those in the formerly pre-eclamptic group who had HF Stage A, HF-B or no HF. Logistic regression analysis was performed to assess the associations of FMD with PE, metabolic syndrome risk factors and obstetric parameters.

Results

The prevalence of HF-B amongst formerly pre-eclamptic women was three-fold higher than that observed for controls (25% vs 8%, $P < 0.05$), while FMD was lower in formerly pre-eclamptic women compared with controls (6.12% vs 8.22%, $P < 0.01$); history of PE remained associated independently with lower FMD after adjusting for metabolic syndrome risk factors and obstetric parameters (β, –1.88; 95% CI, –3.59 to –0.18). However, HF-B did not relate to low FMD in formerly pre-eclamptic women.

Conclusions

Years after pregnancy, formerly preeclamptic women have lower FMD and have HF-B more often compared with healthy parous controls. Nonetheless, HF-B was not related to reduced FMD.

Keywords

Cardiovascular disease; echocardiography; endothelial dysfunction; endothelial function; flow-mediated dilation; heart failure; pre-eclampsia

INTRODUCTION

Cardiovascular disease (CVD) is the number one cause of death in women[1,2]. While there are classical risk factors for CVD that affect both women and men, pre-eclampsia (PE) is a risk factor exclusive to women, increasing the risk of CVD two to seven times in the first 15 years after pregnancy[1,3,4]. PE is a pregnancy-related endothelial disorder and is one of the major contributors to maternal and fetal morbidity and mortality, occurring in 3–5% of all pregnancies[5–8]. PE is the common vascular endpoint of different underlying mechanical and biochemical disorders, mostly conventional cardiovascular risk factors consistent with metabolic syndrome, capable of jeopardizing both placental and endothelial function[9–12]. As metabolic syndrome and the associated cardiovascular risk are sensitive to lifestyle interventions, timely detection of those specifically at risk may offer effective prevention opportunities for cardiovascular risk management in these women.

In the first year after a pre-eclamptic pregnancy, the prevalence of asymptomatic structural heart disease, defined as preclinical heart failure Stage B (HF-B), is about one in four women[13,14]. HF-B is considered the stage of heart failure preceding the mortality-related symptomatic and clinical stages, Stages C and D[15,16]. Endothelial dysfunction correlates with symptomatic heart failure[17,18]. A few years after PE, endothelial dysfunction remains highly prevalent and it is thought that this asymptomatic vascular condition relates to the increased risk of CVD after PE[19–28]. On the one hand, the unfavorable structural heart alterations after PE may relate to traditional cardiovascular risk factors; on the other hand, they could be a result of endothelial dysfunction[1,18]. Therefore, in this study, we assessed the relationship between endothelial function, along with components of metabolic syndrome, and asymptomatic structural heart dysfunction in formerly pre-eclamptic women and healthy parous controls.

METHODS

The protocol of this observational study was approved by the Medical Ethics Committee of the Radboud University Medical Center (NL32718.091.10). The procedures followed were in accordance with institutional guidelines and adhered to the principles of the Declaration of Helsinki and Title 45, US Code of Federal Regulation, Part 46, Protection of Human Subjects, Revised November 13, 2001, Effective December 13, 2001. The study population was recruited between 2009 and 2011.

Study population

At the Radboud University Medical Center, women with a history of PE were evaluated routinely for cardiovascular function at approximately 1 year postpartum. For this study,

those women who were at least 4 years postpartum were reinvited by mail to participate in a second follow-up cardiovascular assessment. The study was completed in the east of the Netherlands, where the average socioeconomic status is known to be representative of the country as a whole and where the prevalence of immigrants is low. We included for this study 92 women with a history of PE without comorbidity (diabetes mellitus, autoimmune disease or pre-existing hypertension) prior to their index pregnancy. Nine of these women were excluded due to incomplete echocardiographic work-up, insufficient to diagnose HF-B, and 16 due to an incomplete flow-mediated dilation (FMD) measurement. Controls were recruited by advertisement in local newspapers, schools and childcare centers in the same catchment area as that from which the formerly pre-eclamptic women originated. Forty-seven control women were included with a history of pregnancy uncomplicated by gestational hypertension, PE, HELLP syndrome, fetal growth restriction, placental abruption or intrauterine fetal death. Of these women, nine were excluded due to incomplete echocardiographic work-up, insufficient to diagnose HF-B, and one due to incomplete FMD measurement. Pregnancy charts were checked to ensure that pregnancies were uncomplicated. In total, 67 formerly pre-eclamptic women and 37 control women were included.

PE was diagnosed, according to the criteria set by the International Society of Hypertension in Pregnancy, as new-onset hypertension, defined as systolic blood pressure (SBP) ≥ 140mmHg and/or diastolic blood pressure (DBP) ≥ 90mmHg after 20weeks' gestation, and proteinuria exceeding 0.3g/day[29]. Early-onset PE was diagnosed as the development of PE before 34weeks of gestation. Preterm PE was defined as PE requiring delivery before 37weeks of gestation.

Five women gave birth to twins. All birth weights were analyzed. Most women in the PE and control groups were of European origin, but two were of Turkish and one was of Moroccan origin. At the time of assessment, none of the women was pregnant, and all had stopped breastfeeding and were not using oral contraceptives. Women who became pregnant after the index pregnancy had to be at least 6months postpartum to be included in the second follow-up cardiovascular assessment.

Cardiovascular assessment

Each cardiovascular risk evaluation started at 08.00h in a temperature-controlled room (22 °C), after an overnight fast. Measurements were performed in the follicular phase of the menstrual cycle, between days 3 and 11 after the onset of menses[30–32]. Participants were not allowed to talk during measurements and external disturbances were kept to a minimum. Measurements were performed following a standardized study protocol by an experienced physician. Cardiovascular screening consisted of measuring body mass (kg; Seca 888 scale, Hamburg, Germany) and height (m) in order to calculate body mass index (BMI). Women rested for at least 15min before measurement of SBP, DBP, mean

arterial pressure (MAP) and heart rate (HR). Measurement lasted for 30min (at 3-min intervals) and was taken with the woman in the upright sitting position using a semi-automatic oscillometric device (Dinamap Vital Signs Monitor 1846; Critikon, Tampa, FL, USA) with a cuff size recommended for arm circumference. Median values were used for analysis. Hypertension was diagnosed as SBP ≥ 140mmHg and/or DBP ≥ 90mmHg and/or antihypertensive medication being taken. Prehypertension was defined as SBP 120–139mmHg and/or DBP 80–89mmHg. Venous blood samples taken at the level of the antecubital vein were analyzed for fasting glucose (mmol/L), fasting insulin (mmol/L) and lipids (mmol/L), including low-density lipoprotein (LDL), high-density lipoprotein (HDL), triglycerides and total cholesterol (Aeroset, Abbot Laboratories, IL, USA). The homeostatic model assessment index for insulin resistance ($HOMA_{IR}$) was calculated as insulin (mU/L)×glucose (mmol/L)/22.5[33]. All patients collected their urine in the 24h before cardiovascular screening. The 24-h urine sample was evaluated for albumin and creatinine to diagnose (micro)albuminuria corrected for creatinine output (g/mol creatinine) (Aeroset). Participants filled out a validated questionnaire consisting of general history, current medication intake, intoxicants (smoking was defined as ≥ 1 cigarette per day), lifestyle factors and family history of CVD (in first line relatives < 60 years of age).

Flow-mediated dilation measurements

Measurement of FMD was used to assess endothelial function as it is a reproducible, accurate and non-invasive method[34,35]. FMD characterizes the change in artery diameter in response to reactive hyperemia[19]. The resulting increase in shear stress leads to the endothelium releasing vasodilators, including nitric oxide, which cause dilation in a healthy artery[19,34,36]. FMD and brachial artery shear pattern measurements were performed under standardized conditions in a temperature-controlled (22 ± 0.5°C), quiet room, according to recent guidelines[28,32,37]. Subjects were supine with the arm placed in an extended position, immobilized with foam, at an angle of ~80° from the torso[28,32]. To induce forearm ischemia, a rapid inflation and deflation pneumatic cuff (D. E. Hokanson, Bellevue, WA, USA) was positioned on the forearm distal to the olecranon[28,32]. The brachial artery was imaged in the distal one-third of the upper arm (2–5cm above the antecubital fossa) using a 10-MHz multifrequency linear array probe attached to a high-resolution ultrasound machine (T3000; Terason Corp., Burlington, MA, USA)[28,32]. Ultrasound was also used to measure continuous Doppler velocity with the lowest possible insonation angle of < 60°[28,32]. Shear rate was calculated as 4×velocity/diameter[32,38].

Thereafter, the rapid inflation/deflation forearm cuff was inflated (> 200mmHg) for 5 min[28,32]. Diameter and flow recordings were resumed 30s before deflation of the cuff and continued for 3min after deflation[32,37]. To minimize investigator bias, FMD analysis was performed using custom-designed edge-detection and wall-tracking Digital Imaging and Communications in Medicine-based software (National Electrical Manufacturers Asso-

ciation, Rosslyn, VA, USA)[28,32,37,39]. Peak diameter was detected automatically according to an algorithm that is described in detail elsewhere[32,40]. Using this technique, data can be analyzed with a temporal resolution of 30Hz and a spatial resolution of ~0.0065cm for diameter and ~1cm/s for velocity[32], and FMD has an intraobserver coefficient of repeated measures of 6.7%[39]. Postdeflation shear rate data (derived from simultaneously acquired velocity and diameter measurements at 30Hz) were used for calculating the area under the shear-rate curve for data up to the point of maximal postdeflation diameter (FMD) for each individual[28,32].

Echocardiographic measurements

Echocardiographic measurements were made using a phased-array echocardiographic Doppler system (Vivid 7, GE Vingmed Ultrasound, Horten, Norway). Two-dimensional, M-mode and Doppler echocardiography were performed in accordance with the recommendation of the American Society of Echocardiography (ASE)[41]. Using M-mode in the parasternal long-axis view, we measured left ventricular end-diastolic (LVEDd) and end-systolic (LVESd) diameters (mm), end-diastolic interventricular septum thickness (IVST; mm) and the posterior (inferolateral) wall thickness (PWT; mm). As recommended by the ASE, left ventricular mass (LVM; g) was determined using the formula $0.8 \times (1.04 ((LVEDd + PWT + IVST)^3 - (LVEDd)^3)) + 0.6$, indexed for body surface area[42]. Relative wall thickness (RWT) was computed using the formula $(2\times PWT)/LVEDd)$[42]. Left ventricular end-diastolic (LVEDV, mL) and end-systolic (LVESV, mL) volumes were determined using the Teichholz formula[43]. Left ventricular ejection fraction (LVEF, %) was calculated using the formula $((LVEDV - LVESV)/(LVEDV))\times 100$. Heart rate (HR, bpm) was calculated by multiplying by 60 the reciprocal of the mean of five consecutive RR intervals on the electrocardiogram. Mean aortic velocity time integral (VTI, cm) was calculated by averaging the outer edge tracings of five consecutive continuous wave Doppler registrations of the left ventricular outflow tract velocity. Stroke volume (SV, mL) was computed by taking the product of VTI and mid-systolic cross-sectional area (cm^2) at the level of the left ventricular outflow tract in the parasternal long-axis view. Cardiac output (CO, L/min) was calculated by multiplying SV by HR. Assessments were executed offline using EchoPAC PC SW (GE Vingmed Ultrasound) version 6.1.2.

Definition of heart failure Stage A

Heart failure Stage A (HF-A) was defined as the presence of hypertension (SBP ≥ 140mmHg and/or DBP ≥ 90mmHg and/or use of antihypertensive medication), atherosclerotic disease, diabetes mellitus (fasting glucose ≥ 6.1mmol/L), obesity (BMI ≥ 30kg/m^2) or metabolic syndrome[16]. A modified metabolic syndrome was defined, using the WHO criteria, as insulin resistance (fasting insulin ≥ 9.2mU/L and/or fasting glucose ≥ 6.1mmol/L and/or $HOMA_{IR}$ ≥ 2.2) and two or more of the following factors: hyperten-

sion (SBP ≥ 140mmHg and/or DBP ≥ 85mmHg and/or use of antihypertensive medication), obesity (BMI ≥ 30kg/m^2), dyslipidemia (triglycerides ≥ 1.69mmol/L and/or HDL < 1.0mmol/L) and/or microalbuminuria (urine albumin to creatinine ratio ≥ 2.5g/mol creatinine)[44].

Definition of heart failure Stage B

HF-B was defined, according to the American Heart Association (AHA)[16], as the presence of a former myocardial infarction, left ventricular hypertrophy (left ventricular mass index (LVMi) > 95g/m^2), concentric remodeling (RWT > 0.42 and LVMi ≤ 95g/m^2), mildly impaired left ventricular ejection fraction (LVEF > 40% and < 55%) or asymptomatic valvular disease[42]. Asymptomatic valvular disease was defined as at least mild aortic valve insufficiency or mild mitral valve insufficiency with mild thickening of the mitral valve. Asymptomatic cardiac abnormality with preserved ejection fraction was defined as HF-B with LVEF ≥ 55%[42].

Data analysis

Statistical analyses were performed using SPSS Statistics version 21.0 (IBM Corp., Armonk, NY, USA). Continuous data were analyzed using the Mann–Whitney U-test for intergroup differences. Continuous data are reported as median with interquartile range (IQR). The Kruskal–Wallis test was used to analyze differences between more than two groups of continuous data. Dichotomous data were analyzed using the chi-square or Fisher's exact test for intergroup differences, reported as *n* (%). Associations between FMD and PE, metabolic syndrome risk factors and obstetric parameters were analyzed using uni- and multivariable linear regression. A two-sided P-value of < 0.05 was considered statistically significant. Based on findings of Melchiore *et al.*[13] on the prevalence of HF-B at 1 year postpartum in formerly preterm pre-eclamptic women (41%) compared with controls (6%), and on our observations[14] in the first year after pre-eclamptic gestation (25%) compared with controls (7%), the sample size needed was estimated using a prevalence of HF-B of 33% in formerly pre-eclamptic women and 6% in controls. The required sample size was calculated using a desired power of 0.80 and a two-sided alpha of 0.05. A minimum of 33 participants for each group was necessary for determining statistical significance. PE is a vascular disease of heterogeneous origin. To compensate for possible larger heterogeneity in hemodynamic assessments in formerly pre-eclamptic women than in controls, we aimed to include measurements of two formerly pre-eclamptic women for every one healthy parous control in the analysis.

RESULTS

Characteristics of the formerly pre-eclamptic and control groups are presented in Table 1. The formerly pre-eclamptic group was on average 4 years younger compared with the control group ($P < 0.01$). Moreover, more women with a history of PE were obese (18% vs 3%, $P < 0.05$) and used antihypertensive medication (18% vs 0%, $P < 0.01$). Formerly pre-eclamptic women underwent postpartum measurement at a shorter median postpartum interval than the control group (5.3 (IQR, 4.4–6.4) vs 8.3 (IQR, 6.6–9.9) years, $P < 0.01$). Birth weight was lower in the formerly pre-eclamptic group compared with the control group (1615 (IQR, 1034–2513) vs 3260 (IQR, 3000–3690) g; $P < 0.01$). Forty out of 67 women in the formerly pre-eclamptic group had a subsequent pregnancy (60%), of which 17 (43%) had recurrent PE.

Table 1. Baseline characteristics of women with history of pre-eclampsia (PE) and those with history of uncomplicated pregnancy (controls).

Characteristic	Formerly PE (*n* = 67)	Controls (*n* = 37)	*P*
Patient			
Age (years)	36 (33-39)	40 (37-43)	**<0.01**
Height (m)	1.68 (1.65-1.73)	1.72 (1.67-1.76)	0.14
Weight (kg)	70 (62-83)	65 (58-76)	0.15
BMI (kg/m^2)	24 (21-29)	23 (21-25)	**<0.05**
Obese (BMI ≥ 30 kg/m^2)	12/67 (18)	1/37 (3)	**<0.05**
Smoker	5/67 (7)	3/37 (8)	1.00
Alcohol use	15/67 (22)	26/37 (70)	**<0.01**
Family history of CVD	30/67 (45)	15/37 (41)	0.68
Antihypertensive treatment	12/67 (18)	0/37 (0)	**<0.01**
Postpartum interval (years)	5.3 (4.4-6.4)	8.3 (6.6-9.9)	**<0.01**
Index pregnancy			
Early-onset PE	40/64 (63)	NA	NA
Preterm PE	51/67 (76)	NA	NA
Primiparous	49/67 (73)	3/36 (8)	**<0.01**
GA at birth (weeks)	33 (30-37)	40 (39-41)	**<0.01**
Birth weight (g)	1615 (1034-2513)	3260 (3000;3690)	**<0.01**
SGA neonate	30/67 (45)	4/37 (11)	**<0.01**
IUFD	6/66 (9)	NA	NA

Data are given as median (interquartile range) or *n*/N (%).
BMI, body mass index; CVD, cardiovascular disease; GA, gestational age; IUFD, intrauterine fetal death; NA, not applicable; SGA, small-for-gestational age.

Formerly pre-eclamptic vs control group

Cardiovascular and metabolic variables are presented in Table 2. Incidence of HF-A was eight-fold higher in the formerly pre-eclamptic group compared with the control group (24% vs 3%, $P < 0.01$). Of the HF-A variables, obesity was more prevalent in the formerly pre-eclamptic group as compared with controls.

HF-B was more common in formerly pre-eclamptic women as compared with controls (25% vs 8%, $P < 0.05$). In formerly pre-eclamptic women with HF-B, none had previous myocardial infarction, 6% had left ventricular (LV) hypertrophy, 65% had concentric remodeling, 29% had mildly impaired LVEF and 6% had asymptomatic valve disease. Of the three controls with HF-B, none had previous myocardial infarction or LV hypertrophy, one had concentric remodeling, two had mildly reduced LVEF, and none had asymptomatic valve disease.

As shown in Table 2, the formerly pre-eclamptic group had higher SBP and HR compared with controls. DBP, MAP, SV, CO, LVEDV, LVEF, EA ratio, LVM index and RWT did not differ between the groups.

Formerly pre-eclamptic women had lower FMD compared with controls (6.12% (IQR, 4.82–8.30%) vs 8.22% (IQR, 5.79–11.33%), $P < 0.01$), whereas baseline diameter of the brachial artery was similar.

Table 2. Cardiovascular and metabolic syndrome variables in formerly pre-eclamptic (PE) women and women with history of uncomplicated pregnancy (controls).

Parameter	Formerly PE ($n = 67$)	Controls ($n = 37$)	P
Heart failure Stage A	16/67 (24)	1/37 (3)	**<0.01**
Hypertension	10/67 (15)	1/37 (3)	0.09
Atherosclerotic disease	1/64 (2)	0/37 (0)	1.00
Diabetes mellitus	3/67 (4)	0/37 (0)	0.55
Obesity (BMI ≥ 30 kg/m^2)	8/67 (12)	0/37 (0)	**<0.05**
Metabolic syndrome	5/67 (7)	0/37 (0)	0.16
Heart failure Stage B	17/67 (25)	3/37 (8)	**<0.05**
Myocardial infarction	0/67 (0)	0/37 (0)	NA
LV hypertrophy	1/67 (1)	0/37 (0)	1.00
Concentric remodeling	11/67 (16)	1/37 (3)	0.05
Mildly impaired LVEF	5/67 (7)	2/37 (5)	1.00
Asymptomatic valve disease	1/67 (1)	0/37 (0)	1.00
HFpEF	12/67 (18)	1/37 (3)	**<0.05**

Table 2. Cardiovascular and metabolic syndrome variables in formerly pre-eclamptic (PE) women and women with history of uncomplicated pregnancy (controls). (*continued*)

Parameter	Formerly PE (*n* = 67)	Controls (*n* = 37)	*P*
Cardiac function			
SBP (mmHg)	116 (109-123)	109 (101-118)	**<0.01**
DBP (mmHg)	72 (68-79)	72 (68-77)	0.70
MAP (mmHg)	85 (81-91)	83 (75-89)	0.11
Heart rate (bpm)	65 (61-78)	62 (55-66)	**<0.01**
Stroke volume (mL)	77 (70-86)	73 (62-86)	0.26
Cardiac output (L/min)	5.1 (4.4-6.1)	4.8 (4.1-6.0)	0.31
LV end diastolic volume (mL)	93 (79-113)	87 (71-99)	0.07
LVEF (%)	63 (60-68)	61 (59-66)	0.36
EA ratio	1.57 (1.36-1.90)	1.49 (1.40-1.73)	0.28
LV mass index (g/m^2)	55 (49-67)	63 (55-67)	0.09
Relative wall thickness	0.35 (0.31-0.39)	0.33 (0.29-0.36)	0.12
FMD			
Baseline diameter (cm)	0.30 (0.27-0.32)	0.30 (0.28-0.32)	0.48
Peak diameter (cm)	0.31 (0.29-0.34)	0.33 (0.30-0.35)	0.12
FMD (%)	6.12 (4.82-8.30)	8.22 (5.79-11.33)	**<0.01**
Shear rate (s^{-1})	22792 (17676-32480)	29484 (21024-34290)	0.06
Metabolic syndrome			
Fasting glucose (mmol/L)	4.8 (4.5-5.0)	4.7 (4.5-5.0)	0.21
Fasting insulin (mU/L)	7.9 (5.9-10.7)	6.2 (4.3-8.1)	**<0.01**
$HOMA_{IR}$	1.7 (1.2-2.5)	1.4 (0.9-1.7)	**<0.01**
Triglycerides (mmol/L)	0.9 (0.7-1.3)	0.8 (0.6-1.1)	0.12
HDL (mmol/L)	1.3 (1.1-1.5)	1.6 (1.4-1.8)	**<0.01**
Albumin/creatinine ratio (g/mol)	0.7 (0.3-1.2)	0.5 (0.4-0.8)	0.51
Pre-hypertension	14/67 (21)	8/37 (22)	0.93
Hypertension untreated	3/67 (4)	1/37 (3)	1.00
Antihypertensive treatment	12/67 (18)	0/37 (0)	**<0.01**

Data are given as median (interquartile range) or *n*/N (%).

BMI, body mass index; DBP, diastolic blood pressure; EA ratio, ratio of early (E) to late (A) ventricular filling velocity; FMD, flow-mediated dilation; HDL, high-density lipoprotein; $HOMA_{IR}$, homeostatic model assessment for insulin resistance; HFpEF, heart failure with preserved ejection fraction; LV, left ventricular; LVEF, left ventricular ejection fraction; MAP, mean arterial pressure; NA, not applicable; SBP, systolic blood pressure.

Of the metabolic syndrome variables, fasting insulin and HOMA were significantly higher and HDL significantly lower in the formerly pre-eclamptic group compared with the control group.

A subsequent pregnancy after the index one in the formerly pre-eclamptic group did not affect the prevalence of HF-A or HF-B, nor FMD or its component measurements, or metabolic syndrome variables (Tables S1 and S2).

The associations between FMD and PE, metabolic risk factors and obstetric parameters are presented in Table 3. On univariable analysis, history of PE, postpartum interval, primiparity, impaired fasting insulin and obesity were associated with FMD peak percentage. The multivariable linear regression model showed R^2 =0.33. In the multivariable model, history of PE remained associated significantly with FMD, with β=−1.88 (95% CI, −3.59 to −0.18). Moreover, impaired fasting insulin had a significant β of −1.63 (95% CI −3.21 to −0.05). The other variables, i.e. postpartum interval, primiparity, age, diabetes mellitus, hypertension, obesity, dyslipidemia and microalbuminuria, were not associated significantly with FMD on multivariable analysis.

Table 3. Univariable and multivariable linear regression model analysis of associations between flow-mediated dilation peak percentage and pre-eclampsia (PE), metabolic syndrome risk factors and obstetric parameters.

	Univariable		Multivariable*	
Parameter	**β (CI)**	**P**	**β (CI)**	**P**
History of PE	-2.40 (-3.64 to -1.16)	**<0.01**	-1.88 (-3.59 to -0.18)	**<0.05**
Postpartum interval	0.31 (0.08 to 0.54)	**<0.01**	0.28 (-0.02 to 0.58)	0.07
Primipartiy	-2.17 (-3.64 to -0.71)	**<0.01**	-1.32 (-2.82 to 0.17)	0.08
Age	0.05 (-0.10 to 0.20)	0.48	-0.15 (-0.33 to 0.03)	0.09
Impaired fasting insulin	-2.16 (-3.54 to -0.79)	**<0.01**	-1.63 (-3.21 to -0.05)	**<0.05**
Diabetes mellitus	-0.77 (-4.56 to 3.02)	0.69	0.39 (-3.29 to 4.08)	0.83
Hypertension	-1.21 (-2.95 to 0.53)	0.17	0.08 (-1.90 to 2.05)	0.94
Obesity	-1.96 (-3.84 to -0.07)	**<0.05**	-0.81 (-2.82 to 1.21)	0.43
Dyslipidemia	-2.36 (-4.85 to 0.13)	0.06	-0.82 (-3.27 to 1.64)	0.51
Microalbuminuria	-0.69 (-2.76 to 1.39)	0.51	0.29 (-1.64 to 2.23)	0.76

*R^2 =0.33, indicating amount of variability in outcome accounted for by predicted variables.

No HF vs HF-A vs HF-B

Table 4 presents the cardiovascular and metabolic syndrome variables in formerly pre-eclamptic women, subdivided according to those without HF, those with cardiovascular risk factor (HF-A) and those with functional or structural cardiac abnormality (HF-B). Of the cardiovascular variables, SBP, DBP and MAP were significantly higher in the HF-A compared with the no-HF subgroup; HR did not differ between these subgroups. Of the cardiac indices, only LVEF was significantly different (lower) in the HF-A compared with the no-HF subgroup. The HF-B subgroup had higher SBP, DBP and MAP compared with

the no-HF subgroup; HR did not differ between these subgroups. Of the cardiac indices, LVEF was lower in the HF-B compared with the no-HF subgroup, and RWT was higher in the HF-B subgroup compared with both the no-HF and HF-A subgroups.

Table 4. Cardiovascular and metabolic syndrome variables in women with history of pre-eclampsia, according to whether they had no heart failure (No HF), HF Stage A (HF-A) or HF Stage B (HF-B).

Parameter	No HF (*n* = 34)	HF-A (*n* = 16)	HF-B (*n* = 17)	*P*
Cardiac assessment				
SBP (mmHg)	112 (107-118)	125 (115-131)*	119 (109-128)*	**<0.01**
DBP (mmHg)	71 (66-74)	76 (69-85)*	74 (71-82)*	**<0.05**
MAP (mmHg)	82 (77-86)	89 (86-97)*	89 (82-93)*	**<0.01**
Heart rate (bpm)	65 (61-77)	66 (60-82)	66 (64-79)	0.68
Stroke volume (mL)	77 (70-86)	83 (71-88)	75 (66-87)	0.42
Cardiac output (L/min)	4.8 (4.3-5.9)	5.7 (4.4-6.3)	5.1 (4.3-6.4)	0.31
LV end diastolic volume (mL)	93 (81-103)	100 (79-121)	90 (72-113)	0.52
LV ejection fraction (%)	66 (63-70)	61 (58-63)*	59 (54-65)*	**<0.01**
E/A ratio	1.68 (1.39-2.12)	1.50 (1.30-1.76)	1.50 (1.12-1.84)	0.18
LV mass index (g/m^2)	55 (50-66)	61 (49-67)	53 (42-72)	0.76
Relative wall thickness	0.33 (0.29-0.37)	0.34 (0.32-0.36)	0.44 (0.36-0.47)*†	**<0.01**
FMD				
Baseline diameter (cm)	0.29 (0.26-0.31)	0.30 (0.28-0.34)	0.30 (0.27-0.34)	0.41
Peak diameter (cm)	0.31 (0.28-0.33)	0.31 (0.29-0.36)	0.32 (0.29-0.36)	0.31
FMD (%)	5.79 (4.72-8.81)	5.31 (4.10-7.02)	6.87 (6.07-7.88)	0.14
Shear rate (s^{-1})	21228 (18579-29731)	25334 (15614-40402)	28143 (12864-39895)	0.87
Metabolic syndrome				
Fasting glucose (mmol/L)	4.7 (4.4-4.9)	5.3 (4.9-5.8)*	4.7 (4,5-4.9) †	**<0.01**
Fasting insulin (mU/L)	6.7 (5.1-8.9)	10.3 (7.5-13.5)*	9.0 (6.2-14.6)*	**<0.01**
$HOMA_{IR}$	1.3 (1.1-1.9)	2.5 (1.9-3.4)*	1.9 (1.2-3.0)*	**<0.01**
Triglycerides (mmol/L)	0.8 (0.7-1.1)	1.2 (0.9-1.4)*	0.8 (0.7-1.3) †	**<0.05**
HDL (mmol/L)	1.3 (1.1-1.5)	1.3 (1.1-1.4)	1.3 (1.1-1.5)	0.85
Albumin/creatinine ratio (g/mol)	0.4 (0.1-1.1)	0.8 (0.4-5.1)	0.7 (0.4-1.1)	0.18
Pre-hypertension	4/34 (12)	4/16 (25)	6/17 (35)	0.11
Hypertension untreated	0/34 (0)	3/16 (19)*	0/17 (0)	**<0.05**
Antihypertensive treatment	0/34 (0)	7/16 (44)*	5/17 (29)*	**<0.01**

Data are given as median (interquartile range) or *n*/N (%).
*$P < 0.05$ vs no HF. †$P < 0.05$ vs HF-A.
DBP, diastolic blood pressure; E/A ratio, ratio of early (E) to late (A) ventricular filling velocity; FMD, flow-mediated dilation; HDL, high-density lipoprotein; $HOMA_{IR}$, homeostatic model assessment for insulin resistance; LV, left ventricular; MAP, mean arterial pressure; SBP, systolic blood pressure.

The baseline diameter of the brachial artery was comparable between the three subgroups. Moreover, FMD (%), FMD peak diameter and shear rate did not differ between the subgroups. Of the metabolic syndrome variables, fasting glucose, fasting insulin, HOMA and triglycerides were significantly higher in the HF-A subgroup compared with the no-HF subgroup. Moreover, more women in the HF-A subgroup had untreated hypertension and were using antihypertensive medication compared with the no-HF subgroup. Fasting insulin and HOMA were higher in the HF-B compared with the no-HF subgroup. Furthermore, more women in the HF-B subgroup were using antihypertensive medication compared with the no-HF subgroup.

DISCUSSION

To the best of our knowledge, this is the first demonstration of the assumed association between endothelial dysfunction, measured by FMD, and prevalence of HF-B after pre-eclampsia. First, we showed that formerly pre-eclamptic women have lower endothelium-dependent FMD compared with women with a history of only normotensive gestation, indicating attenuated endothelial function in the formerly pre-eclamptic group. Moreover, compared with controls, formerly pre-eclamptic women had an eight-fold higher prevalence of cardiovascular risk factor (HF-A) and three-fold higher prevalence of HF-B. Nonetheless, we did not observe any association between endothelial dysfunction and the prevalence of HF-A or HF-B in formerly pre-eclamptic women.

PE is associated with endothelial dysfunction that may persist during the first years after PE[7,9,10,12,19–28.] In this study, we found that at least 4 years postpartum, endothelial function, as indicated by FMD, was significantly lower in formerly pre-eclamptic women than in healthy controls, which is in line with earlier findings[19–28] and in contrast with other studies with a follow-up period of at least 10 years[20]. We also found that PE was associated independently with reduced FMD after correction for metabolic risk factors, as was insulin.

Vessel dilation is mediated by endothelium-dependent release of nitric oxide (NO) in response to reactive hyperemia and increased endothelial shear stress occurring after deflation of a perfusion-obstructive cuff[19,34,36]. As such, healthy endothelium has an important vasoactive function in stabilizing blood pressure intrinsically in response to alterations in flow, by the production of rapidly released short-acting NO, which instantly lowers underlying vessel muscle tone[34,45]. On the one hand, shallow FMD may therefore reflect impaired endothelial function. On the other hand, in general, the observed decreased endothelial function after PE can also originate from impaired bioavailability of NO, restricted vasodilatory capacity due to mechanical changes stiffening the arterial wall or diminished signaling in smooth-muscle cells[46]. A few postpartum studies have

showed reduced FMD originating from NO-dependent mechanisms, suggesting a less prominent effect of vascular stiffening in hampering FMD[21,26–28]. However, one study observed that formerly pre-eclamptic women had reduced endothelium-dependent and NO-mediated FMD, as compared with controls[23]. Moreover, endothelial function could be normalized by aerobic exercise[28]. Even though we did not perform FMD with NO donor administration, given the young age of the cohort, endothelial dysfunction is most likely the cause of reduced FMD in the formerly pre-eclamptic group[21].

Impaired FMD is considered a strong predictor for cardiovascular events, independent of other traditional risk factors, and may be an important mediator between PE and the two- to seven-fold increased risk of remote CVD at a relatively young age[4,47–49]. A meta-analysis by Inaba *et al.* showed that a 1% decrease in FMD is related to an 8% increased risk of CVD events in population-based convenience cohort studies[49]. Moreover, several studies showed impaired FMD in symptomatic stages of HF (i.e. HF-C or -D)[50]. Therefore, we expected to find a positive relationship between impaired FMD after PE and HF-B. In our cohort, we did not find such a relationship; although not expected, this is in line with the findings of a study by Muiesan *et al.*, in which FMD was studied in relation to different LV geometric patterns in hypertensive patients[51]. They observed that the presence of endothelial dysfunction was not associated with differences in LV geometric patterns, suggesting that independent and different mechanisms may account for the presence of LV hypertrophy and endothelial dysfunction[51]. Moreover, the use of antihypertensive medication in the HF-B subgroup may also have attenuated the differences in endothelial function between the HF-B subgroup and the HF-A and no-HF subgroups. Antihypertensive treatment may reverse cardiac remodeling, enhance cardiac function and improve endothelial function, by reducing afterload or shear stress, or by their antioxidant activity[52,53]. The role of changes in morphological, mechanical and functional properties of peripheral conduit arteries in relation to HF still needs to be elucidated.

This study has several limitations that should be taken into account. First, most of the formerly pre-eclamptic women were of European ethnic origin. Therefore, our results might not be fully generalizable to women of other ethnic origins. Second, HF is a cluster of different entities that are likely to have different physiological backgrounds that might have influenced our findings. However, we used the currently used definition of the AHA in the hope that this gives an accurate reflection of HF-B. Dividing the HF-B group into subgroups would have resulted in very low sample sizes with insufficient power. Subdividing the formerly pre-eclamptic women into three subgroups and therefore reducing the number of women per group increased the type 1 error risk. In anticipation of this, we analyzed our data non-parametrically. Despite smaller numbers, we did detect clinically relevant significant differences, which also shed light on the pathophysiological course of cardiac adjustments in women at risk for CVD. Therefore, it would be useful in future

studies to include more women. Third, both groups had different recruitment procedures as healthy women do not routinely visit a gynecologist in the Netherlands. Therefore, we had to recruit controls by advertisement. It could be that women who replied had subtle signs of CVD that led them to question their risk. However, they may also have been concerned about their health, which could suggest that they have a healthy lifestyle. Moreover, controls had a longer postpartum interval, which might also induce certain bias as postpartum recovery can take, in certain cases, a few months to complete. However, it is not known at what interval it is optimal to perform cardiovascular screening. In this study, short-term pregnancy effects were excluded.

In conclusion, we showed lower FMD in formerly pre-eclamptic women 5–8 years postpartum as compared with women with a history of healthy pregnancy. Formerly pre-eclamptic women had an eight-fold higher prevalence of HF-A and a three-fold higher prevalence of HF-B compared with controls. However, no difference in FMD was found between formerly PE patients with HF-B and those without, suggesting different mechanisms underlying the subclinical stages of HF.

REFERENCES

1. Go AS, Mozaffarian D, Roger VL, Benjamin EJ, Berry JD, Blaha MJ, Dai S, Ford ES, Fox CS, Franco S, Fullerton HJ, Gillespie C, Hailpern SM, Heit JA, Howard VJ, Huffman MD, Judd SE, Kissela BM, Kittner SJ, Lackland DT, Lichtman JH, Lisabeth LD, Mackey RH, Magid DJ, Marcus GM, Marelli A, Matchar DB, McGuire DK, Mohler ER 3rd, Moy CS, Mussolino ME, Neumar RW, Nichol G, Pandey DK, Paynter NP, Reeves MJ, Sorlie PD, Stein J, Towfighi A, Turan TN, Virani SS, Wong ND, Woo D, Turner MB; American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Heart disease and stroke statistics—2014 update: A report from the american heart association. *Circulation* 2014; 129: e28–e292.
2. Mosca L, Barrett-Connor E, Wenger NK. Sex/gender differences in cardiovascular disease prevention: What a difference a decade makes. *Circulation* 2011; 124: 2145–2154.
3. Mosca L, Benjamin EJ, Berra K, Bezanson JL, Dolor RJ, Lloyd-Jones DM, Newby LK, Pina IL, Roger VL, Shaw LJ, Zhao D, Beckie TM, Bushnell C, D'Armiento J, Kris-Etherton PM, Fang J, Ganiats TG, Gomes AS, Gracia CR, Haan CK, Jackson EA, Judelson DR, Kelepouris E, Lavie CJ, Moore A, Nussmeier NA, Ofili E, Oparil S, Ouyang P, Pinn VW, Sherif K, Smith SC Jr, Sopko G, Chandra Strobos N, Urbina EM, Vaccarino V, Wenger NK. Effectiveness-based guidelines for the prevention of cardiovascular disease in women—2011 update: A guideline from the American Heart Association. *Circulation* 2011; 123: 1243–1262.
4. Bellamy L, Casas JP, Hingorani AD, Williams DJ. Pre-eclampsia and risk of cardiovascular disease and cancer in later life: Systematic review and meta-analysis. *BMJ* 2007; 335: 974.
5. ACOG Committee on Practice Bulletins—Obstetrics. ACOG Practice Bulletin. Diagnosis and management of preeclampsia and eclampsia. Number 33, January 2002. *Obstet Gynecol* 2002; 99: 159 167.
6. Zhang J, Meikle S, Trumble A. Severe maternal morbidity associated with hypertensive disorders in pregnancy in the united states. *Hypertens Pregnancy* 2003; 22: 203–212.
7. Roberts JM, Gammill HS. Preeclampsia: Recent insights. *Hypertension* 2005; 46: 1243–1249.
8. Roberts JM, Cooper DW. Pathogenesis and genetics of pre-eclampsia. *Lancet* 2001; 357: 53–56.
9. Powe CE, Levine RJ, Karumanchi SA. Preeclampsia, a disease of the maternal endothelium: The role of antiangiogenic factors and implications for later cardiovascular disease. *Circulation* 2011; 123: 2856 2869.
10. Brennan LJ, Morton JS, Davidge ST. Vascular dysfunction in preeclampsia. *Microcirculation* 2014; 21: 4–14.
11. Scholten RR, Hopman MT, Sweep FC, Van de Vlugt MJ, Van Dijk AP, Oyen WJ, Lotgering FK, Spaanderman ME. Co-occurrence of cardiovascular and prothrombotic risk factors in women with a history of preeclampsia. *Obstet Gynecol* 2013; 121: 97–105.
12. Roberts JM. Endothelial dysfunction in preeclampsia. *Semin Reprod Endocrinol* 1998; 16: 5–15
13. Melchiore K, Sutherland GR, Liberati M, Thilaganathan B. Preeclampsia is associated with persistent postpartum cardiovascular impairment. *Hypertension* 2011; 58: 709–715.
14. Ghossein-Doha C, van Neer J, Wissink B, Breetveld N, de Windt LJ, van Dijk AP, van der Vlugt MJ, Janssen MC, Heidema WM, Scholten RR, Spaanderman ME. Preeclampsia, an important female specific risk factor for asymptomatic heart failure. *Ultrasound Obstet Gynecol* 2017; 49: 143–149.
15. Ammar KA, Jacobsen SJ, Mahoney DW, Kors JA, Redfield MM, Burnett JC Jr, Rodeheffer RJ. Prevalence and prognostic significance of heart failure stages: Application of the American College Of Cardiology/American Heart Association heart failure staging criteria in the community. *Circulation* 2007; 115: 1563–1570.
16. Jessup M, Abraham WT, Casey DE, Feldman AM, Francis GS, Ganiats TG, Konstam MA, Mancini DM, Rahko PS, Silver MA, Stevenson LW, Yancy CW. 2009 focused update: ACCF/AHA guidelines for the diagnosis and management of heart failure in adults: A report of the American College of Cardiology

Foundation/American Heart Association Task Force on Practice Guidelines: Developed in collaboration with the International Society for Heart and Lung Transplantation. *Circulation* 2009; 119: 1977–2016.
17. Marti CN, Gheorghiade M, Kalogeropoulos AP, Georgiopoulou VV, Quyyumi AA, Butler J. Endothelial dysfunction, arterial stiffness, and heart failure. *J Am Coll Cardiol* 2012; 60: 1455–1469.
18. Brunner H, Cockcroft JR, Deanfield J, Donald A, Ferrannini E, Halcox J, Kiowski W, Luscher TF, Mancia G, Natali A, Oliver JJ, Pessina AC, Rizzoni D, Rossi GP, Salvetti A, Spieker LE, Taddei S, Webb DJ. Endothelial function and dysfunction. Part II: Association with cardiovascular risk factors and diseases. A statement by the Working Group on Endothelins and Endothelial Factors of The European Society of Hypertension. *J Hypertens* 2005; 23: 233–246.
19. Weissgerber TL. Flow-mediated dilation: Can new approaches provide greater mechanistic insight into vascular dysfunction in preeclampsia and other diseases? *Curr Hypertens Rep* 2014; 16: 487.
20. Weissgerber TL, Milic NM, Milin-Lazovic JS, Garovic VD. Impaired flow-mediated dilation before, during, and after preeclampsia: A systematic review and meta-analysis. *Hypertension* 2016; 67: 415 423.
21. Chambers JC, Fusi L, Malik IS, Haskard DO, De Swiet M, Kooner JS. Association of maternal endothelial dysfunction with preeclampsia. *JAMA* 2001; 285: 1607–1612.
22. Tyldum EV, Backe B, Stoylen A, Slordahl SA. Maternal left ventricular and endothelial functions in preeclampsia. *Acta Obstet Gynecol Scand* 2012; 91: 566–573.
23. Hamad RR, Eriksson MJ, Silveira A, Hamsten A, Bremme K. Decreased flow-mediated dilation is present 1 year after a pre-eclamptic pregnancy. *J Hypertens* 2007; 25: 2301–2307.
24. Hamad RR, Eriksson MJ, Berg E, Larsson A, Bremme K. Impaired endothelial function and elevated levels of pentraxin 3 in early-onset preeclampsia. *Acta Obstet Gynecol Scand* 2012; 91: 50–56.
25. Goynumer G, Yucel N, Adali E, Tan T, Baskent E, Karadag C. Vascular risk in women with a history of severe preeclampsia. *J Clin Ultrasound* 2013; 41: 145–150.
26. Germain AM, Romanik MC, Guerra I, Solari S, Reyes MS, Johnson RJ, Price K, Karumanchi SA, Valdes G. Endothelial dysfunction: A link among preeclampsia, recurrent pregnancy loss, and future cardiovascular events? *Hypertension* 2007; 49: 90–95.
27. Paez O, Alfie J, Gorosito M, Puleio P, de Maria M, Prieto N, Majul C. Parallel decrease in arterial distensibility and in endothelium-dependent dilatation in young women with a history of pre-eclampsia. *Clin Exp Hypertens* 2009; 31: 544–552.
28. Scholten RR, Thijssen DJ, Lotgering FK, Hopman MT, Spaanderman ME. Cardiovascular effects of aerobic exercise training in formerly preeclamptic women and healthy parous control subjects. *Am J Obstet Gynecol* 2014; 211: 516.e1–516.e11.
29. Brown MA, Lindheimer MD, de Swiet M, Van Assche A, Moutquin JM. The classification and diagnosis of the hypertensive disorders of pregnancy: Statement from the International Society for the Study of Hypertension in Pregnancy (ISSHP). *Hypertens Pregnancy* 2001; 20: IX–XIV.
30. Adkisson EJ, Casey DP, Beck DT, Gurovich AN, Martin JS, Braith RW. Central, peripheral and resistance arterial reactivity: Fluctuates during the phases of the menstrual cycle. *Exp Biol Med* 2010; 235: 111–118.
31. Williams MR, Westerman RA, Kingwell BA, Paige J, Blombery PA, Sudhir K, Komesaroff PA. Variations in endothelial function and arterial compliance during the menstrual cycle. *J Clin Endocrinol Metab* 2001; 86: 5389–5395.
32. Scholten RR, Spaanderman ME, Green DJ, Hopman MT, Thijssen DH. Retrograde shear rate in formerly preeclamptic and healthy women before and after exercise training: Relationship with endothelial function. *Am J Physiol Heart Circ Physiol* 2014; 307: H418–H425.
33. Bonora E, Targher G, Alberiche M, Bonadonna RC, Saggiani F, Zenere MB, Monauni T, Muggeo M. Homeostasis model assessment closely mirrors the glucose clamp technique in the assessment of insulin

sensitivity: Studies in subjects with various degrees of glucose tolerance and insulin sensitivity. *Diabetes Care* 2000; 23: 57–63.

34. Deanfield JE, Halcox JP, Rabelink TJ. Endothelial function and dysfunction: Testing and clinical relevance. *Circulation* 2007; 115: 1285–1295.
35. Donald AE, Charakida M, Cole TJ, Friberg P, Chowienczyk PJ, Millasseau SC, Deanfield JE, Halcox JP. Non-invasive assessment of endothelial function: Which technique? *J Am Coll Cardiol* 2006; 48: 1846–1850.
36. Green DJ, Dawson EA, Groenewoud HM, Jones H, Thijssen DH. Is flow-mediated dilation nitric oxide mediated?: A meta-analysis. *Hypertension* 2014; 63: 376–382.
37. Thijssen DH, Black MA, Pyke KE, Padilla J, Atkinson G, Harris RA, Parker B, Widlansky ME, Tschakovsky ME, Green DJ. Assessment of flow-mediated dilation in humans: A methodological and physiological guideline. *Am J Physiol Heart Circ Physiol* 2011; 300: H2–H12.
38. Parker BA, Trehearn TL, Meendering JR. Pick your poiseuille: Normalizing the shear stimulus in studies of flow-mediated dilation. *J Appl Physiol* (1985) 2009; 107: 1357–1359.
39. Woodman RJ, Playford DA, Watts GF, Cheetham C, Reed C, Taylor RR, Puddey IB, Beilin LJ, Burke V, Mori TA, Green D. Improved analysis of brachial artery ultrasound using a novel edge detection software system. *J Appl Physiol* (1985) 2001; 91: 929–937.
40. Black MA, Cable NT, Thijssen DH, Green DJ. Importance of measuring the time course of flow mediated dilatation in humans. *Hypertension* 2008; 51: 203–210.
41. Sahn DJ, DeMaria A, Kisslo J, Weyman A. Recommendations regarding quantitation in M-mode echocardiography: Results of a survey of echocardiographic measurements. *Circulation* 1978; 58: 1072 1083.
42. Lang RM, Bierig M, Devereux RB, Flachskampf FA, Foster E, Pellikka PA, Picard MH, Roman MJ, Seward J, Shanewise JS, Solomon SD, Spencer KT, Sutton MS, Stewart WJ; Chamber Quantification Writing Group; American Society of Echocardiography's Guidelines and Standards Committee; European Association of Echocardiography. Recommendations for chamber quantification: a report from the American Society of Echocardiography's Guidelines and Standards Committee and the Chamber Quantification Writing Group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology. *J Am Soc Echocardiogr* 2005; 18: 1440–1463.
43. Teichholz LE, Kreulen T, Herman MV, Gorlin R. Problems in echocardiographic volume determinations: Echocardiographic-angiographic correlations in the presence of absence of asynergy. *Am J Cardiol* 1976; 37: 7–11.
44. Alberti KG, Zimmet PZ. Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: Diagnosis and classification of diabetes mellitus provisional report of a WHO consultation. *Diabet Med* 1998; 15: 539–553.
45. Corson MA, James NL, Latta SE, Nerem RM, Berk BC, Harrison DG. Phosphorylation of endothelial nitric oxide synthase in response to fluid shear stress. *Circ Res* 1996; 79: 984–991.
46. Lampinen KH, Ronnback M, Kaaja RJ, Groop PH. Impaired vascular dilatation in women with a history of pre-eclampsia. *J Hypertens* 2006; 24: 751–756.
47. Hirsch L, Shechter A, Feinberg MS, Koren-Morag N, Shechter M. The impact of early compared to late morning hours on brachial endothelial function and long-term cardiovascular events in healthy subjects with no apparent coronary heart disease. *Int J Cardiol* 2011; 151: 342–347.
48. Shechter M, Shechter A, Koren-Morag N, Feinberg MS, Hiersch L. Usefulness of brachial artery flow-mediated dilation to predict long-term cardiovascular events in subjects without heart disease. *Am J Cardio*l 2014; 113: 162–167.
49. Inaba Y, Chen JA, Bergmann SR. Prediction of future cardiovascular outcomes by flow-mediated vasodilatation of brachial artery: A meta-analysis. *Int J Cardiovasc Imaging* 2010; 26: 631–640.

50. Marechaux S, Samson R, van Belle E, Breyne J, de Monte J, Dedrie C, Chebai N, Menet A, Banfi C, Bouabdallaoui N, Le Jemtel TH, Ennezat PV. Vascular and microvascular endothelial function in heart failure with preserved ejection fraction. *J Card Fail* 2016; 22: 3–11.
51. Muiesan ML, Salvetti M, Monteduro C, Corbellini C, Guelfi D, Rizzoni D, Castellano M, Agabiti Rosei E. Flow-mediated dilatation of the brachial artery and left ventricular geometry in hypertensive patients. *J Hypertens* 2001; 19: 641–647.
52. Goldberg LR, Jessup M. Stage B heart failure: Management of asymptomatic left ventricular systolic dysfunction. *Circulation* 2006; 113: 2851–2860.
53. Virdis A, Ghiadoni L, Taddei S. Effects of antihypertensive treatment on endothelial function. *Curr Hypertens Rep* 2011; 13: 276–281.

Supplemental information

Supplemental Table 1. Baseline characteristics of women with history of pre-eclampsia (PE) subdivided in women who did not became pregnant again after the index pregnancy (no subsequent pregnancy) and women who did become pregnant after the index pregnancy (subsequent pregnancy).

	No subsequent pregnancy (*n* = 27)	Subsequent pregnancy (*n* = 40)	*P*
Patient			
Age (years)	36 (32-40)	36 (34-39)	0.91
Height (m)	1.69 (1.65-1.73)	1.68 (1.65-1.74)	0.83
Weight (kg)	73 (63-88)	69 (61-81)	0.41
BMI (kg/m^2)	25 (22-29)	24 (21-28)	0.31
Obesity (BMI ≥ 30 kg/m^2)	6/27 (22)	6/40 (15)	0.52
Smoker	4/27 (15)	1/40 (3)	0.15
Alcohol use	5/27 (19)	10/40 (25)	0.53
Family history of CVD	10/27 (37)	20/40 (50)	0.30
Antihypertensive treatment	3/27 (11)	9/40 (23)	0.34
Postpartum interval (years)	4.6 (4.3-5.8)	5.4 (4.6-7.2)	**<0.05**
Index pregnancy			
Early-onset PE	19/27 (70)	21/37 (57)	0.27
Preterm PE	24/27 (89)	27/40 (68)	**<0.05**
Primiparous	20/27 (74)	29/40 (73)	0.89
GA at birth (weeks)	33 (30-35)	35 (31-37)	0.22
Birth weight (g)	1511 (955-2075)	1730 (1066-2800)	0.20
SGA neonate	13/27 (48)	17/40 (43)	0.65
IUFD	0/27 (0)	6/39 (15)	0.07

Data are given as median (interquartile range) or *n*/N (%).
BMI, body mass index; CVD, cardiovascular disease; GA, gestational age; IUFD, intrauterine fetal death; NA, not applicable; SGA, small-for-gestational age.

Supplemental Table 2. Cardiovascular and metabolic syndrome variables in former pre-eclamptic women (PE) subdivided in women who did not became pregnant again after the index pregnancy (no subsequent pregnancy) and women who did become pregnant after the index pregnancy (subsequent pregnancy).

	No subsequent pregnancy (*n* = 27)	Subsequent pregnancy (*n* = 40)	P
Heart failure Stage A	5/27 (19)	11/40 (28)	0.40
Hypertension	4/27 (15)	6/40 (15)	1.00
Atherosclerotic disease	0/26 (0)	1/38 (3)	1.00
Diabetes mellitus	1/27 (4)	2/40 (5)	1.00
Obesity (BMI ≥ 30 kg/m^2)	3/27 (11)	5/40 (13)	1.00
Metabolic syndrome	2/27 (7)	3/40 (8)	1.00
Heart Failure Stage B	7/27 (26)	10/40 (25)	0.93
Myocardial infarction	0/27 (0)	0/40 (0)	NA
LV hypertrophy	1/27 (4)	0/40 (0)	0.40
Concentric remodeling	4/27 (15)	7/40 (18)	1.00
Mildly impaired LVEF	2/27 (7)	3/40 (8)	1.00
Asymptomatic valve disease	0/27 (0)	1/40 (3)	1.00
HFpEF	5/27 (19)	7/40 (18)	1.00
Cardiac function			
SBP (mmHg)	116 (110-127)	116 (109-123)	0.52
DBP (mmHg)	73 (70-80)	72 (66-76)	0.19
MAP (mmHg)	85 (82-91)	85 (78-91)	0.42
Heart rate (bpm)	66 (63-80)	65 (60-78)	0.31
Stroke volume (mL)	79 (70-88)	77 (70-86)	0.78
Cardiac output (L/min)	5.3 (4.4-6.2)	4.9 (4.3-5.9)	0.58
LV end diastolic volume (mL)	94 (82-102)	91 (76-121)	0.62
LVEF (%)	61 (59-66)	64 (60-68)	0.12
E/A ratio	1.59 (1.43-1.93)	1.56 (1.29-1.89)	0.48
LV mass index (g/m^2)	61 (50-70)	55 (47-64)	0.28
Relative wall thickness	0.34 (0.31-0.39)	0.35 (0.30-0.41)	0.92
FMD			
Baseline diameter (cm)	0.30 (0.28-0.31)	0.29 (0.27-0.32)	0.72
Peak diameter (cm)	0.31 (0.29-0.34)	0.31 (0.29-0.35)	0.85
FMD (%)	6.12 (4.76-7.11)	6.18 (5.07-9.01)	0.40
Shearrate (s^{-1})	22890 (17936-29002)	22665 (15998-36248)	0.64

Supplemental Table 2. Cardiovascular and metabolic syndrome variables in former pre-eclamptic women (PE) subdivided in women who did not became pregnant again after the index pregnancy (no subsequent pregnancy) and women who did become pregnant after the index pregnancy (subsequent pregnancy). (*continued*)

	No subsequent pregnancy (*n* = 27)	Subsequent pregnancy (*n* = 40)	P
Metabolic syndrome			
Fasting glucose (mmol/L)	4.8 (4.5-5.0)	4.8 (4.5-5.2)	0.56
Fasting insulin (mU/L)	8.0 (6.1-14.6)	7.8 (5.3-10.0)	0.26
$HOMA_{IR}$	1.6 (1.2-3.1)	1.8 (1.2-2.4)	0.39
Triglycerides (mmol/L)	0.9 (0.7-1.2)	0.9 (0.7-1.3)	0.90
HDL (mmol/L)	1.3 (1.1-1.4)	1.3 (1.1-1.5)	0.42
Albumin/creatinine ratio (g/mol)	0.4 (0.1-1.1)	0.7 (0.4-1.6)	0.14
Pre-hypertension	7/27 (26)	7/40 (18)	0.41
Hypertension untreated	1/27 (4)	2/40 (5)	1.00
Antihypertensive treatment	3/27 (11)	9/40 (23)	0.34

Data are given as median (interquartile range) or *n*/N (%).

BMI, body mass index; DBP, diastolic blood pressure; EA ratio, ratio of early (E) to late (A) ventricular filling velocity; FMD, flow-mediated dilation; HDL, high-density lipoprotein; $HOMA_{IR}$, homeostatic model assessment for insulin resistance; HFpEF, heart failure with preserved ejection fraction; LV, left ventricular; LVEF, left ventricular ejection fraction; MAP, mean arterial pressure; NA, not applicable; SBP, systolic blood pressure.

Low plasma volume and increased pressure load relate to concentric left ventricular remodeling after preeclampsia; a longitudinal study

N.M. Breetveld[1], R.J. Alers[1], L. Geerts[1], S.M.J. van Kuijk[2], A.P. van Dijk[3], M.J. van der Vlugt[3], W.M. Heidema[4], J. van Neer[1], V.P.M. van Empel[5], H.P. Brunner-La Rocca[5], R.R. Scholten[4], C. Ghossein-Doha[1], M.E.A. Spaanderman[1]

[1] Department of Obstetrics and Gynaecology, Research School GROW, Maastricht University Medical Centre (MUMC+), Maastricht, The Netherlands

[2] Department of Clinical Epidemiology and Medical Technology Assessment (KEMTA), Maastricht University Medical Centre (MUMC+), Maastricht, The Netherlands

[3] Department of Cardiology, Radboud University Medical Centre (Radboudumc), Nijmegen, The Netherlands

[4] Department of Obstetrics and Gynecology, Radboud University Medical Centre (Radboudumc), Nijmegen, The Netherlands

[5] Department of Cardiology, Maastricht University Medical Centre (MUMC+), Maastricht, The Netherlands

Accepted for publication in JAHA, journal of the American Heart Association.

ABSTRACT

Background

During uncomplicated pregnancy, left ventricular remodeling occurs in an eccentric way. In contrast, during pre-eclamptic gestation, the left ventricle hypertrophies concentrically, concurrent with loss in circulatory volume and increased blood pressure. Concentric cardiac structure persists in a substantial proportion of women and may be associated with pressure and volume load after pre-eclampsia. We hypothesize that low volume load as indicated by plasma volume (PV) after pre-eclampsia and increased pressure load is associated with remote concentric remodeling.

Method and Results

In this longitudinal cohort study, we included 100 formerly pre-eclamptic women. Two visits were performed; at 0.8 years postpartum and the second visit 4.8 years postpartum. During visit one we measured blood pressure and PV (I^{125} dilution technique, low PV ≤ 48 mL/kg lean body mass (LBM)). During the second visit we assessed cardiac geometry by cardiac ultrasound. Concentric remodeling was defined as relative wall thickness (RWT) > 0.42 and left ventricular mass index (LVMi) ≤ 95 g/m^2. We adjusted multivariable analysis for primiparity, systolic blood pressure, PV mL/kg LBM and antihypertensive medication at visit one.

Low PV is associated with remote concentric remodeling (odds ratio (OR): 4.37, 95% CI 1.06-17.40 and adjusted OR 4.67, CI 95% 1.02-21.42. Arterial pressure load (systolic, diastolic and mean arterial pressure) is also associated with development of concentric remodeling (OR 1.15, 95% CI 0.99-1.35 OR 1.24 , 95% CI 0.98-1.58 and OR 1.20, 95% CI 0.98-1.47 respectively).

Conclusions

In former pre-eclamptic women, development towards left ventricular concentric remodeling is associated with low volume load and increased pressure load.

Key words

Plasma volume, concentric remodeling, pre-eclampsia, echocardiography, blood pressure.

INTRODUCTION

Pre-eclampsia (PE), a gestational hypertensive disease, is characterized by new-onset hypertension and proteinuria, and complicates 3-5% of all pregnancies[1]. PE is associated with a 2-7 fold increased risk for cardiovascular disease (CVD) within 15 years after pregnancy and has been recognized as an important women-specific CVD risk factor[2, 3].

PE and CVD share many classical risk factors as hypertension, hyperinsulinemia, obesity and dyslipidemia[4-6]. The elevated risk for CVD after PE may in part relate to abnormal cardiovascular (CV) risk profiles in these women, but may also partly be contributed to differences in patterns of cardiac remodeling during pregnancy and incomplete cardiac recovery afterwards[7-10]. During normotensive pregnancies, the left ventricle (LV) remodels in an eccentric way, while during PE the LV remodels in an aberrant concentric way, which remains present in 11-26% of affected women in the first decade after delivery[11-13]. Eccentric cardiac remodeling during normal pregnancy is viewed upon as a physiologically reversible phenomenon as a response to decreased gestational pressure load along with concomitant increased volume load[12, 14, 15]. Concentric remodeling during pre-eclamptic gestation may be the result of increased pressure load along with lower volume load[16].

In hypertensive individuals concentric remodeling, amongst other forms of remodeling, was significantly associated with more CVD and death[17, 18]. Interestingly, compared to eccentric remodeling, concentric remodeling is associated with cardiac fibrosis and this stiffened cardiac concentric condition is associated with a fourfold risk of subsequent cardiovascular events[17, 19]. Concentric remodeling is thought to be an important step in the progression from asymptomatic heart disease to symptomatic heart failure, often in response to chronic pressure overload[16].

After pre-eclamptic pregnancy, many women continue to have persistently higher blood pressure and decreased plasma volume (PV) compared to healthy parous women[7-9, 20, 21]. It is not known to what extent both pressure load and volume load shortly after delivery is associated with persistent or de-novo concentric remodeling in the following decade. Cardiac remodeling is a dynamic and progressive process, susceptible to pressure and volume modulating medication[22-26]. Better insight in the system biology of concentric remodeling is of clinical value to predict the possible effect of modulating pressure and volume load including angiotensin converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARB) on reversibility of concentric remodeling in these women in order to decrease their CV risk[24-26]. This is of importance because the LV continues to remodel when the stressor persists[27]. Therefore, we performed in former pre-eclamptic women, a longitudinal study to evaluate whether pressure and/or volume load, assessed shortly after delivery, is associated with concentric remodeling in the following decade. We hypothesize that low PV after pre-eclampsia and increased pressure load is associated with concentric remodeling in the subsequent years.

METHODS

The Medical Ethics committee of the Radboud University Medical Center (NL32718.091.10) approved the protocol of this explorative longitudinal cohort study. Before participation, all subjects provided written informed consent. The followed procedures were in conformity with institutional guidelines and adhered to the principles of the Declaration of Helsinki and Title 45, U.S. Code of Federal Regulation, Part 46, Protection of Human Subjects, Revised November 13, 2001, effective December 13, 2001. We invited women who previously had a clinical cardiovascular risk assessment following a pregnancy complicated by PE for a second follow-up screening between 2009 and 2011.

Study population

Formerly pre-eclamptic women were recruited at their routine 6 weeks postpartum medical appointment and were asked to participate in the first cardiovascular screening assessment, at a median interval of 0.8 years postpartum. They underwent blood pressure measurements and PV measurements. A second visit was planned at 4.8 years postpartum. During this second cardiovascular evaluation, we performed blood pressure measurements and cardiac ultrasound (Figure 1). Inclusion criteria were women with a history of pre-eclampsia, not pregnant, not breastfeeding and not using oral contraceptives. Women who had become pregnant again after their index pregnancy had to be at least 6 months postpartum for their second measurement. Exclusion criteria were pre-existing comorbidity (diabetes mellitus, autoimmune diseases or pre-existing hypertension) prior to their index pregnancy. Other exclusion criteria were an unsuccessful PV measurement at visit 1 and/or inadequate cardiac ultrasound at visit 2. All subjects were recruited from the eastern region of the Netherlands, a region with an average socioeconomic status. PE was diagnosed according to the International Society of Hypertension in Pregnancy criteria as: new-onset hypertension (systolic blood pressure (SBP) ≥ 140 mmHg and/or diastolic blood pressure (DBP) ≥ 90 mmHg) after 20 weeks of gestation and proteinuria > 0.3g/day[28]. Early-onset PE was defined as PE developing < 34 weeks of gestation. Preterm PE was defined as PE requiring delivery before 37 weeks gestation. Small-for-gestational age was defined as a birth weight below or equal to the 10^{th} percentile based on the Dutch reference curves[29]. Four women gave birth to twins. All birth weights were analyzed in our analysis.

First visit: cardiovascular assessment

The first visit consisted of the standard cardiovascular assessment, which is embedded in standard clinical care. The examinations started at 08:00 a.m. in a temperature controlled room (22°C) after an overnight fast. Body weight (kg, Seca 888, Hamburg, Germany) and height (m) were measured to calculate body mass index (BMI). BMI ≥ 30 kg/m^2 was defined as obesity. After at least 15 minutes of acclimatization, SBP, DBP and mean

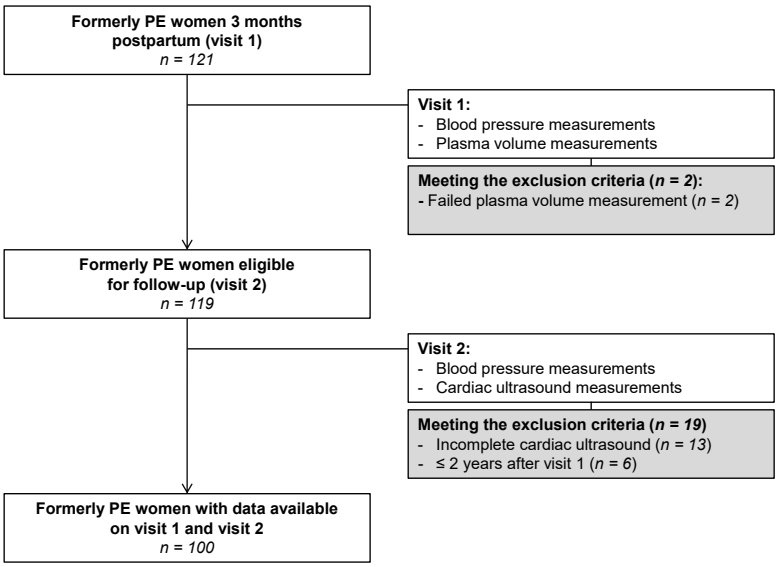


Figure 1. Flowchart of included formerly pre-eclamptic (PE) women in our explorative longitudinal cohort study.

arterial pressure (MAP) were measured for 30 minutes (at a three minute interval) in upright sitting position, using a semi-automatic oscillometric device (Dinamap Vital Signs Monitor 1846; Critikon, Tampa, Florida (USA)). The cuff-size was appropriate for arm circumference. We used the median values for statistical analysis. During the 30 minutes blood pressure measurement, participants were not allowed to talk and external disturbances were minimalized. Hypertension was defined as SBP ≥ 140 mmHg and/or DBP ≥ 90 mmHg and/or the use of antihypertensive medication. Prehypertension was defined as SBP ranging from 120 - 139 mm Hg and/or DBP ranging from 80 - 89 mm Hg. Participants were asked to complete a questionnaire at both visits consisting of general history, current medication intake, intoxications (smoking is defined as ≥ 1 cigarette a day), lifestyle factors and family history for CVD (in first line relatives < 60 years).

During the first visit, PV was measured using the iodine^{125} albumin indicator dilution technique (iodine^{125} human serum albumin (^{125}I-HSA)) as described elsewhere and indexed for body mass (lean body mass (LBM)) [30-32]. LBM was calculated using the formula:

$$\text{LBM} = \text{Body mass} - ((1.20 \times \text{BMI}) + (0.23 \times \text{age}) - 5.4) \times \text{body mass} / 100^{32, 33}.$$

Body mass index (kg/m^2) is calculated as weight (kg) divided by height in meters^2. Normal PV was defined as a PV index > 48 mL/kg LBM and we consider a low PV as a PV index ≤ 48 mL/kg LBM[21, 34].

Second visit: follow-up cardiovascular assessment

At the second visit, we performed the same protocol to determine blood pressure and performed cardiac ultrasound to determine cardiac structure and function. Echocardiographic measurements were obtained using a phased array echocardiographic Doppler ultrasound system (ViVid 7, GE Vingmed Ultrasound, Horten, Norway). The assessments were performed offline using EchoPAC PC SW Vingmed Ultrasound, Version 6.1.2. We performed two-dimensional, M-mode and Doppler echocardiography according to the guidelines of the American Society of Echocardiography (ASE)[35]. Using M-mode in the parasternal long-axis view, we measured left ventricular end-diastolic and end-systolic diameters (LVEDd and LVESd, respectively in mm), as well as end-diastolic thickness of the interventricular septum (IVST, in mm) and of the posterior wall (PWT, in mm). Left ventricular mass (LVM) (in g) was calculated using the formula = $0.8 \times (1.04 ((LVEDd + PWT + IVST)^3 – (LVEDd)^3)) + 0.6$ and indexed for body surface area (LVM index (LVMi)), as recommended by the ASE[36]. The relative wall thickness (RWT) was calculated using the formula RWT = $2 \times$ PWT / LVEDd as recommended by the ASE[36]. LV end-diastolic volume (LVEDV, in mL) and end-systolic volume (LVESV, in mL) were estimated using the Teichholz formula[37]. Left ventricular ejection fraction (LVEF, %) was calculated by $((LVEDV – LVESV) / (LVEDV)) \times 100$.

Heart rate (HR, in bpm) was obtained by calculating the reciprocal of the mean of five consecutive RR-intervals on the electrocardiogram multiplied by 60. We estimated the mean aortic velocity time integral (VTI) by averaging the outer edge tracings of five consecutive continuous-wave Doppler recordings of the LV outflow tract velocity. By taking the product of VTI and the mid-systolic cross-sectional area at the level of the LV outflow tract in the parasternal long-axis view, we obtained stroke volume (SV, in mL). Cardiac output (CO, in L/min) was obtained by multiplying SV by heart rate. Cardiac index (CI) was calculated as CI = CO / body surface area. Total peripheral vascular resistance (TPVR in $dyn \cdot s \cdot cm^{-5}$) was obtained using the formula TPVR = $80 \times$ MAP (in mmHg) / CO[20]. Total peripheral vascular resistance index (TPVRi), normalized for body surface area, was calculated as TPVR = $80 \times$ MAP (in mmHg) / CI[20].

Left ventricular hypertrophy was defined as LVMi > 95 g/m^2, concentric remodeling was defined as RWT > 0.42 and LVMi ≤ 95 g/m^2, mildly impaired left ventricular ejection fraction was defined as LVEF > 40 and < 55%[36]. We defined asymptomatic valvular disease as mild aortic valve insufficiency, mild thickening of mitral valve or central aortic valve insufficiency.

Data analysis

For all statistical analyses, we used SPSS version 21.0 (IBM SPSS Statistics, Armonk NY, USA) and R version 3.6.1. Data are expressed as mean with standard deviation for continuous variables and number with percentage for dichotomous variables. Postpartum

intervals were reported as median with interquartile range (IQR). We used the independent t-test to test for group differences of continuous variables. Differences in proportions between groups were tested using the Chi-square test if at least 5 cases were present in each category and the Fisher exact test if one of the categories contained less than 5 cases. Postpartum intervals were analyzed using the Mann-Whitney U test for intergroup differences. A logistic regression was performed to test the associations between both volume load and pressure load at the first visit with the presence of concentric remodeling at the second visit. We selected potential confounders based on clinical reasoning, as opposed to statistical significance. Using multivariable logistic regression we adjusted the associations for primiparity, antihypertensive medication, and either systolic blood pressure or PV mL/kg LBM dependent on the variable to be tested. Logistic regression with the Firth correction was used as the number of events was limited. Results were reported as odds ratio (OR) and 95% confidence intervals computed using the profile penalized log likelihood. P-values were computed using the likelihood ratio test. A two-sided p-value of < 0.05 was considered statistically significant.

RESULTS

We included 121 formerly pre-eclamptic women in our longitudinal cohort study who had their first visit at a median interval of 0.8 years postpartum and their second visit at a median interval of 4.8 years postpartum. At visit 1, 2 women were excluded due to a failed PV measurement. At visit 2 when we examined blood pressure and cardiac ultrasound, 19 women were excluded: 13 women due to an incomplete cardiac ultrasound evaluation and 6 women because of a time interval of ≤ 2 years between both visits (Figure 1). Ultimately 100 women met our criteria for both visits. The included patients (n = 100) differed from the excluded patients (n = 21) by having had more often a follow-up pregnancy (68% vs 38%, $P < 0.05$, respectively) and a lower prevalence of smoking at visit 1 (5% vs 24%, $P < 0.05$, respectively). All of the included participants, except for 2, were Caucasian. One woman was of Turkish ancestry and one woman was of Moroccan ancestry.

Of the 100 women eligible for our statistical analysis, 18 women (18%) showed concentric remodeling at 4.8 years postpartum while 82 (82%) had no concentric remodeling. Among the 18 women with concentric remodeling, 1 (6%) had asymptomatic valve disease (mild aortic valve regurgitation) and none had reduced LVEF. In the no concentric remodeling group, 2 women (2%) had asymptomatic valve disease (1 woman with mild mitral valve regurgitations with mild thickening of mitral valve and 1 woman with mild aortic valve regurgitation) and 6 women (7%) had mildly impaired LVEF.

Table 1 demonstrates the baseline characteristics of both groups. There were no statistically significant differences in obstetrical characteristics between both groups, except less women were primiparous at the first visit in the subsequently concentric remodeling

Table 1. Patient characteristics at visit 1 and 2 in former pre-eclamptic women with and without concentric remodeling defined at visit 2. Data are presented as mean with standard deviation or number with percentage.

	Concentric remodeling (*n* = 18)	No concentric remodeling (*n* = 82)	*P*-value
Index pregnancy			
Early-onset PE, *n* (%)	11/15 (73)	50/80 (63)	0.42
Preterm PE, *n* (%)	13/18 (72)	62/82 (76)	0.77
Primiparous at 0.8 years, *n* (%)	8/18 (44)	67/82 (82)	**<0.01**
Primiparous at 4.8 years, *n* (%)	3/18 (17)	21/82 (26)	0.55
Parity at 0.8 years, *n* (%)	1.7 ± 0.7	1.2 ± 0.6	**<0.05**
Parity at 4.8 years, *n* (%)	2.2 ± 0.7	1.9 ± 0.7	0.16
GA at birth, weeks	33 ± 5	34 ± 4	0.55
Birth weight, g	1717 ±1086	1868 ± 942	0.55
SGA neonate, *n* (%)	10/18 (56)	31/82 (38)	0.17
IUFD, *n* (%)	4/18 (22)	6/81 (7)	0.08
Follow-up pregnancy, *n* (%)	11/18 (61)	57/82 (70)	0.49
Recurrent PE, *n* (%)	5/11 (45)	18/57 (32)	0.49
Patient characteristics at visit 1			
Postpartum, median years (IQR)	1.3 (0.5 to 2.6)	0.7 (0.5 to 1.9)	0.31
Age, years	32 ± 5	33 ± 4	0.34
Weight, kg	76 ±13	71 ± 19	0.27
BMI, kg/m^2	26.5 ± 3.2	24.8 ± 6.4	0.28
Obesity, BMI ≥ 30 kg/m^2, *n* (%)	4/18 (22)	11/82 (13)	0.46
Smoking, *n* (%)	1/18 (6)	4/82 (5)	1.00
Alcohol, *n* (%)	2/18 (11)	13/82 (16)	1.00
Family history of CVD, *n* (%)	9/18 (50)	27/82 (33)	0.17
Antihypertensive treatment, *n* (%)	4/18 (22)	14/81 (17)	0.74
Patient characteristics at visit 2			
Postpartum, median years (IQR)	5.7 (4.3 to 6.9)	4.8 (4.1 to 6.1)	0.30
Age, years	35 ± 5	36 ± 4	0.36
Weight, kg	79 ± 15	72 ± 18	0.19
BMI, kg/m^2	27.2 ± 3.8	25.3 ± 6.3	0.21
Obesity, BMI ≥ 30 kg/m^2, *n* (%)	6/18 (33)	12/82 (15)	0.09
Smoking, *n* (%)	1/18 (6)	6/82 (7)	1.00
Alcohol, *n* (%)	2/18 (11)	22/82 (27)	0.23
Family history of CVD, *n* (%)	11/18 (61)	43/82 (52)	0.50
Antihypertensive treatment, *n* (%)	6/18 (33)	14/82 (17)	0.19

PE, pre-eclampsia; GA, gestational age; SGA, small-for-gestational age; IUFD, intrauterine fetal death; IQR, interquartile range; BMI, body mass index; CVD, cardiovascular disease.

group (44%) compared with the no concentric remodeling group at follow-up (82%). There were no statistically significant differences in age, weight, BMI, obesity, smoking, alcohol consumption, family history of CVD, antihypertensive treatment and postpartum interval between both groups at 0.8 and subsequent 4.8 years postpartum.

Concentric remodeling versus no concentric remodeling

Table 2 presents the hemodynamic indices, measured at the first evaluation after index pregnancy (median 0.8 years postpartum, IQR 0.5 to 2.1 years postpartum). There were no statistically significant differences in SBP, DBP and MAP between the groups. HR did not differ between the concentric remodeling group and no concentric remodeling group. TPVR was significantly lower in the concentric remodeling group at follow-up compared to the no concentric remodeling group. TPVR index, prehypertension, hypertension and untreated hypertension were comparable between both groups. PV was lower in the concentric remodeling group at follow-up compared with the no concentric remodeling group (54 ± 6 versus 59 ± 7 mL/kg LBM, $P < 0.05$, respectively). Consequently, the concentric remodeling group seemed to have more often low PV (≤ 48 mL/kg LBM) compared with the no concentric remodeling group (22% vs 6%, respectively $P = 0.05$).

Table 2. Hemodynamics and volume load at visit 1 in former pre-eclamptic women. The group is subdivided in women with concentric remodeling and no concentric remodeling defined at visit 2 in formerly pre-eclamptic women. Data are presented as mean with standard deviation or number with percentage.

	Concentric remodeling (*n* = 18)	No concentric remodeling (*n* = 82)	*P*-value
Hemodynamics			
SBP, mmHg	126 ± 17	119 ± 15	0.06
DBP, mmHg	74 ± 12	69 ± 10	0.07
MAP, mmHg	92 ±13	86 ± 12	0.08
HR, bpm	69 ± 7	69 ± 11	0.93
TPVR, x 10^3 dyn·s·cm^{-5}	1.3 ± 0.4	1.5 ± 0.4	**<0.05**
TPVR index, x 10^3 dyn·s·cm^{-5}	2.5 ± 0.8	2.8 ± 0.7	0.13
Prehypertension, *n* (%)	5/18 (28)	15/82 (18)	0.35
Hypertension, *n* (%)	6/18 (33)	20/82 (24)	0.55
Hypertension untreated, *n* (%)	2/18 (11)	6/82 (7)	0.63
Plasma volume			
PV mL/kg LBM	54 ± 6	59 ± 7	**<0.05**
Low PV, *n* (%)*	4/18 (22)	5/82 (6)	0.05

SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure; HR, heart rate; TPVR, total peripheral vascular resistance; PV, plasma volume; kg, kilogram; LBM, lean body mass;
*Low PV mL kg/LBM is defined as PV index ≤ 48 mL/kg LBM.

Table 3 demonstrates the odds ratio's on concentric remodeling of volume and pressure load measured at visit 1. PV mL/kg LBM at the first evaluation associates inversely with remote concentric remodeling (odds ratio (OR): 0.91, 95% confidence interval (CI): 0.84-0.99), and remained so after adjustments for SBP, primiparity and antihypertensive treatment measured at visit 1 (adjusted OR (aOR) 0.91, 95% CI 0.82-0.99). Moreover, low PV was associated with concentric remodeling at follow-up (OR 4.37, 95% CI 1.06-17.40), also after adjustments (aOR 4.67, 95% CI 1.02-21.42). Arterial pressure load is associated with the risk development of concentric remodeling at follow-up, but part of this effect seemed to originate from concurrent decrease in volume load, as after correction the effect of pressure load on the concentric cardiac phenotype was less.

Table 3.Volume and pressure load at visit 1 in former pre-eclamptic women with the odds ratio on remote concentric remodeling defined at visit 2.

	Crude OR	P-value crude OR	Adjusted OR	P-value adjusted OR
Plasma volume				
PV mL/kg LBM	0.91 (95% CI 0.84-0.99)	**<0.05**	0.91 (95% CI 0.82-0.99) †	**<0.05**
Low PV*	4.37 (95% CI 1.06-17.40)	**<0.01**	4.67 (95% CI 1.02-21.42) †	**<0.05**
Pressure load				
SBP (per 5 mmHg)	1.15 (95% CI 0.99-1.35)	0.07	1.08 (95% CI 0.90-1.29)‡	0.39
DBP (per 5 mmHg)	1.24 (95% CI 0.98-1.58)	0.08	1.12 (95% CI 0.85-1.50)‡	0.41
MAP (per 5 mmHg)	1.20 (95% CI 0.98-1.47)	0.08	1.12 (95% CI 0.89-1.42)‡	0.34

OR, odds ratio; CI, confidence interval; PV, plasma volume; kg, kilogram; LBM, lean body mass; SBP, systolic blood pressure; DBP, diastolic blood pressure, MAP, mean arterial pressure.
* Low PV mL/kg LBM is defined as PV ≤ 48 mL/kg LBM.
† adjusted for SBP, primiparity and antihypertensive treatment measured at visit 1.
‡ adjusted for PV mL/kg LBM, primiparity and antihypertensive treatment measured at visit 1.

Table 4 shows the hemodynamic and cardiac measurements at visit 2 (median 4.8 years postpartum, IQR 4.2 to 6.4 years postpartum) in both groups. The concentric remodeling group differed from the no concentric remodeling group by having a higher DBP. Moreover, SBP and MAP showed a trend towards significance with a higher blood pressure in the concentric remodeling group compared with the no concentric remodeling group. HR, TPVR, TPVR index were comparable between the two groups. Prehypertension was more prevalent in the concentric remodeling group (39%) compared to the no concentric remodeling group (16%). The presence of hypertension and untreated hypertension did not differ between both groups. Of the cardiac measurements, RWT, IVST and PWT were higher in women with concentric remodeling while LVEDd, LVEDd index and LVESd were lower in the concentric remodeling group.

Table 4. Hemodynamic and cardiac indices at visit 2 in former pre-eclamptic women with and without concentric remodeling defined at visit 2. Data are presented as mean with standard deviation or number with percentage.

	Concentric remodeling (*n* = 18)	No concentric remodeling (*n* = 82)	*P*-value
Hemodynamics			
SBP, mmHg	123 ± 11	116 ± 13	0.06
DBP, mmHg	79 ± 9	72 ± 10	**<0.05**
MAP, mmHg	91 ± 10	86 ± 11	0.08
HR, bpm	66 ± 9	66 ± 11	0.93
TPVR, x 10^3 dyn·s·cm^{-5}	1.4 ± 0.3	1.4 ± 0.3	0.93
TPVR index, x 10^3 dyn·s·cm^{-5}	2.6 ± 0.5	2.5 ± 0.6	0.50
Prehypertension, *n* (%)	7/18 (39)	13/82 (16)	**<0.05**
Hypertension, *n* (%)	6/18 (33)	19/82 (23)	0.38
Hypertension untreated, *n* (%)	0/18 (0)	5/82 (6)	0.58
Cardiac measurements			
RWT	0.46 ± 0.03	0.32 ± 0.05	**<0.01**
LVM, g	120 ± 29	107 ± 28	0.09
LVM index, g/m^2	63 ± 12	58 ± 13	0.16
SV, mL	82 ±17	80 ± 18	0.65
CO, l/min	5.4 ±1.0	5.2 ± 1.1	0.46
CI, l/min/m^2	2.8 ± 0.4	2.8 ± 0.6	0.99
LVEF, %	63 ± 5	63 ± 6	0.94
LVEDd, cm	4.1 ± 0.3	4.6 ± 0.4	**<0.01**
LVEDd index, cm/m^2	2.2 ± 0.2	2.5 ± 0.2	**<0.01**
LVESd, cm	2.6 ± 0.4	2.9 ± 0.4	**<0.05**
IVST, cm	0.87 ± 0.12	0.73 ± 0.16	**<0.01**
PWT, cm	0.95 ± 0.09	0.74 ± 0.12	**<0.01**
LAD, cm	3.6 ± 0.5	3.5 ± 0.5	0.60

SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure; HR, heart rate, TPVR, total peripheral vascular resistance; RWT, relative wall thickness; LVM, left ventricular mass; SV, stroke volume; CO, cardiac output; CI, cardiac index; LVEF, left ventricular ejection fraction; LVEDd, left ventricular end diastolic diameter; LVESd, left ventricular end systolic diameter; IVST, interventricular septal thickness; PWT, posterior wall thickness; LAD, left atrium diameter.

DISCUSSION

In this current explorative longitudinal cohort study, we observed that low volume load as indicated by PV and increased pressure load in the first year after pre-eclamptic gestation relates to an increased risk to develop later concentric cardiac remodeling.

Formerly pre-eclamptic women have an increased risk for CVD and share cardiovascular risk factors which may, at least in part, explain the relation between both diseases[3-6, 38]. Besides the elevated prevalence of common CVD risk factors, that mostly predispose to macrovascular disease, the concentric cardiac adaptation to hypertensive complicated pregnancy may play an (additional) role in the associated elevated remote risk for CVD, especially when the additional increase in LV mass in women with PE does not resolve after delivery[7-11]. In the first decade after delivery 25% of formerly pre-eclamptic women have structural or functional cardiac abnormalities, consistent with asymptomatic heart failure stage B, mostly along with a concentric phenotype[11, 13, 39]. This type of heart failure is thought to originate from a systemic proinflammatory state with the involvement of microvascular endothelial inflammation[40]. Both traditional cardiovascular risk factors and incomplete deconditioning from the vascular complicated pregnancy are thought to contribute to the increased risk of future heart failure[41, 42]. It is believed that this increased risk is susceptible to preventive intervention while the disease is still in a preclinical stage.

Structural cardiac remodeling is an important compensatory mechanism to maintain the pumping capacity of the heart in response to alterations in either volume or pressure load[16, 43]. Volume and pressure load-induced stimuli induce various signalling pathways leading to a hypertrophic response of the cardiomyocytes[44, 45]. This induces eccentric cardiac hypertrophy with concomitant widening of the ventricle in uncomplicated normotensive pregnancies or concentric adjustments with relative loss of ventricular volume when facing muscular hypertrophy in hypertensive pregnancies[16, 44, 45]. Cardiac myocyte hypertrophy is dose-dependently associated with increased circulatory load. On the one hand, the difference in concentric or eccentric cardiac adaptation in our cohort is associated more to volume load than pressure load, in which each additional mL/kg LBM PV lowered the odds on concentric cardiac phenotype. On the other hand, the contribution of blood pressure should not be underestimated as we observed that blood pressure seems to be associated with the odds on concentric remodelling at follow-up. Nonetheless, when correcting for low volume load, part of the effect of pressure load on concentric remodeling at follow-up disappeared, suggesting that part of the effects that are associated with pressure load could originate from volume load. At any rate, both volume and pressure load affected the development towards concentric cardiac remodeling in a dose dependent fashion.

Given the large prevalence of persistent or de-novo elevated blood pressure in formerly pre-eclamptic women, especially in women with low PV, low volume status may be an

alarming characteristic even in apparently healthy normotensive formerly pre-eclamptic women[30, 46].

Clinically, in normotensive formerly pre-eclamptic women, on the one hand, pre-pregnancy low PV is associated with recurrent hypertensive complicated pregnancy, growth restriction and preterm birth and, on the other hand, low PV is associated with remote hypertension within the first decade after the hypertensive index pregnancy[30, 47]. PV is considered to mirror cardiovascular reserve capacity in case of healthy cardiac functioning[47]. 65-75% of the blood volume is localized in the venous system and can be mobilised in times of increased arterial demand as in pregnancy or during exercise[48-50]. PV can be fundamentally diminished, either genetically or secondary to a structurally small venous compartment in line with the fetal origin of adult disease complex (Barkers hypothesis) [47, 51, 52]. Alternatively, low PV status may result from a functionally more constricted venous system diminishing venous dimensions and (resting) elastic properties of the venous wall and with it decreasing the venous capacitance as part of sympathetic over-activity, such as seen in obesity or the metabolic syndrome[30, 49, 53]. Given the commonly present low PV status in formerly pre-eclamptic women and the increased tendency to develop chronic hypertension, one could anticipate on a synergistic detrimental effect of volume and pressure load on concentric cardiac remodeling in these women while aging[7-9, 20, 21]. From this perspective, close monitoring of blood pressure and timely intervention with blood pressure modulating medication, not only capable in lowering pressure load but also increasing volume load may be most promising in the effective and preventive treatment of concentric remodeling. Along these lines, as such, diuretics as primary treatment option for hypertension in these women should not be advisable.

Limitations

There are a few limitations in this study. First, most women in our study were Caucasian. Therefore, our study results might not be entirely generalized to other populations. Second, although we adjusted for the use of antihypertensive medication in our analysis, we cannot completely rule out the effect of antihypertensive drugs at the time of the measurements, as cardiac remodeling also independently results from other biochemical factors apart from blood pressure and PV. Third, the observational nature of our study and the lack of a matched control group does not allow us to conclude whether the relationship between volume status and persistence of concentric remodeling is causal or not and to evaluate the potential effect of complicated- or uncomplicated pregnancy itself on cardiac changes in time. Therefore, additional studies confirming our findings are needed.

CONCLUSION

One out of six formerly pre-eclamptic women have a concentric remodeled left ventricle 4.8 years after gestation. In these women, concentric remodeling is associated with low volume load and increased pressure load.

PERSPECTIVES

Recognizing the role of diminished volume load along with elevated blood pressure, even without reaching the threshold of overt hypertension, may help in the clinical fine-tuning of preventive measures in these women to prevent the development of heart failure.

ACKNOWLEDGEMENTS

None.

SOURCES OF FUNDING

The study topic receives financial support from the "Nederlandse Hart Stichting" (Dutch Heart Foundation).

DISCLOSURES

None.

AFFILIATIONS

From Department of Obstetrics and Gynecology, Research School Grow, Maastricht University Medical Center (MUMC+), Maastricht, The Netherlands (N.M.B., R.J.A., L.G, J.v.N., C.G.-D., M.E.A.S.); Clinical Epidemiology and Medical Technology Assessment (KEMTA), Maastricht University Medical Center (MUMC+), Maastricht, The Netherlands (S.M.J.v.K.); Department of Cardiology, Radboud University Medical Center (Radboudumc), Nijmegen, The Netherlands (A.P.v.D., M.J.v.d.V.); Department of Obstetrics and Gynecology, Radboud University Medical Center (Radboudumc), Nijmegen, The

Netherlands (W.M.H., R.R.S.); Department of Cardiology, Maastricht University Medical Center (MUMC+), Maastricht, The Netherlands (V.P.M.v.E., H.P.B.-L.R).

REFERENCES

1. Roberts JM and Cooper DW. Pathogenesis and genetics of pre-eclampsia. *Lancet*. 2001;357:53-6.
2. Mosca L, Benjamin EJ, Berra K, Bezanson JL, Dolor RJ, Lloyd-Jones DM, Newby LK, Pina IL, Roger VL, Shaw LJ, Zhao D, Beckie TM, Bushnell C, D'Armiento J, Kris-Etherton PM, Fang J, Ganiats TG, Gomes AS, Gracia CR, Haan CK, Jackson EA, Judelson DR, Kelepouris E, Lavie CJ, Moore A, Nussmeier NA, Ofili E, Oparil S, Ouyang P, Pinn VW, Sherif K, Smith SC, Jr., Sopko G, Chandra-Strobos N, Urbina EM, Vaccarino V and Wenger NK. Effectiveness-based guidelines for the prevention of cardiovascular disease in women--2011 update: a guideline from the american heart association. *Circulation*. 2011;123:1243-62.
3. Bellamy L, Casas JP, Hingorani AD and Williams DJ. Pre-eclampsia and risk of cardiovascular disease and cancer in later life: systematic review and meta-analysis. *BMJ (Clinical research ed)*. 2007;335:974.
4. English FA, Kenny LC and McCarthy FP. Risk factors and effective management of preeclampsia. *Integrated blood pressure control*. 2015;8:7-12.
5. Benjamin EJ, Blaha MJ, Chiuve SE, Cushman M, Das SR, Deo R, de Ferranti SD, Floyd J, Fornage M, Gillespie C, Isasi CR, Jimenez MC, Jordan LC, Judd SE, Lackland D, Lichtman JH, Lisabeth L, Liu S, Longenecker CT, Mackey RH, Matsushita K, Mozaffarian D, Mussolino ME, Nasir K, Neumar RW, Palaniappan L, Pandey DK, Thiagarajan RR, Reeves MJ, Ritchey M, Rodriguez CJ, Roth GA, Rosamond WD, Sasson C, Towfighi A, Tsao CW, Turner MB, Virani SS, Voeks JH, Willey JZ, Wilkins JT, Wu JH, Alger HM, Wong SS and Muntner P. Heart Disease and Stroke Statistics-2017 Update: A Report From the American Heart Association. *Circulation*. 2017;135 e146-e603.
6. Craici I, Wagner S and Garovic VD. Preeclampsia and future cardiovascular risk: formal risk factor or failed stress test? *Therapeutic advances in cardiovascular disease*. 2008;2:249-59.
7. Manten GT, Sikkema MJ, Voorbij HA, Visser GH, Bruinse HW and Franx A. Risk factors for cardiovascular disease in women with a history of pregnancy complicated by preeclampsia or intrauterine growth restriction. *Hypertension in pregnancy*. 2007;26:39-50.
8. Smith GN, Walker MC, Liu A, Wen SW, Swansburg M, Ramshaw H, White RR, Roddy M and Hladunewich M. A history of preeclampsia identifies women who have underlying cardiovascular risk factors. *American journal of obstetrics and gynecology*. 2009;200:58.e1-8.
9. Hermes W, Franx A, van Pampus MG, Bloemenkamp KW, Bots ML, van der Post JA, Porath M, Ponjee GA, Tamsma JT, Mol BW and de Groot CJ. Cardiovascular risk factors in women who had hypertensive disorders late in pregnancy: a cohort study. *American journal of obstetrics and gynecology*. 2013;208:474.e1-8.
10. Melchiorre K, Sharma R and Thilaganathan B. Cardiovascular implications in preeclampsia: an overview. *Circulation*. 2014;130:703-14.
11. Melchiorre K, Sutherland GR, Liberati M and Thilaganathan B. Preeclampsia is associated with persistent postpartum cardiovascular impairment. *Hypertension*. 2011;58:709-15.
12. de Haas S, Ghossein-Doha C, Geerts L, van Kuijk SMJ, van Drongelen J and Spaanderman MEA. Cardiac remodelling in normotensive pregnancy and in pregnancy complicated by hypertension: systematic review and meta-analysis. *Ultrasound in obstetrics & gynecology : the official journal of the International Society of Ultrasound in Obstetrics and Gynecology*. 2017;50:683-696.
13. Ghossein-Doha C, van Neer J, Wissink B, Breetveld NM, de Windt LJ, van Dijk AP, van der Vlugt MJ, Janssen MC, Heidema WM, Scholten RR and Spaanderman ME. Pre-eclampsia: an important risk factor for asymptomatic heart failure. *Ultrasound in obstetrics & gynecology : the official journal of the International Society of Ultrasound in Obstetrics and Gynecology*. 2017;49:143-149.
14. de Haas S, Ghossein-Doha C, van Kuijk SM, van Drongelen J and Spaanderman ME. Physiologic adaptation of maternal plasma volume during pregnancy: a systematic review and meta-analysis. *Ultrasound*

in obstetrics & gynecology : the official journal of the International Society of Ultrasound in Obstetrics and Gynecology. 2016;49:177-187.

15. Simmons LA, Gillin AG and Jeremy RW. Structural and functional changes in left ventricle during normotensive and preeclamptic pregnancy. *American journal of physiology Heart and circulatory physiology*. 2002;283:H1627-33.
16. Cantor EJ, Babick AP, Vasanji Z, Dhalla NS and Netticadan T. A comparative serial echocardiographic analysis of cardiac structure and function in rats subjected to pressure or volume overload. *Journal of molecular and cellular cardiology*. 2005;38:777-86.
17. Muiesan ML, Salvetti M, Monteduro C, Bonzi B, Paini A, Viola S, Poisa P, Rizzoni D, Castellano M and Agabiti-Rosei E. Left ventricular concentric geometry during treatment adversely affects cardiovascular prognosis in hypertensive patients. *Hypertension*. 2004;43:731-8.
18. Verdecchia P, Schillaci G, Borgioni C, Ciucci A, Battistelli M, Bartoccini C, Santucci A, Santucci C, Reboldi G and Porcellati C. Adverse prognostic significance of concentric remodeling of the left ventricle in hypertensive patients with normal left ventricular mass. *Journal of the American College of Cardiology*. 1995;25:871-8.
19. Heymans S, Gonzalez A, Pizard A, Papageorgiou AP, Lopez-Andres N, Jaisser F, Thum T, Zannad F and Diez J. Searching for new mechanisms of myocardial fibrosis with diagnostic and/or therapeutic potential. *European journal of heart failure*. 2015;17:764-71.
20. Spaanderman ME, Ekhart TH, van Eyck J, Cheriex EC, de Leeuw PW and Peeters LL. Latent hemodynamic abnormalities in symptom-free women with a history of preeclampsia. *American journal of obstetrics and gynecology*. 2000;182:101-7.
21. Aardenburg R, Spaanderman ME, Ekhart TH, van Eijndhoven HW, van der Heijden OW and Peeters LL. Low plasma volume following pregnancy complicated by pre-eclampsia predisposes for hypertensive disease in a next pregnancy. *Br J Obstet Gynaecol*. 2003;110:1001-6.
22. Yasumoto K, Takata M, Ueno H, Tomoda F and Inoue H. Relation of circulating blood volume to left ventricular geometry in essential hypertension. *Hypertension research : official journal of the Japanese Society of Hypertension*. 2002;25:703-10.
23. Grossman W, Jones D and McLaurin LP. Wall stress and patterns of hypertrophy in the human left ventricle. *J Clin Invest*. 1975;56:56-64.
24. Burnier M. Angiotensin II type 1 receptor blockers. *Circulation*. 2001;103:904-12.
25. Paul M, Poyan Mehr A and Kreutz R. Physiology of local renin-angiotensin systems. *Physiological reviews*. 2006;86:747-803.
26. Matchar DB, McCrory DC, Orlando LA, Patel MR, Patel UD, Patwardhan MB, Powers B, Samsa GP and Gray RN. Systematic review: comparative effectiveness of angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers for treating essential hypertension. *Annals of internal medicine*. 2008;148:16-29.
27. Frohlich ED and Susic D. Pressure overload. *Heart failure clinics*. 2012;8:21-32.
28. Brown MA, Lindheimer MD, de Swiet M, Van Assche A and Moutquin JM. The classification and diagnosis of the hypertensive disorders of pregnancy: statement from the International Society for the Study of Hypertension in Pregnancy (ISSHP). *Hypertension in pregnancy*. 2001;20:IX-XIV.
29. Kloosterman GJ. [Intrauterine growth and intrauterine growth curves]. *Maandschrift voor kindergeneeskunde*. 1969;37:209-25.
30. Scholten RR, Lotgering FK, Hopman MT, Van Dijk A, Van de Vlugt M, Janssen MC and Spaanderman ME. Low Plasma Volume in Normotensive Formerly Preeclamptic Women Predisposes to Hypertension. *Hypertension*. 2015;66:1066-72.

31. Mujais SK, Tarazi RC, Dustan HP, Fouad FM and Bravo EL. Hypertension in obese patients: hemodynamic and volume studies. *Hypertension*. 1982;4:84-92.
32. Krabbendam I, Courtar DA, Janssen BJ, Aardenburg R, Peeters LL and Spaanderman ME. Blunted autonomic response to volume expansion in formerly preeclamptic women with low plasma volume. *Reprod Sci*. 2009;16:105-12.
33. Deurenberg P, Weststrate JA and Seidell JC. Body mass index as a measure of body fatness: age- and sex-specific prediction formulas. *Br J Nutr*. 1991;65:105-14.
34. Courtar DA, Spaanderman ME, Aardenburg R, Janssen BJ and Peeters LL. Low plasma volume coincides with sympathetic hyperactivity and reduced baroreflex sensitivity in formerly preeclamptic patients. *J Soc Gynecol Investig*. 2006;13:48-52.
35. Sahn DJ, DeMaria A, Kisslo J and Weyman A. Recommendations regarding quantitation in M-mode echocardiography: results of a survey of echocardiographic measurements. *Circulation*. 1978;58:1072-83.
36. Lang RM, Bierig M, Devereux RB, Flachskampf FA, Foster E, Pellikka PA, Picard MH, Roman MJ, Seward J, Shanewise JS, Solomon SD, Spencer KT, Sutton MS and Stewart WJ. Recommendations for chamber quantification: a report from the American Society of Echocardiography's Guidelines and Standards Committee and the Chamber Quantification Writing Group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology. *Journal of the American Society of Echocardiography : official publication of the American Society of Echocardiography*. 2005;18:1440-63.
37. Teichholz LE, Kreulen T, Herman MV and Gorlin R. Problems in echocardiographic volume determinations: echocardiographic-angiographic correlations in the presence of absence of asynergy. *The American journal of cardiology*. 1976;37:7-11.
38. Brown MC, Best KE, Pearce MS, Waugh J, Robson SC and Bell R. Cardiovascular disease risk in women with pre-eclampsia: systematic review and meta-analysis. *European journal of epidemiology*. 2013;28:1-19.
39. Breetveld NM, Ghossein-Doha C, van Kuijk SM, van Dijk AP, van der Vlugt MJ, Heidema WM, van Neer J, van Empel V, Brunner-La Rocca HP, Scholten RR and Spaanderman ME. Prevalence of asymptomatic heart failure in formerly pre-eclamptic women: a cohort study. *Ultrasound in obstetrics & gynecology : the official journal of the International Society of Ultrasound in Obstetrics and Gynecology*. 2017;49:134-142.
40. Paulus WJ and Tschope C. A novel paradigm for heart failure with preserved ejection fraction: comorbidities drive myocardial dysfunction and remodeling through coronary microvascular endothelial inflammation. *Journal of the American College of Cardiology*. 2013;62:263-71.
41. Ghossein-Doha C, Khalil A and Lees CC. Maternal hemodynamics: a 2017 update. *Ultrasound in obstetrics & gynecology : the official journal of the International Society of Ultrasound in Obstetrics and Gynecology*. 2017;49:10-14.
42. Zandstra M, Stekkinger E, van der Vlugt MJ, van Dijk AP, Lotgering FK and Spaanderman ME. Cardiac diastolic dysfunction and metabolic syndrome in young women after placental syndrome. *Obstetrics and gynecology*. 2010;115:101-8.
43. Mann DL. Heart failure: beyond practice guidelines. *Texas Heart Institute journal*. 2006;33:201-3.
44. Rohini A, Agrawal N, Koyani CN and Singh R. Molecular targets and regulators of cardiac hypertrophy. *Pharmacological research*. 2010;61:269-80.
45. Heineke J and Molkentin JD. Regulation of cardiac hypertrophy by intracellular signalling pathways. *Nature reviews Molecular cell biology*. 2006;7:589-600.
46. Ghossein-Doha C, Peeters L, van Heijster S, van Kuijk S, Spaan J, Delhaas T and Spaanderman M. Hypertension After Preeclampsia Is Preceded by Changes in Cardiac Structure and Function. *Hypertension*. 2013;62:382-90.

47. Scholten RR, Sep S, Peeters L, Hopman MT, Lotgering FK and Spaanderman ME. Prepregnancy low-plasma volume and predisposition to preeclampsia and fetal growth restriction. *Obstetrics and gynecology*. 2011;117:1085-93.
48. Pang CC. Measurement of body venous tone. *Journal of pharmacological and toxicological methods*. 2000;44:341-60.
49. Scholten RR, Hopman MT, Lotgering FK and Spaanderman ME. Aerobic Exercise Training in Formerly Preeclamptic Women: Effects on Venous Reserve. *Hypertension*. 2015;66:1058-65.
50. Sakai K, Imaizumi T, Maeda H, Nagata H, Tsukimori K, Takeshita A and Nakano H. Venous distensibility during pregnancy. Comparisons between normal pregnancy and preeclampsia. *Hypertension*. 1994;24:461-6.
51. Barker DJ and Fall CH. Fetal and infant origins of cardiovascular disease. *Archives of disease in childhood*. 1993;68:797-9.
52. Barker DJ. Fetal origins of coronary heart disease. *BMJ (Clinical research ed)*. 1995;311:171-4.
53. Krabbendam I, Janssen BJ, Van Dijk AP, Jongsma HW, Oyen WJ, Lotgering FK and Spaanderman ME. The relation between venous reserve capacity and low plasma volume. *Reprod Sci*. 2008;15:604-12.

General Discussion

INTRODUCTION

Preeclampsia (PE) is a pregnancy-related hypertensive disorder complicating 3-5% of all pregnancies and is associated with a two-to sevenfold increased risk of developing ischemic cardiac disease within 15 years after pregnancy[1, 2]. It is believed that PE is an obstetric resultant of placental microvascular dysfunction[1, 3]. Traditional cardiovascular risk factors can lead to an elevated risk of placental dysfunction, as well as an increase in risk of cardiovascular disease in women with a history of preeclampsia[4-6]. It is hypothesized that in women with a hypertensive pregnancy complication, cardiac remodeling both reflects an adjustment to increased strain but also represents pathologic stress to the myocardium at a young age. During preeclampsia, the unfavorable increase in left ventricular mass and loss in diastolic function does not always normalize after giving birth[7, 8].

This thesis provides insight on cardiovascular (CV) function during and after preeclamptic pregnancies and the risk for remote CV disease (CVD) in these women. First, it describes the adaptation of and changes in systolic cardiac function over the course of gestation in normotensive and hypertensive pregnancies. Secondly, it elaborates on the prevalence of subclinical heart failure (HF-B) and how this subclinical phase relates to endothelial function and circulatory plasma volume after preeclampsia. Finally, the calculated risk for remote CVD based on predefined risk scores is described.

CARDIAC GEOMETRY DURING PREGNANCY

Normotensive pregnancy is characterized by increased volume load and decreased pressure load, most likely triggered by an early pregnancy drop in total peripheral vascular resistance (TPVR)[9, 10]. The reduction in cardiac afterload during the first-trimester and imminent decline in blood pressure activates compensatory mechanisms by stimulating central autonomic mechanisms and by activating the renin-angiotensin-aldosterone system (RAAS) to re-establish the circulatory filling state and blood pressure stabilizing rise in cardiac output (CO)[10, 11]. In the clinical phase of a preeclamptic pregnancy, TPVR increases along with blood pressure[10, 12]. Moreover, in a recent meta-analysis, de Haas *et al.* showed that plasma volume expansion was 13.3% lower in complicated pregnancies (pregnancy-induced hypertension, preeclampsia or fetal growth restriction) than in normotensive pregnancies (0.80 L (32.3%) versus 1.13 L (45.6%), respectively)[13]. The reason for these differences in circulatory volume is unknown but may relate to inadequate plasma volume expansion, loss in gained volume and with it edema formation or differences in pre-pregnancy volume[10]. In contrast to the clinical phase, preclinical responses

have been more divergent based on clinical onset of the disease, and are characterized by subnormal first trimester circulatory adjustments and suboptimal placentation[10, 12].

Early-onset PE seems to be preceded by low cardiac index along with high TPVR while this is not well described in women destined to develop late-onset PE, with some authors indicating at least normal cardiac index and slightly increased TPVR at mid-gestation, while others report supra-normal CO along with low TPVR[10, 12]. However, although the latter authors did not normalize hemodynamic measurements for body surface area or body mass index, despite of significant differences in the anthropometric parameters in the analyzed study groups, the hyperdynamic circulatory state may underlie the BMI associated increased risk of PE[10, 12, 14, 15].

During normal pregnancy, the heart undergoes remodeling which can be compared to morphological alterations seen in athletes, which is referred to as eccentric hypertrophy, a process of proportional increase in chamber dimensions and left ventricular wall thickness (relative wall thickness = RWT)[8, 10, 16]. A recent meta-analysis studied the pattern of cardiac remodeling in normotensive and hypertensive pregnancy[16]. During normotensive pregnancy, left ventricular mass (LVM) increased by 28 g (24%) and RWT increased by 0.03 (10%) while in pregnancy complicated by hypertension, LVM and RWT increased disproportionally and respectively 3 and 5 times more than during normotensive pregnancy, (92 g (95%) and 0.14 (56%), respectively)[16].

Although the underlying causal mechanism of developing concentric remodeling during PE has not been evaluated, based on physiological principles, increased pressure- and attenuated volume load, along with vasoactive(neuro)hormonal factors stimulating various signaling pathways that are essential for the induction of a hypertrophic response of the cardiomyocyte[10, 17, 18]. LV remodeling in preeclampsia is asymmetrical, predominantly involving the basal anteroseptum[19].

Even though almost all evident geometric changes become visible from second trimester onwards, Melchiorre *et al.* showed that women destined to develop preterm PE, LV mild diastolic dysfunction (30%) and segmental impaired myocardial relaxation (70%) was highly present, along with increased afterload (higher mean arterial pressure and TPVR index) and LV concentric hypertrophy[10, 12, 20].

SYSTOLIC AND DIASTOLIC CARDIAC FUNCTION IN PREGNANCY

Regardless of the primary favorable effect of an increased wall thickness to reduce wall stress, concentric LV remodeling co-occurs with an increase in extracellular matrix, with increased fibroblasts and collagen accumulation between individual myocytes[18]. As such, concentric remodeling preludes loss in diastolic function as consequence of reduced ventricular compliance[10]. A study by Vaught *et al.* described lower values for diastolic

function in PE women with severe features like severe hypertension and end-organ dysfunction compared with healthy pregnant women, supporting this theory[21]. These findings are in line with other studies, describing a high prevalence of LV global diastolic dysfunction in predominantly preterm PE women[8, 22, 23]. There are conflicting findings of global left ventricular systolic function in PE, nevertheless, when corrected for heart rate dependency and load, preserved contractility during PE was suggested[10, 12, 24].

In chapter 2 of this thesis, we present the changes in systolic function during pregnancy based on a systematic review and meta-analysis. During normotensive pregnancies, LVEDV, LVESV increased while EF showed an initial small rise in early second trimester to normalize towards baseline afterwards. In contrast to normotensive pregnancies, during gestational hypertensive pregnancies, the left ventricle is apparently unable to maintain contractility, reflected by 10% reduced ejection fraction. The underlying mechanisms leading to the reduction in cardiac contractility needs to be elucidated.

Impaired contractility, measured as decreased ejection fraction appears in end-stage cardiac disease expression[10]. Before abnormalities in conventional measures of LV performance like ejection fraction become visible, in patients with subclinical LV dysfunction impaired myocardial contractility and relaxation may precede the development of overt systolic and/or diastolic dysfunction[25]. Speckle tracking echocardiography (STE) is a new echocardiographic technique, which may be capable to estimate more subtle functional myocardial abnormalities and LV diastolic and systolic dynamics[10, 25]. Moreover, STE enables more detailed information in hypertensive patients (also in the early phase of hypertension) to recognize systolic dysfunction in patients with normal LV ejection fraction[25]. Using 3D STE, Cong *et al.* found that in women with early-onset preeclampsia all strain directions appear to be impaired whereas in late onset preeclampsia all but LV global radial strain were impaired compared to normal pregnancy[10, 26].

Because of the promising idea of the clinical application of STE in preeclampsia, several research groups are now investigating the role of STE in different subtypes of complicated pregnancy.

SUBCLINICAL HEART FAILURE AFTER PREECLAMPSIA

Heart failure (HF) is generally viewed as a progressive disorder that begins with some injury to, or stress on, the myocardium and proceeds from asymptomatic to symptomatic stages[27, 28]. The principal manifestation of this progression is a change in the structure and geometry of the left ventricle[27, 28]. According to the American Heart Association (AHA), asymptomatic stages of HF include HF stage A which are those with risk factors but without structural heart disease (HF-A) and HF-stage B defined as the presence of a former myocardial infarction, left ventricular hypertrophy, concentric remodeling,

mildly impaired left ventricular ejection fraction or asymptomatic valvular disease (HF-B)[27]. These asymptomatic stages precedes the symptomatic stages C and D[27]. Ammar *et al.* showed that the 5 year survival reduced most sharply at the transition of HF-B (96%) to HF-C (75%)[29]. Moreover, this transition is accompanied by a fivefold increase in mortality risk[29]. Untreated asymptomatic LV dysfunction have a 10% risk of developing HF symptoms and a 8% risk of death or HF hospitalization annually[30, 31]. The transition from asymptomatic to symptomatic HF disease is affected by the presence of traditional cardiovascular and cardio-metabolic risk factors[27, 32].

Melchiorre *et al.* described that in the first year after preterm preeclampsia, women still show an abnormal LV geometric pattern and diastolic dysfunction, 41% and 52%, respectively[7]. Moreover, in chapter 4 we showed that after an preeclamptic pregnancy, 75% of those diagnosed with asymptomatic heart failure demonstrate impaired diastolic function but preserved ejection fraction (HFpEF) at 4 years postpartum. In general, HFpEF is thought to develop from a 'systemic pro-inflammatory state' induced by comorbidities and accompanied with microvascular endothelial inflammation, and these elements are also involved in the etiology of PE[33, 34]. Besides the elevated prevalence of cardiac abnormalities after a preeclamptic pregnancy, a quarter of women with a history of preterm PE report symptoms like less interest, intrusive recollections, psychogenic amnesia, difficulty sleeping and concentrating problems and 17% after term PE report these symptoms[35].

It could be that the microvascular dysfunction after PE may lead to cognitive impairment because a recent study have indicated that former preeclamptic women have greater changes in temporal white matter and lower cortical gray matter volume in comparison with women with a normotensive pregnancy in the past[36]. However, the earlier mentioned symptoms of cognitive impairment are similar to those patients in the general population with chronic heart failure[37]. If we take this into account, the CV deterioration in women with a history of PE is probably related to an underlying microvascular dysfunction which could be worsened by untreated (pre)hypertension, probably sooner than matched women who had normotensive pregnancies.

HEART FAILURE STAGE B AFTER PREECLAMPSIA

The cardiovascular risk factors, that are increased after a preeclamptic pregnancy[38-41] could influence the PE-induced cardiac remodeling resolving process. We observed in our study, a prevalence of 23% of HF-B at 1 and 4 years postpartum in former preeclamptic women. The same prevalence at both timepoints suggest a persistent cardiac function, however there is a shift in women who are recovering of this disease between the two timepoints (more than 60%) and women who developed HF-B (about 20%). Moreover, the prevalence of either diastolic or systolic dysfunction were different at both timepoints.

We suggest that diastolic dysfunction, the most prevalent form of HF-B in our women at 4 years postpartum, could be a more persistent condition compared to the systolic dysfunction variant. HF can be subdivided in a reduced ejection fraction (HFrEF) or with a preserved EF (HFpEF), where women outnumber men (2:1 ratio)[42]. The prevalence of subclinical HFpEF increased more than two-fold, between 1 and 4 years postpartum. It is tempting to speculate that the shift in concentric remodeling between both visits and the borderline significant increase of HFpEF demonstrate a mechanistic response to the persistently high blood pressure that lead to an increased concentric remodeling[43]. In two of our studies, we have evaluated the relation between pressure load, volume load and endothelial function on aberrant cardiac remodeling.

RISK FACTORS FOR HEART FAILURE AFTER PREECLAMPSIA

Cardiovascular disease and preeclampsia share many classical risk factors like dyslipidemia, hyperinsulinemia, hypertension and obesity[44-46]. The increased CVD risk after preeclamptic pregnancy, could partially relate to abnormal cardiovascular risk profiles in PE women, but also partially be contributed to differences in patterns of cardiac remodeling during pregnancy and uncomplete cardiac recovery afterwards[12, 39-41]. We have mentioned already that during normotensive pregnancies, the left ventricular (LV) remodels in an eccentric way while during PE, the LV remodels in the aberrant concentric way[8, 10, 16]. Cardiac remodeling is a dynamic and progressive process, which is likely to be influenced by pressure and volume modulating medication[47-51].

After PE, many women remain having on average a persistently elevated blood pressure and decreased PV compared to healthy parous women[39-41, 52, 53]. In chapter 6 we present a longitudinal cohort study where we found that both elevated SBP as well as low plasma volume 0.8 years after delivery raised the risk on concentric remodeling at 4.8 years postpartum. These findings indicate a significant role not only for pressure load, but also volume load as indicated by plasma volume. Moreover, former PE women with a low plasma volume have an odds ratio of 4-5 to develop concentric remodeling and with it heart failure stage B. Our observations suggest that it should be re-evaluated whether diuretics are the most suitable therapy for lowering the blood pressure in formerly PE women, especially with already diminished PV.

Many studies showed that PE is associated with endothelial dysfunction that may persist during the first years after PE[34, 54-66]. This is in line with our findings (chapter 5) in which we showed a lower endothelial function, measured with flow mediated dilation (FMD) at 4 years postpartum compared to healthy controls. On the other hand endothelial dysfunction is also correlated with symptomatic heart failure[67, 68]. In our study, we found that PE was indeed independently associated with reduced flow mediated dilation

(FMD) after adjusting for metabolic risk factors. Moreover, formerly PE women had an eight-fold higher prevalence of HF-A and a three-fold higher prevalence of HF-B. Nevertheless, no association was found between the prevalence of HF-A or HF-B on the one hand with endothelial dysfunction on the other hand. This was in contrast to our expectations, since we expected to find a positive relation between impaired FMD after PE and HF-B. The use of antihypertensive treatment in part of individuals of the HF-B group may have attenuated the differences in endothelial function between the HF-B group and the other groups. In fact, antihypertensive treatment may reverse cardiac remodeling, enhance cardiac function and improve endothelial function either by reducing afterload, shear stress or by improvement of volume load[32, 69]. However, it is in line with previous research that endothelial dysfunction was not associated with differences in LV geometric patterns[70]. Moreover, maybe we are looking at a different type of heart failure seen in these women. FMD is giving us information about the macrovascular system, but it could be that we are looking at a microvascular problem in these preeclamptic women.

CARDIOVASCULAR DISEASE RISK AFTER PREECLAMPSIA

CVD disease is the number one cause of death in women[71, 72]. Until now it is unknown whether PE itself as a gender specific disorder increases this CVD risk independently or whether it is a result of risk factors that are known to be associated with both CVD and PE. Women with a previous preeclampsia demonstrate more often constituents of the metabolic syndrome, like insulin resistance, hypertension, dyslipidemia, obesity and micro-albuminuria compared to women with a healthy pregnancy[38-41]. These risk factors may be modifiable when detected in time[73], underscoring the importance of cardiovascular follow-up in these specific group of young women. It could be favorable to estimate the person-specific CVD risk in former preeclamptic women. Currently, no tailored risk score is available to determine the cardiovascular disease risk in women with a history of preeclampsia. In other risk populations, several risk scores are applicable and have been proven of predictive value. The Framingham risk score calculator is the most widely used and well validated strategy to assess personalized risk[74, 75]. In chapter 3 we aimed to compare to CVD predicted risk in the next 10- and 30- years (computed with the Framingham risk score calculator) between women with a history of PE and women with an uncomplicated pregnancy in the past and subsequently compared subgroups within the former PE group based on onset of disease and/or whether hypertension was developed.

Against our expectations, as group, women with a history of PE had comparable risk estimates compared to healthy parous controls. Other risk factors that are known to be increased after PE (e.g. cholesterol, BMI), except for hypertension, did not contribute substantially to the modelled CVD increased risk in our studied population. However,

treated hypertensive women with a history of PE had a twofold CVD risk, compared to both normotensive formerly PE women and controls. Moreover, we found the highest prevalence of hypertension after early-onset PE. Our results suggest that the increased risk of CVD after PE is primarily related to blood pressure control and not with subclinical classical cardiovascular risk factors. Our study is a translation of the increased CVD risk after PE to a predicting risk score to the patient. Our findings stress again the importance of CVD screening and follow-up in former PE patients with a special focus on early-onset PE and blood pressure measurement and treatment

The Framingham risk score is the most compared risk calculator and widely used in North American countries[76]. There are also other risk models for ischemic heart disease (IHD) and stroke, which are SCORE, CUORE and the Reynolds risk score[76, 77]. Of the different risk models, the Framingham risk score is the only model to predict the 10- and 30- year CVD risk[78]. Nevertheless, the Framingham risk score has not been validated in women with a history of PE. Maybe this risk score is not fully applicable in this specific group. Although we were unable to substantiate an intrinsic detrimental effect of PE itself on remote CV health, we cannot completely rule out PE to be an independent risk factor for CVD that should be included in the CVD risk prediction independent of other conventional risk factors.

Originally, the Framingham risk prediction calculator is developed using older population of men and women[79], and may not be immediately applicable into our study population with women with an average age of 37 years. So it could be that the risk prediction may underestimate the risk score in our population. To determine alternate cut-offs for the 10-year and 30-year risk estimates for CV events, a very long-term follow-up would be required of a large cohort of postpartum women.

CARDIOVASCULAR RISK MANAGEMENT AFTER PREECLAMPSIA

Although we know that former PE women have this increased CVD risk, a careful follow-up program is still not implemented. It is not known how much time after the pregnancy, women should be examined to rule out the pregnancy-induced alterations in the cardiovascular system. Earlier research have noted that former preeclamptic women may benefit of a cardiovascular screening for cardiovascular disease at 1 -2 years postpartum[7]. Our studies suggest that it is necessary that it may be indicated that women should have an additional assessment a few years later, regarding the high prevalence of heart failure stage B a few years later and because women shift from no HF to heart failure stage B and vice versa in these years. The outcomes of the follow-up measurements should be used to counsel these women, with a long-term risk management plan and advice. Nijdam *et al.* concluded in 2009 that the follow-up of former preeclamptic women is insufficient

and undeveloped in the primary care in the Netherlands[80]. To date, there is an increasing number of obstetricians that would advise women after preeclampsia on preventive interventions like blood pressure measurements and increasing their physical activity[81]. However, when we look at the percentages (46-65% advised yearly blood pressure measurements in 2014 for late and early preeclampsia, respectively) there are still possibilities to improve the awareness for reducing CVD[81]. Almost half of the gynecologists still miss an chance in CVD counseling and management in former PE women[81]. We should consider a structured follow-up path for these women and create more awareness to address the relevance of a CVD screening, not only for the general practitioners and obstetricians but also for women involved.

CONCLUSION

Taken together, our findings underscore the cardiovascular complications during and after a preeclamptic pregnancy. Although almost only Caucasian women were studied, making generalizability not applicable to all women, the studies in this thesis provide experimental evidence for a high prevalence of endothelial dysfunction and features of the metabolic syndrome in former PE patients a few years postpartum. Heart failure stage B was prevalent in 1 out of 4 former PE patients. Moreover, we showed that these women had a low volume and high pressure load, all associated with heart failure stage B. Especially, hypertensive young women after a preeclamptic pregnancy had higher predicted cardiovascular risk score in the next 10-30 years. It is important that former preeclamptic women should have a CVD screening and follow-up, with a special focus on blood pressure and echocardiography measuring systolic and diastolic function. Importantly, these risk assessments should not only be offered to these women 1 year after their complicated pregnancy, but our results showed that an additional assessment a few years later is also necessary.

FUTURE PERSPECTIVES

Even though the survival rates of clinical HF have improved over time, within 5 years after diagnosis the absolute mortality rates of HF remain approximately 50%[30]. To date, there is no proven effective treatment in patients with clinical HFpEF in randomized clinical trials[82]. HF, especially in women, significantly decrease quality of life, specifically in the domains of physical functioning, vitality, mental health, wellbeing and depressive symptoms[83]. There are therapeutic agents to intervene in the CV continuum, like angiotensin converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs)

which can modify the process of cardiac remodeling by influencing the cascade of renin-angiotensin system[84]. There is no difference between ARBs and ACE inhibitors in total mortality or cardiovascular outcomes in people with primary hypertension, however ARBs can cause slightly fewer adverse effects compared to ACE inhibitors[85]. On the other hand, ACE inhibitors are less expensive than ARBs.

Hence, preventing the transition between asymptomatic HF to clinical overt HF is paramount in improving disease prognosis at the moment.

At present, we still not have a complete understanding of the pathophysiology link between preeclampsia and cardiovascular disease. Whether PE induces CVD or whether PE and CVD are a common vascular result of the same susceptibility, needs to be unraveled. When we enhance our knowledge, the screening and management of these former preeclamptic women will improve to prevent or stop the progression of cardiovascular disease in relatively young women. In order to get a better interpretation of the link between PE and CVD and the corresponding cardiovascular risk factors, a large cohort of women should have a cardiovascular screening before, during and after their pregnancy. With the help of the outcomes of this series, a new research program has been developed in Maastricht; the Queen of Hearts study. This study has started to include a large cohort of women with a healthy pregnancy in the past and women with a history of preeclampsia to examine biomarkers and cardiovascular risk factors. This trial will allow us to make an early identification in a preclinical stage of CVD in high-risk women. Other trials have been added to the Queen of Hearts study in order to determine whether pharmacological therapy is effective at preventing progression or development towards heart failure in former preeclamptic women. With these results, we hopefully get a better understanding to prevent cardiovascular disease in these relatively young women.

REFERENCES

1. Roberts JM and Cooper DW. Pathogenesis and genetics of pre-eclampsia. *Lancet*. 2001;357:53-6.
2. Bellamy L, Casas JP, Hingorani AD and Williams DJ. Pre-eclampsia and risk of cardiovascular disease and cancer in later life: systematic review and meta-analysis. *BMJ (Clinical research ed)*. 2007;335:974.
3. Granger JP, Alexander BT, Llinas MT, Bennett WA and Khalil RA. Pathophysiology of preeclampsia: linking placental ischemia/hypoxia with microvascular dysfunction. *Microcirculation*. 2002;9:147-60.
4. Stekkinger E, Zandstra M, Peeters LL and Spaanderman ME. Early-onset preeclampsia and the prevalence of postpartum metabolic syndrome. *Obstetrics and gynecology*. 2009;114:1076-84.
5. Zandstra M, Stekkinger E, van der Vlugt MJ, van Dijk AP, Lotgering FK and Spaanderman ME. Cardiac diastolic dysfunction and metabolic syndrome in young women after placental syndrome. *Obstetrics and gynecology*. 2010;115:101-8.
6. Ray JG, Vermeulen MJ, Schull MJ, McDonald S and Redelmeier DA. Metabolic syndrome and the risk of placental dysfunction. *Journal of obstetrics and gynaecology Canada : JOGC = Journal d'obstetrique et gynecologie du Canada : JOGC*. 2005;27:1095-101.
7. Melchiorre K, Sutherland GR, Liberati M and Thilaganathan B. Preeclampsia is associated with persistent postpartum cardiovascular impairment. *Hypertension*. 2011;58:709-15.
8. Simmons LA, Gillin AG and Jeremy RW. Structural and functional changes in left ventricle during normotensive and preeclamptic pregnancy. *American journal of physiology Heart and circulatory physiology*. 2002;283:H1627-33.
9. Duvekot JJ, Cheriex EC, Pieters FA, Menheere PP and Peeters LH. Early pregnancy changes in hemodynamics and volume homeostasis are consecutive adjustments triggered by a primary fall in systemic vascular tone. *American journal of obstetrics and gynecology*. 1993;169:1382-92.
10. Ghossein-Doha C, Hooijschuur MCE and Spaanderman MEA. Pre-Eclampsia: A Twilight Zone Between Health and Cardiovascular Disease? *Journal of the American College of Cardiology*. 2018;72:12-16.
11. Meah VL, Cockcroft JR, Backx K, Shave R and Stohr EJ. Cardiac output and related haemodynamics during pregnancy: a series of meta-analyses. *Heart (British Cardiac Society)*. 2016;102:518-26.
12. Melchiorre K, Sharma R and Thilaganathan B. Cardiovascular implications in preeclampsia: an overview. *Circulation*. 2014;130:703-14.
13. de Haas S, Ghossein-Doha C, van Kuijk SM, van Drongelen J and Spaanderman ME. Physiological adaptation of maternal plasma volume during pregnancy: a systematic review and meta-analysis. *Ultrasound in obstetrics & gynecology : the official journal of the International Society of Ultrasound in Obstetrics and Gynecology*. 2017;49:177-187.
14. Bosio PM, McKenna PJ, Conroy R and O'Herlihy C. Maternal central hemodynamics in hypertensive disorders of pregnancy. *Obstetrics and gynecology*. 1999;94:978-84.
15. Easterling TR, Benedetti TJ, Schmucker BC and Millard SP. Maternal hemodynamics in normal and preeclamptic pregnancies: a longitudinal study. *Obstetrics and gynecology*. 1990;76:1061-9.
16. De Haas S, Ghossein-Doha C, Geerts L, van Kuijk SMJ, van Drongelen J and Spaanderman MEA. Cardiac remodeling in normotensive pregnancy and in pregnancy complicated by hypertension: systematic review and meta-analysis. *Ultrasound in obstetrics & gynecology : the official journal of the International Society of Ultrasound in Obstetrics and Gynecology*. 2017;50:683-696.
17. Cantor EJ, Babick AP, Vasanji Z, Dhalla NS and Netticadan T. A comparative serial echocardiographic analysis of cardiac structure and function in rats subjected to pressure or volume overload. *Journal of molecular and cellular cardiology*. 2005;38:777-86.
18. Spinale FG. Myocardial matrix remodeling and the matrix metalloproteinases: influence on cardiac form and function. *Physiological reviews*. 2007;87:1285-342.

19. Melchiorre K, Sutherland GR, Baltabaeva A, Liberati M and Thilaganathan B. Maternal cardiac dysfunction and remodeling in women with preeclampsia at term. *Hypertension*. 2011;57:85-93.
20. Melchiorre K, Sutherland G, Sharma R, Nanni M and Thilaganathan B. Mid-gestational maternal cardiovascular profile in preterm and term pre-eclampsia: a prospective study. *BJOG : an international journal of obstetrics and gynaecology*. 2013;120:496-504.
21. Vaught AJ, Kovell LC, Szymanski LM, Mayer SA, Seifert SM, Vaidya D, Murphy JD, Argani C, O'Kelly A, York S, Ouyang P, Mukherjee M and Zakaria S. Acute Cardiac Effects of Severe Pre Eclampsia. *Journal of the American College of Cardiology*. 2018;72:1-11.
22. Valensise H, Vasapollo B, Gagliardi G and Novelli GP. Early and late preeclampsia: two different maternal hemodynamic states in the latent phase of the disease. *Hypertension*. 2008;52:873-80.
23. Melchiorre K, Sutherland GR, Watt-Coote I, Liberati M and Thilaganathan B. Severe myocardial impairment and chamber dysfunction in preterm preeclampsia. *Hypertension in pregnancy*. 2012;31:454-71.
24. Lang RM, Pridjian G, Feldman T, Neumann A, Lindheimer M and Borow KM. Left ventricular mechanics in preeclampsia. *American heart journal*. 1991;121:1768-75.
25. D'Andrea A, Radmilovic J, Ballo P, Mele D, Agricola E, Cameli M, Rossi A, Esposito R, Novo G, Mondillo S, Montisci R, Gallina S, Bossone E and Galderisi M. Left ventricular hypertrophy or storage disease? the incremental value of speckle tracking strain bull's-eye. *Echocardiography (Mount Kisco, NY)*. 2017;34:746-759.
26. Cong J, Fan T, Yang X, Shen J, Cheng G and Zhang Z. Maternal cardiac remodeling and dysfunction in preeclampsia: a three-dimensional speckle-tracking echocardiography study. *The international journal of cardiovascular imaging*. 2015;31:1361-8.
27. Jessup M, Abraham WT, Casey DE, Feldman AM, Francis GS, Ganiats TG, Konstam MA, Mancini DM, Rahko PS, Silver MA, Stevenson LW and Yancy CW. 2009 focused update: ACCF/AHA Guidelines for the Diagnosis and Management of Heart Failure in Adults: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines: developed in collaboration with the International Society for Heart and Lung Transplantation. *Circulation*. 2009;119:1977-2016.
28. Ghossein-Doha C, Khalil A and Lees CC. Maternal hemodynamics: a 2017 update. *Ultrasound in obstetrics & gynecology : the official journal of the International Society of Ultrasound in Obstetrics and Gynecology*. 2017;49:10-14.
29. Ammar KA, Jacobsen SJ, Mahoney DW, Kors JA, Redfield MM, Burnett JC, Jr. and Rodeheffer RJ. Prevalence and prognostic significance of heart failure stages: application of the American College of Cardiology/American Heart Association heart failure staging criteria in the community. *Circulation*. 2007;115:1563-70.
30. Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE, Jr., Drazner MH, Fonarow GC, Geraci SA, Horwich T, Januzzi JL, Johnson MR, Kasper EK, Levy WC, Masoudi FA, McBride PE, McMurray JJ, Mitchell JE, Peterson PN, Riegel B, Sam F, Stevenson LW, Tang WH, Tsai EJ, Wilkoff BL, American College of Cardiology F and American Heart Association Task Force on Practice G. 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *Journal of the American College of Cardiology*. 2013;62:e147-239.
31. Jong P, Yusuf S, Rousseau MF, Ahn SA and Bangdiwala SI. Effect of enalapril on 12-year survival and life expectancy in patients with left ventricular systolic dysfunction: a follow-up study. *Lancet*. 2003;361:1843-8.
32. Goldberg LR and Jessup M. Stage B heart failure: management of asymptomatic left ventricular systolic dysfunction. *Circulation*. 2006;113:2851-60.

33. Paulus WJ and Tschope C. A novel paradigm for heart failure with preserved ejection fraction: comorbidities drive myocardial dysfunction and remodeling through coronary microvascular endothelial inflammation. *Journal of the American College of Cardiology*. 2013;62:263-71.
34. Powe CE, Levine RJ and Karumanchi SA. Preeclampsia, a disease of the maternal endothelium: the role of antiangiogenic factors and implications for later cardiovascular disease. *Circulation*. 2011;123:2856-69.
35. Engelhard IM, van Rij M, Boullart I, Ekhart TH, Spaanderman ME, van den Hout MA and Peeters LL. Posttraumatic stress disorder after pre-eclampsia: an exploratory study. *General hospital psychiatry*. 2002;24:260-4.
36. Siepmann T, Boardman H, Bilderbeck A, Griffanti L, Kenworthy Y, Zwager C, McKean D, Francis J, Neubauer S, Yu GZ, Lewandowski AJ, Sverrisdottir YB and Leeson P. Long-term cerebral white and gray matter changes after preeclampsia. *Neurology*. 2017;88:1256-1264.
37. Bennett SJ and Sauve MJ. Cognitive deficits in patients with heart failure: a review of the literature. *The Journal of cardiovascular nursing*. 2003;18:219-42.
38. van Rijn BB, Nijdam ME, Bruinse HW, Roest M, Uiterwaal CS, Grobbee DE, Bots ML and Franx A. Cardiovascular disease risk factors in women with a history of early-onset preeclampsia. *Obstetrics and gynecology*. 2013;121:1040-8.
39. Smith GN, Walker MC, Liu A, Wen SW, Swansburg M, Ramshaw H, White RR, Roddy M and Hladunewich M. A history of preeclampsia identifies women who have underlying cardiovascular risk factors. *American journal of obstetrics and gynecology*. 2009;200:58.e1-8.
40. Manten GT, Sikkema MJ, Voorbij HA, Visser GH, Bruinse HW and Franx A. Risk factors for cardiovascular disease in women with a history of pregnancy complicated by preeclampsia or intrauterine growth restriction. *Hypertension in pregnancy*. 2007;26:39-50.
41. Hermes W, Franx A, van Pampus MG, Bloemenkamp KW, Bots ML, van der Post JA, Porath M, Ponjee GA, Tamsma JT, Mol BW and de Groot CJ. Cardiovascular risk factors in women who had hypertensive disorders late in pregnancy: a cohort study. *American journal of obstetrics and gynecology*. 2013;208:474.e1-8.
42. Scantlebury DC and Borlaug BA. Why are women more likely than men to develop heart failure with preserved ejection fraction? *Current opinion in cardiology*. 2011;26:562-8.
43. Ghossein-Doha C, Spaanderman M, van Kuijk SM, Kroon AA, Delhaas T and Peeters L. Long Term Risk to Develop Hypertension in Women With Former Preeclampsia: A Longitudinal Pilot Study. *Reproductive sciences (Thousand Oaks, Calif)*. 2014;21:846-853.
44. English FA, Kenny LC and McCarthy FP. Risk factors and effective management of preeclampsia. *Integrated blood pressure control*. 2015;8:7-12.
45. Benjamin EJ, Blaha MJ, Chiuve SE, Cushman M, Das SR, Deo R, de Ferranti SD, Floyd J, Fornage M, Gillespie C, Isasi CR, Jimenez MC, Jordan LC, Judd SE, Lackland D, Lichtman JH, Lisabeth L, Liu S, Longenecker CT, Mackey RH, Matsushita K, Mozaffarian D, Mussolino ME, Nasir K, Neumar RW, Palaniappan L, Pandey DK, Thiagarajan RR, Reeves MJ, Ritchey M, Rodriguez CJ, Roth GA, Rosamond WD, Sasson C, Towfighi A, Tsao CW, Turner MB, Virani SS, Voeks JH, Willey JZ, Wilkins JT, Wu JH, Alger HM, Wong SS and Muntner P. Heart Disease and Stroke Statistics-2017 Update: A Report From the American Heart Association. *Circulation*. 2017;135:e146-e603.
46. Craici I, Wagner S and Garovic VD. Preeclampsia and future cardiovascular risk: formal risk factor or failed stress test? *Therapeutic advances in cardiovascular disease*. 2008;2:249-59.
47. Yasumoto K, Takata M, Ueno H, Tomoda F and Inoue H. Relation of circulating blood volume to left ventricular geometry in essential hypertension. *Hypertension research : official journal of the Japanese Society of Hypertension*. 2002;25:703-10.

48. Grossman W, Jones D and McLaurin LP. Wall stress and patterns of hypertrophy in the human left ventricle. *J Clin Invest*. 1975;56:56-64.
49. Burnier M. Angiotensin II type 1 receptor blockers. *Circulation*. 2001;103:904-12.
50. Paul M, Poyan Mehr A and Kreutz R. Physiology of local renin-angiotensin systems. *Physiological reviews*. 2006;86:747-803.
51. Matchar DB, McCrory DC, Orlando LA, Patel MR, Patel UD, Patwardhan MB, Powers B, Samsa GP and Gray RN. Systematic review: comparative effectiveness of angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers for treating essential hypertension. *Annals of internal medicine*. 2008;148:16-29.
52. Spaanderman ME, Ekhart TH, van Eyck J, Cheriex EC, de Leeuw PW and Peeters LL. Latent hemodynamic abnormalities in symptom-free women with a history of preeclampsia. *American journal of obstetrics and gynecology*. 2000;182:101-7.
53. Aardenburg R, Spaanderman ME, Ekhart TH, van Eijndhoven HW, van der Heijden OW and Peeters LL. Low plasma volume following pregnancy complicated by pre-eclampsia predisposes for hypertensive disease in a next pregnancy. *British journal of obstetrics and gynaecology*. 2003;110:1001 6.
54. Roberts JM and Gammill HS. Preeclampsia: recent insights. *Hypertension*. 2005;46:1243-9.
55. Brennan LJ, Morton JS and Davidge ST. Vascular dysfunction in preeclampsia. *Microcirculation*. 2014;21:4-14.
56. Roberts JM. Endothelial dysfunction in preeclampsia. *Seminars in reproductive endocrinology*. 1998;16:5-15.
57. Weissgerber TL. Flow-mediated dilation: can new approaches provide greater mechanistic insight into vascular dysfunction in preeclampsia and other diseases? *Current hypertension reports*. 2014;16:487.
58. Weissgerber TL, Milic NM, Milin-Lazovic JS and Garovic VD. Impaired Flow-Mediated Dilation Before, During, and After Preeclampsia: A Systematic Review and Meta-Analysis. *Hypertension*. 2016;67:415-23.
59. Chambers JC, Fusi L, Malik IS, Haskard DO, De Swiet M and Kooner JS. Association of maternal endothelial dysfunction with preeclampsia. *Jama*. 2001;285:1607-12.
60. Tyldum EV, Backe B, Stoylen A and Slordahl SA. Maternal left ventricular and endothelial functions in preeclampsia. *Acta obstetricia et gynecologica Scandinavica*. 2012;91:566-73.
61. Hamad RR, Eriksson MJ, Silveira A, Hamsten A and Bremme K. Decreased flow-mediated dilation is present 1 year after a pre-eclamptic pregnancy. *Journal of hypertension*. 2007;25:2301-7.
62. Hamad RR, Eriksson MJ, Berg E, Larsson A and Bremme K. Impaired endothelial function and elevated levels of pentraxin 3 in early-onset preeclampsia. *Acta obstetricia et gynecologica Scandinavica*. 2012;91:50-6.
63. Goynumer G, Yucel N, Adali E, Tan T, Baskent E and Karadag C. Vascular risk in women with a history of severe preeclampsia. *Journal of clinical ultrasound : JCU*. 2013;41:145-50.
64. Germain AM, Romanik MC, Guerra I, Solari S, Reyes MS, Johnson RJ, Price K, Karumanchi SA and Valdes G. Endothelial dysfunction: a link among preeclampsia, recurrent pregnancy loss, and future cardiovascular events? *Hypertension*. 2007;49:90-5.
65. Paez O, Alfie J, Gorosito M, Puleio P, de Maria M, Prieto N and Majul C. Parallel decrease in arterial distensibility and in endothelium-dependent dilatation in young women with a history of pre-eclampsia. *Clin Exp Hypertens*. 2009;31:544-52.
66. Scholten RR, Thijssen DJ, Lotgering FK, Hopman MT and Spaanderman ME. Cardiovascular effects of aerobic exercise training in formerly preeclamptic women and healthy parous control subjects. *American journal of obstetrics and gynecology*. 2014;211:516.e1-516.e11.
67. Brunner H, Cockcroft JR, Deanfield J, Donald A, Ferrannini E, Halcox J, Kiowski W, Luscher TF, Mancia G, Natali A, Oliver JJ, Pessina AC, Rizzoni D, Rossi GP, Salvetti A, Spieker LE, Taddei S and Webb DJ.

Endothelial function and dysfunction. Part II: Association with cardiovascular risk factors and diseases. A statement by the Working Group on Endothelins and Endothelial Factors of theEuropean Society of Hypertension. *Journal of hypertension*. 2005;23:233-46.

68. Marti CN, Gheorghiade M, Kalogeropoulos AP, Georgiopoulou VV, Quyyumi AA and Butler J. Endothelial dysfunction, arterial stiffness, and heart failure. *Journal of the American College of Cardiology*. 2012;60:1455-69.
69. Virdis A, Ghiadoni L and Taddei S. Effects of antihypertensive treatment on endothelial function. *Current hypertension reports*. 2011;13:276-81.
70. Muiesan ML, Salvetti M, Monteduro C, Corbellini C, Guelfi D, Rizzoni D, Castellano M and Agabiti-Rosei E. Flow-mediated dilatation of the brachial artery and left ventricular geometry in hypertensive patients. *Journal of hypertension*. 2001;19:641-7.
71. Go AS, Mozaffarian D, Roger VL, Benjamin EJ, Berry JD, Blaha MJ, Dai S, Ford ES, Fox CS, Franco S, Fullerton HJ, Gillespie C, Hailpern SM, Heit JA, Howard VJ, Huffman MD, Judd SE, Kissela BM, Kittner SJ, Lackland DT, Lichtman JH, Lisabeth LD, Mackey RH, Magid DJ, Marcus GM, Marelli A, Matchar DB, McGuire DK, Mohler ER, 3rd, Moy CS, Mussolino ME, Neumar RW, Nichol G, Pandey DK, Paynter NP, Reeves MJ, Sorlie PD, Stein J, Towfighi A, Turan TN, Virani SS, Wong ND, Woo D, Turner MB, American Heart Association Statistics C and Stroke Statistics S. Heart disease and stroke statistics--2014 update: a report from the American Heart Association. *Circulation*. 2014;129:e28-e292.
72. Mosca L, Barrett-Connor E and Wenger NK. Sex/gender differences in cardiovascular disease prevention: what a difference a decade makes. *Circulation*. 2011;124:2145-54.
73. Brown MC, Best KE, Pearce MS, Waugh J, Robson SC and Bell R. Cardiovascular disease risk in women with pre-eclampsia: systematic review and meta-analysis. *European journal of epidemiology*. 2013;28:1-19.
74. Wilson PW, D'Agostino RB, Levy D, Belanger AM, Silbershatz H and Kannel WB. Prediction of coronary heart disease using risk factor categories. *Circulation*. 1998;97:1837-47.
75. Greenland P, Alpert JS, Beller GA, Benjamin EJ, Budoff MJ, Fayad ZA, Foster E, Hlatky MA, Hodgson JM, Kushner FG, Lauer MS, Shaw LJ, Smith SC, Jr., Taylor AJ, Weintraub WS, Wenger NK, Jacobs AK, Smith SC, Jr., Anderson JL, Albert N, Buller CE, Creager MA, Ettinger SM, Guyton RA, Halperin JL, Hochman JS, Kushner FG, Nishimura R, Ohman EM, Page RL, Stevenson WG, Tarkington LG and Yancy CW. 2010 ACCF/AHA guideline for assessment of cardiovascular risk in asymptomatic adults: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *Journal of the American College of Cardiology*. 2010;56:e50-103.
76. Hermes W, Tamsma JT, Grootendorst DC, Franx A, van der Post J, van Pampus MG, Bloemenkamp KW, Porath M, Mol BW and de Groot CJ. Cardiovascular risk estimation in women with a history of hypertensive pregnancy disorders at term: a longitudinal follow-up study. *BMC pregnancy and childbirth*. 2013;13:126.
77. Berks D, Hoedjes M, Raat H, Duvekot JJ, Steegers EA and Habbema JD. Risk of cardiovascular disease after pre-eclampsia and the effect of lifestyle interventions: a literature-based study. *BJOG : an international journal of obstetrics and gynaecology*. 2013;120:924-31.
78. Pencina MJ, D'Agostino RB, Sr., Larson MG, Massaro JM and Vasan RS. Predicting the 30-year risk of cardiovascular disease: the framingham heart study. *Circulation*. 2009;119:3078-84.
79. D'Agostino RB, Sr., Vasan RS, Pencina MJ, Wolf PA, Cobain M, Massaro JM and Kannel WB. General cardiovascular risk profile for use in primary care: the Framingham Heart Study. *Circulation*. 2008;117:743-53.
80. Nijdam ME, Timmerman MR, Franx A, Bruinse HW, Numans ME, Grobbee DE and Bots ML. Cardiovascular risk factor assessment after pre-eclampsia in primary care. *BMC family practice*. 2009;10:77.

81. van Kesteren F, Visser S, Hermes W, Teunissen PW, Franx A, van Pampus MG, Mol BW and de Groot CJ. Counselling and management of cardiovascular risk factors after preeclampsia. *Hypertension in pregnancy*. 2016;35:55-61.
82. Andersen MJ and Borlaug BA. Heart failure with preserved ejection fraction: current understandings and challenges. *Current cardiology reports*. 2014;16:501.
83. Lesman-Leegte I, Jaarsma T, Coyne JC, Hillege HL, Van Veldhuisen DJ and Sanderman R. Quality of life and depressive symptoms in the elderly: a comparison between patients with heart failure and age- and gender-matched community controls. *Journal of cardiac failure*. 2009;15:17-23.
84. Ferrario CM. Cardiac remodelling and RAS inhibition. *Therapeutic advances in cardiovascular disease*. 2016;10:162-71.
85. Li EC, Heran BS and Wright JM. Angiotensin converting enzyme (ACE) inhibitors versus angiotensin receptor blockers for primary hypertension. *The Cochrane database of systematic reviews*. 2014:Cd009096.

Factsheet

Deze factsheet zal worden gepubliceerd bij de hart voor HELLP stichting. Deze stichting zet zich in voor meer begrip, (h)erkenning en acceptatie voor vrouwen die pre-eclampsie en/of het HELLP syndroom hebben gehad.

INLEIDING

Vrouwen die **zwangerschapsvergiftiging/pre-eclampsie** hebben ontwikkeld, hebben een groter risico op hart- en vaatziekten (HVZ)[1]. In deze factsheet zullen nieuwe conclusies gepresenteerd worden, aan de hand van recent promotie-onderzoek.

RISICO OP HART- EN VAATZIEKTEN NA DE ZWANGERSCHAP

- Aan de hand van een risico-score is uitgerekend wat het risico is op hart- en vaatziekten bij vrouwen die pre-eclampsie hebben gehad en een controle groep, die een ongecompliceerde zwangerschap hebben gehad (zie Tabel 1). Het risico is 5-10 jaar na de zwangerschap berekend, gebaseerd op lipidenwaardes van deze vrouwen. Het risico op HVZ is gelijk voor de controle groep, in vergelijking met de pre-eclampsie groep (Tabel 1)[2].
- Daarna is de groep pre-eclampsie vrouwen verdeeld in een groep zonder bloeddrukverlagende medicatie (normotensief) en met bloeddrukmedicatie (hypertensief) (Tabel 1)[2].
- Het risico op hart- en vaatziekten is twee keer zo groot voor de pre-eclampsie groep met hypertensie (Tabel 1)[2].
- Bijna 1 op de 5 voormalig pre-eclampsie patiënten was hypertensief en had dus een hoger HVZ risico[2].

Tabel 1. Risicoscores voor HVZ.

	Controle groep	Pre-eclampsie groep	Pre-eclampsie, normotensief	Pre-eclampsie, hypertensief
10 jaar HVZ risico	1.5%	1.6%	1.5%	3.1%
30 jaar HVZ risico	9.0%	9.0%	8.0%	19.0%

HVZ = hart- en vaatziekten, normotensief = geen bloeddrukverlagende medicatie, hypertensief = wel bloeddrukverlagende medicatie.

RISICO OP HARTFALEN NA DE PE ZWANGERSCHAP

Hartfalen – Prevalentie

- Hartfalen kan worden verdeeld in vier stadia (Tabel 2)[3].
- 23% van de vrouwen heeft op 1 en 4 jaar na de bevalling hartfalen stadium B[4].

Tabel 2. Hartfalen stadia.

	Hartfalen stadium A	Hartfalen stadium B	Hartfalen stadium C	Hartfalen stadium C
Kenmerken	Risicofactoren	Structurele afwijkingen aan het hart, geen symptomen	Structurele afwijkingen aan het hart, wel symptomen	Aanhoudend hartfalen waarvoor speciale zorg nodig is

Hartfalen - Endotheelfunctie

- Pre-eclampsie is een aandoening van de vaatwand (endotheel)[5].
- De endotheelfunctie (functie van de vaatwand) is 4 jaar na de zwangerschap minder goed in vergelijking met vrouwen, die een ongecompliceerde zwangerschap hebben gehad.
- Vrouwen met pre-eclampsie hadden een 8 keer hogere kans op Hartfalen stadium A (voor uitleg stadia zie Tabel 2)[6].
- Vrouwen met pre-eclampsie hadden een 3 keer hogere kans op Hartfalen stadium B (voor uitleg stadia zie Tabel 2)[6].
- De endotheelfunctie was niet slechter bij vrouwen met hartfalen stadium A en/ of hartfalen stadium B in vergelijking met controle vrouwen[6]. Dit suggereert dat er mogelijk andere mechanismes dan de functie van de vaatwand zijn, die bijdragen aan hartfalen stadium B bij deze vrouwen.

Hartfalen – Plasma volume

- Bloedplasma is een onderdeel van het totale volume aan bloed in het lichaam en bestaat uit water met daarin opgeloste zouten en eiwitten[7].
- Na de pre-eclampsie zwangerschap, hebben deze vrouwen een lager plasma volume vergeleken met vrouwen, die een ongecompliceerde zwangerschap hebben gehad[8].
- Een lager plasmavolume en een hoge bloeddruk gemeten 0.8 jaar na de zwangerschap was gerelateerd aan meer hartfalen stadium B 4.8 jaar na de zwangerschap[9].
- Mocht een vrouw na de zwangerschap nog steeds een hoge bloeddruk hebben, moet er goed nagedacht worden wanneer er met bloeddrukverlagers gestart dient te worden. Middelen die een gunstig effect hebben op de hartstructuur (ACE-remmers of angiotensine receptor blokkers) verdienen een voorkeur.

CONCLUSIE

- Tijdens de zwangerschap past het hart zich anders aan bij vrouwen met pre-eclampsie, in vergelijking met vrouwen, die een ongecompliceerde zwangerschap hebben gehad.
- Vrouwen met pre-eclampsie hebben een sterk verhoogd risico op het krijgen van hartfalen en daarmee hart- en vaatziekten op een relatief jonge leeftijd.

- Een zorgvuldige follow-up is belangrijk met speciale aandacht voor bloeddruk en echocardiografie.
- Een follow-up meting 1 jaar na de zwangerschap is belangrijk, maar recente resultaten laten zien, dat een aanvullende follow-up meting een aantal jaar later ook noodzakelijk is.

REFERENTIES

1. Bellamy L, Casas JP, Hingorani AD and Williams DJ. Pre-eclampsia and risk of cardiovascular disease and cancer in later life: systematic review and meta-analysis. *BMJ (Clinical research ed)*. 2007;335:974.
2. Breetveld NM, Ghossein-Doha C, van Kuijk SMJ, van Dijk AP, van der Vlugt MJ, Heidema WM, Scholten RR and Spaanderman MEA. Cardiovascular disease risk is only elevated in hypertensive, Formerly pre-eclamptic women. *BJOG*. 2015;122:1092-1100.
3. Jessup M, Abraham WT, Casey DE, Feldman AM, Francis GS, Ganiats TG, Konstam MA, Mancini DM, Rahko PS, Silver MA, Stevenson LW and Yancy CW. 2009 focused update: ACCF/AHA Guidelines for the Diagnosis and Management of Heart Failure in Adults: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines: developed in collaboration with the International Society for Heart and Lung Transplantation. *Circulation*. 2009;119:1977-2016.
4. Breetveld NM, Ghossein-Doha C, van Kuijk SMJ, van Dijk AP, van der Vlugt MJ, Heidema WM, van Neer J, van Empel V, Brunner-LA Rocca H.P, Scholten RR and Spaanderman MEA. Prevalence of asymptomatic heart failure in formerly pre-eclamptic women: A cohort study. *Ultrasound Obstet Gynecol.* 2017;49:134-142.
5. Roberts JM, Gammill HS. Preeclampsia: Recent insights. *Hypertension* 2005; 46: 1243–1249
6. Breetveld NM, Ghossein-Doha C, Sengers MJJM, Geerts L, van Kuijk SMJ, van Dijk AP, van der Vlugt MJ, Heidema WM, Brunner-LA Rocca H.P, Scholten RR and Spaanderman MEA. Decreased endothelial function and increased subclinical heart failure in women several years after pre-eclampsia. *Ultrasound Obstet Gynecol.* 2018; 52;196-204
7. Website Hematologie Nederland. https://hematologienederland.nl/patientinfo/wat-is-hematologie/. NVvH. 11-03-2020.
8. Spaanderman ME, Ekhart TH, van Eyck J, Cheriex EC, de Leeuw PW and Peeters LL. Latent hemodynamic abnormalities in symptom-free women with a history of preeclampsia. *American journal of obstetrics and gynecology*. 2000;182:101-7.
9. Breetveld NM, Alers RJ, Geerts L, van Kuijk SMJ, van Dijk AP, van der Vlugt MJ, Heidema WM, van Neer J, van Empel VPM, Brunner-La Rocca H.P, Scholten RR, Ghossein-Doha C and Spaanderman MEA. Low plasma volume and increased pressure load relate to concentric left ventricular remodeling after preeclampsia; a longitudinal study. *Accepted for publication in JAHA, journal of the American Heart Association.*

List of publications

N.M. Breetveld, C. Ghossein-Doha, S.M.J van Kuijk, A.P. van Dijk, M.J. van der Vlugt, W.M. Heidema, R.R. Scholten, M.E.A Spaanderman. Cardiovascular disease is only elevated in hypertensive, formerly preeclamptic women. *British journal of obstetrics and gynaecology*. 2015 Jul;122(8):1092-1100. doi: 10.1111/1471-0528.13057.

N.M. Breetveld, C. Ghossein-Doha, S.M.J. van Kuijk, A.P. van Dijk, M.J. van der Vlugt, W.M. Heidema, J. van Neer, V. van Empel, H.P. Brunner-La Rocca, R.R. Scholten. M.E.A. Spaanderman. Prevalence of asymptomatic heart failure in formerly pre-eclamptic women: a cohort study. *Ultrasound in Obstetrics & Gynecology*. 2017 Jan; 49(1):134-142. doi: 10.1002/uog.16014.

C. Ghossein-Doha, J. van Neer, B. Wissink, **N.M. Breetveld**, L.J. de Windt, A.P.J. van Dijk, M.J. van der Vlugt, M.C.H. Janssen, W.M. Heidema, R.R. Scholten. M.E.A. Spaanderman. Pre-eclampsia: an important risk factor for asymptomatic heart failure. *Ultrasound in Obstetrics & Gynecology*. 2017 Jan;49(1):143-149. doi: 10.1002/uog.17343.

N.M. Breetveld, C. Ghossein-Doha, J. van Neer, M.J.J.M Sengers, L. Geerts, S.M.J van Kuijk, A.P. van Dijk, M.J. van der Vlugt, W.M. Heidema, H.P. Brunner-La Rocca, R.R. Scholten, M.E.A. Spaanderman. Decreased endothelial function and increased subclinical heart failure in women several years after pre-eclampsia. *Ultrasound in Obstetrics & Gynecology.* 2018 Aug;52(2): 196-204. doi: 10.1002/uog.17534.

N.M. Breetveld, R.J. Alers, L. Geerts, S.M.J van Kuijk, A.P. van Dijk, M.J. van der Vlugt, W.M. Heidema, J. van Neer, V.P.M. van Empel, H.P. Brunner-La Rocca, R.R. Scholten, C. Ghossein-Doha, M.E.A Spaanderman. Low plasma volume and increased pressure load relate to concentric left ventricular remodeling after preeclampsia; a longitudinal study. *Accepted for publication in JAHA, journal of the American Heart Association.*

S. de Haas, **N.M. Breetveld**, L. Geerts, S.M.J van Kuijk, J. van Drongelen, Z. Mohseni, M.E.A. Spaanderman, C. Ghossein-Doha. Adaptation of cardiac systolic function to pregnancy: a systematic review and meta-analysis. *To be submitted to Journal of Hypertension.*

Samenvatting

Deze thesis beschrijft de hart- en vaatfunctie bij vrouwen tijdens en na een doorgemaakte pre-eclampsie en de relatie met het verhoogde risico op hart- en vaatziekten (HVZ) later in het leven.

In **Hoofstuk 1** wordt een algemene introductie gegeven met de doelstellingen van dit proefschrift.

In **Hoofdstuk 2** wordt de grootte en het beloop van verandering in de systolische hartfunctie tijdens de zwangerschap beschreven. Aan de hand van een meta-analyse en systemisch methodologische beoordeling hebben we alle studies bestudeerd, die de systolische functie bij normotensieve zwangere vrouwen hebben weergegeven en deze vergeleken met vrouwen met een hypertensieve zwangerschap. Tijdens gezonde zwangerschappen stijgt het eind-systolisch volume van de linkerkamer en de ejectiefractie van de linkerkamer met 18% en 4% respectievelijk, terwijl tijdens hypertensieve zwangerschappen het eind-systolisch volume van de linkerkamer met 50% meer toeneemt en de ejectiefractie van de linkerkamer met 10% daalt ten opzichte van een normotensieve zwangerschap.

In **Hoofdstuk 3** worden de voorspelde 10- en 30-jaar risicoscores voor hart- en vaatziekten in voormalige pre-eclampsie vrouwen beschreven, 5-10 jaar na de zwangerschap in vergelijking met vrouwen die een gezonde zwangerschap hebben gehad. Deze risicoscore is berekend aan de hand van de Framingham Risico Score. Voormalige pre-eclamptische vrouwen hebben als groep een vergelijkbaar berekende risicoscore, vergeleken met de controle groep, in tegenstelling tot eerder geobserveerde getallen in observationele studies. Dit roept de vraag op of de huidige risico-modellen voor het ontwikkelen van hart- en vaatziekten geschikt zijn voor deze specifieke jonge vrouwen. Wel blijkt dat voormalig pre-eclamptische vrouwen met hoge bloeddruk een tweevoudig verhoogd voorspeld risico hebben op het ontwikkelen van hart- en vaatziekten in de komende 10-30 jaar ten opzichte van voormalig pre-eclamptische vrouwen zonder hoge bloeddruk: de 10- en 30-jaar HVZ mediane risico scores, gebaseerd op de lipidenwaardes van de vrouwen, waren achtereenvolgens 3.1% versus 1.5% en 19.0% versus 8.0%.

In **Hoofdstuk 4** wordt middels een prospectief cohort onderzoek de prevalentie aangetoond van asymptomatische structurele hartveranderingen (hartfalen stadium B) bij voormalige pre-eclamptische vrouwen, 1 en 4 jaar na de bevalling. Bij deze vrouwen observeerden we een prevalentie van 23% van hartfalen stadium B op beide meetmomenten. Dit suggereert een persisterende cardiale dysfunctie, maar op individueel niveau is er een verschuiving in vrouwen die herstellen van deze aandoening tussen de twee tijdstippen (meer dan 60%) en vrouwen die hartfalen stadium B alsnog ontwikkelden (ongeveer 20%). Bovendien was de prevalentie van ofwel diastolische of systolische dysfunctie verschillend op beide tijdstippen en blijkt de concentrische vormverandering van het hart de meest voorkomende vorm van hartfalen stadium B, 4 jaar na de bevalling.

In **Hoofdstuk 5** wordt de associatie tussen zowel hartfalen stadium B en endotheeldysfunctie bij voormalige pre-eclamptische vrouwen beschreven. In deze cross-sectionele studie wordt aangetoond dat voormalig pre-eclamptische vrouwen een acht keer hogere prevalentie van hartfalen stadium A hadden (risicofactoren voor hartfalen) en een drie keer hoger voorkomen van hartfalen stadium B in vergelijking met vrouwen die een gezonde zwangerschap hebben gehad. Bovendien hadden voormalige pre-eclamptische vrouwen 4 jaar na de bevalling, een slechtere endotheelfunctie, gemeten met de zogenaamde "flow mediated dilation technique" in vergelijking met de controle groep die enkel normotensieve zwangerschappen heeft doorgemaakt. In tegenstelling tot onze verwachtingen werd er geen relatie gevonden tussen hartfalen stadium A of hartfalen stadium B met endotheeldysfunctie, bepaald in de arm slagader.

In **Hoofdstuk 6** wordt de associatie tussen concentrische vormverandering van het hart en plasmavolume, een maat die met name de aderlijke reserves van de bloedsomloop weerspiegeld, bij voormalige pre-eclampsie vrouwen beschreven. In dit longitudinaal cohort onderzoek zagen we dat 18% van de voormalige pre-eclamptische vrouwen concentrische vormveranderingen van het hart hebben, een paar jaar na de zwangerschap. Ook wordt in deze studie aangetoond, dat vrouwen met concentrische vormverandering van het hart vastgesteld op 4.8 jaar na de bevalling, vaker een gering plasmavolume hebben 0.8 jaar na de probleemvolle zwangerschap. Middels een gecorrigeerde multivariabele analyse hebben we aangetoond, dat een gering circulerend volume 0.8 jaar na de bevalling onafhankelijk geassocieerd is met latere concentrische vormverandering van het hart, 4.8 jaar na de probleemvolle zwangerschap. Bovendien is elke toename in mmHg in drukbelasting ook geassocieerd met meer kans op het ontwikkelen van concentrische vormverandering van het hart in de jaren na de bevalling en daarmee ook de kans met hartfalen stadium B (OR 1.15, 95% CI 0.99-1.35, OR 1.24, 95% CI 0.98-1.58 en OR 1.20, 95% CI 0.98-1.47, respectievelijk).

In **Hoofdstuk 7** worden de resultaten uit dit proefschrift bediscussieerd en wordt er een uiteenzetting gegeven van de huidige literatuur omtrent hart- en vaatfunctie bij vrouwen met een doorgemaakte pre-eclampsie.

Samengevat leggen onze bevindingen de nadruk op de cardiovasculaire complicaties tijdens en na een zwangerschap gecompliceerd door pre-eclampsie. De studies in dit proefschrift leveren bewijs voor een hoge prevalentie van hartfalen stadium B en risicofactoren voor hart- en vaatziekten bij voormalige pre-eclamptische vrouwen in het eerste decennium na de zwangerschap. Daarnaast toonden we aan dat in deze populatie een gering plasmavolume (volume aanbod) en hoge bloeddruk (drukbelasting aan het hart) geassocieerd zijn met hartfalen stadium B. Dit manuscript toont het belang aan van herhaaldelijke cardiovasculaire evaluatie met speciale aandacht voor bloeddruk en echocardiografie. Gezien de verschuiving in risicofactoren en cardiale fenotype is van belang dat deze risico beoordeling niet eenmalig plaatsvindt, maar herhaald zou moeten worden.

Summary

This thesis provides insight in cardiovascular (CV) function during and after preeclamptic pregnancies and the increased risk for remote CV disease (CVD) later in life in these women.

Chapter 1 presents a general introduction with the objectives of this thesis.

Chapter 2 presents insight in the magnitude and course of change in systolic cardiac function during pregnancy. The course of change is assessed through meta-analysis and systematic review where we reviewed all studies on systolic function in normotensive pregnant women and women with a pregnancy complicated by a hypertensive disorder. During normotensive pregnancies, there is a significant rise in left ventricular end systolic volume and left ventricular ejection fraction (18% and 4%, respectively), while during hypertensive pregnancies left ventricular end systolic volume increases more with 50% and left ventricular ejection fraction decreases with 10% compared with a normotensive pregnancy.

Chapter 3 describes the predicted 10- and 30-year risk scores for CVD in former preeclamptic women, 5-10 years after their pregnancy compared with healthy parous controls. CVD risk is calculated based on the Framingham Risk Score. Formerly preeclamptic women, as a group, had a comparable risk score compared to the control group in contrast to earlier observed numbers in observational studies. This raises the question if the current risk models for the development of cardiovascular disease are suitable for these specific young women. However, hypertensive former preeclamptic women have a twofold increased risk of developing CVD risk in the next 10-30 years compared to formerly preeclamptic women without hypertension: 10- and 30-year CVD median risks weighing subjects' lipids were 3.1% versus 1.5% and 19.0% versus 8.0%, respectively.

Chapter 4 describes the prevalence of asymptomatic structural heart alterations (heart failure stage B) in former preeclamptic women at 1 and 4 years postpartum, in a prospective cohort study. We observed a prevalence of 23% of heart failure stage B at both timepoints in these women. This suggests a persistent cardiac function, however, at an individual level, there is a shift in women who are recovering of this disease between the two timepoints (more than 60%) and women who developed heart failure stage B (about 20%). Moreover, the prevalence of either diastolic or systolic dysfunction were different at both timepoints, where concentric remodeling was the most prevalent form of heart failure stage B at 4 years postpartum.

Chapter 5 describes the association with both heart failure stage B and endothelial dysfunction in former pre-eclamptic women. We showed in this cross-sectional cohort study that formerly preeclamptic women had an eight-fold higher prevalence of heart failure stage A (risk factors for heart failure) and a three-fold higher prevalence of heart failure stage B compared to healthy parous controls. Furthermore, at 4 years postpartum, formerly preeclamptic women had a lower endothelial function measured with the "flow-mediated dilation technique" compared to the control group who experienced only

normotensive pregnancies. In contrast to our expectations, no association was found between the prevalence of heart failure stage A or heart failure stage B and endothelial dysfunction measured with flow mediated dilation measured at brachial artery level.

Chapter 6 describes the association between concentric remodeling and plasma volume, a measurement which reflects in particular the venous reserves of the blood circulatory system, in former pre-eclamptic women. We observed in this longitudinal cohort study that 18% of former preeclamptic women have concentric remodeling a few years after pregnancy. Moreover, we showed that women with concentric remodeling 4.8 years postpartum more often have a low plasma volume 0.8 years after their complicated pregnancy. An adjusted multivariable analysis shows that a low plasma volume 0.8 years postpartum was independently associated with later concentric remodeling at 4.8 years postpartum. Moreover, each mmHg rise in arterial blood pressure (systolic, diastolic and mean arterial pressure) is also associated with more risk of developing concentric remodeling in the years postpartum and with it heart failure stage B (OR 1.15, 95% CI 0.99-1.35, OR 1.24, 95% CI 0.98-1.58 and OR 1.20, 95% CI 0.98-1.47, respectively).

Chapter 7 elaborates on the findings of this manuscript and gives an explanation of the currently available literature on CV function in formerly preeclamptic women

In summary, our findings underline the cardiovascular complications during and after a preeclamptic pregnancy. The studies in this thesis provides evidence for a high prevalence of heart failure stage B and CV risk factors in former preeclamptic patients in the first decade after pregnancy. Moreover, we show that these women have a diminished plasma volume (volume load) and high pressure load which are associated with heart failure stage B. It is important that former preeclamptic women undergo a CV screening and follow-up, with a special focus on blood pressure and echocardiography. As the prevalence of CV risk factors and cardiac phenotype change postpartum, these risk assessments should not only be offered once but repeated follow-up after a few years is necessary.

Valorisatie

Dit hoofdstuk beschrijft de waardecreatie, die verkregen kan worden uit de resultaten van de studies in dit proefschrift en hoe deze vertaald kunnen worden naar de klinische praktijk. Het omschrijft hoe deze kennis ten goede komt aan het maatschappelijk belang en in het bijzonder de vrouw die pre-eclampsie heeft gehad.

INLEIDING

Hart- en vaatziekten (HVZ) zijn doodsoorzaak nummer één bij vrouwen[1, 2]. Dit heeft te maken met het atypische klachten patroon bij vrouwen, man-vrouw verschillen in onderliggende systeem biologie en de huidige diagnostische hulpmiddelen. Hierdoor wordt deze ziekte bij vrouwen vaak pas in een laat stadium herkend. In deze late stadia is het ziekteproces vaak moeilijk om te keren of te herstellen. Daarom is het belangrijk om in een vroege fase vrouwen op te kunnen sporen, die daadwerkelijk een verhoogd risico lopen op hart- en vaatziekten. Bij mensen gevoelig voor hart- en vaataandoeningen, start dit proces al vroeg in het leven en zou met de nodige aanpassingen in leefstijl (mediterraan dieet en beweging) of passende medicamenteuze preventiemiddelen, om ongunstige veranderingen in hart en vaten te voorkomen of verbeteren (cholesterolverlagende middelen of angiotensine converting enzyme (ACE)-remmers of angiotensine receptor blokkers (ARB's)), tegengegaan kunnen worden.

Dit belangrijk agendapunt is door de enquête van de Nederlandse Hartstichting verkozen tot nummer 2 op de prioriteitenlijst voor wetenschappelijk onderzoek[3]. Behalve conventionele risicofactoren, die het risico op HVZ zowel bij vrouwen als mannen verhogen, zijn er ook onderbelichte vrouwspecifieke risicofactoren[1, 4]. Een vrouwspecifieke risicofactor die van cruciaal belang is, vormt zwangerschapsvergiftiging (pre-eclampsie)[4]. Deze zwangerschapsaandoening wordt gekarakteriseerd door het ontwikkelen van hypertensie en proteïnurie tijdens de zwangerschap[5]. Onderliggend is een op dat moment aanwezige vaatdysfunctie. Vrouwen die een vroege zwangerschapsvergiftiging hebben doorgemaakt, hebben een 7.7 keer verhoogd risico op het ontwikkelen van HVZ[6].

Zwangerschapsvergiftiging is een vaatwandziekte, die meestal zichtbaar wordt in de tweede helft van de zwangerschap. Aangedane vrouwen hebben meer risico op een groei vertraagd kind, epileptische aanvallen en zelfs sterfte. Op de lange termijn hebben deze vrouwen een verhoogd risico op HVZ, ongeveer 15 jaar eerder dan hun leeftijdsgenoten, die een gezonde zwangerschap hebben doorgemaakt. Intermediaire ziektematen of risicofactoren, zoals subklinisch hartfalen en endotheeldysfunctie enerzijds en geringe circulatoire reserves (gering plasma volume), dislipidemie, glucose metabolisme stoornissen en hoge bloeddruk (metabool syndroom) anderzijds, zouden sterk kunnen bijdragen aan betere determinatie van vrouwen daadwerkelijk at risk.

De studies in dit proefschrift beschrijven het risico op hart- en vaatziekten bij deze specifieke groep vrouwen en de relatie tussen enerzijds pre-eclampsie en anderzijds subklinisch hartfalen, endotheelfunctie en laag plasma volume. Volgens het model (Hoofdstuk 1 Figuur 1) stijgt na pre-eclampsie het risico op HVZ gradueel, om binnen enkele jaren (maar nog op relatief jonge leeftijd) de klinische grens te bereiken. Risicofactoren zouden deze progressie kunnen versnellen. Echter is het tot nu toe nog onbekend, in welke orde dat gebeurt en welke risicofactoren na pre-eclampsie zwaarder wegen dan andere. Het is dus van klinisch belang om een betere inventarisatie te hebben van de factoren, die een essentiële rol spelen in het krijgen van hart- en vaatziekten in deze specifieke jonge vrouwelijke populatie

ZWANGERSCHAP ALS STRESSTEST

Zwangerschap is een unieke gezondheidstest voor hart en vaten. Pre-eclampsie wordt verder gekenmerkt door een ongezonde verdikking van de hartspier, die ook gezien wordt bij niet zwangere patiënten met jaren bestaande chronische hypertensie. Deze verdikking van de hartspier gaat bij vrouwen vaak vooraf aan hartfalen en leidt in veel gevallen tot een stugger hart, dat zich minder makkelijk laat vullen (diastole dysfunctie). Bij iets minder dan de helft van deze vrouwen blijven de ongunstige aanpassingen van het hart aan pre-eclampsie na de bevalling bestaan. Volgens de Amerikaanse cardiologische definitie vallen deze afwijkingen onder asymptomatisch hartfalen stadium B (HF-B)[7]. HF-B en milde diastole dysfunctie zijn veelal omkeerbare veranderingen, mits tijdig ontdekt. Wanneer HF met symptomen gepaard gaat, is deze niet meer omkeerbaar en kan men hooguit de klachten verminderen; een vermindering, die ondanks verbetering van de hartstructuur, niet tot verandering van de prognose leidt. Transitie van het asymptomatische stadium B naar het symptomatische stadium C gaat gepaard met een 5x groter overlijdensrisico[8]. Daarom is vroegtijdige herkenning en voorkomen van progressie van asymptomatisch naar symptomatisch HF de enige logische strategie.

RELEVANTIE

In 2018 was het aantal levende geboorten in Nederland 168.525[9], uitgaande van een prevalentie van pre-eclampsie van 3-5%[10], komt dit uit op een jaarlijks aantal geboorten van 5056 tot 8426 van vrouwen, die een gecompliceerde zwangerschap met pre-eclampsie doormaken. Jaarlijks komen er dus gemiddeld 6741 vrouwen bij de al reeds bestaande groep met vrouwen met pre-eclampsie in de voorgeschiedenis.

Aangezien deze patiëntengroep van grote omvang is, is het belangrijk om vrouwen hierover te informeren. Vaak weten zij niet goed wat de cardiovasculaire consequenties zijn van het doormaken van pre-eclampsie en hebben zij veel vragen. Daarom is er een factsheet gemaakt met to the point resultaten van onder andere dit proefschrift, zodat de vrouwen die pre-eclampsie hebben meegemaakt op de hoogte worden gehouden over welke nieuwe bevindingen er tot nu toe zijn gedaan.

Naast het informeren van patiënten en hen van adviezen te voorzien van de noodzaak van een follow-up ná de zwangerschap, is het belangrijk dat huisartsen en gynaecologen een duidelijker besef hebben, dat deze patiëntengroep een grote kans heeft op hart- en vaatziekten en daarom dus in de gaten moet worden gehouden. Het gebeurt nog te vaak dat we vrouwen uit het oog verliezen, terwijl juist deze vrouwen baat zouden kunnen hebben bij passende follow-up, om daarmee hun HVZ risico te verminderen. Daarnaast laat dit proefschrift ook zien, dat een eenmalige follow-up niet voldoende is om hartfalen uit te sluiten en dat een aanvullende follow-up een aantal jaar later erg belangrijk is.

Naast de resultaten voor de patiënt, de arts en de wetenschap hebben mijn uitkomsten ook meegeholpen aan de tot stand brenging van de Queen of Hearts studie. Deze studie wordt gefinancierd door de Nederlandse Hartstichting en is een groot wetenschappelijk onderzoek naar de aanwezigheid van de risicofactoren van hart- en vaatziekten en biomarkers voor subklinisch hartfalen bij vrouwen, die in het verleden pre-eclampsie hebben doorgemaakt.

Door onderzoek naar vrouwspecifieke biomarkers voor hartfalen en geassocieerde risicoprofiel, kan er een gepersonaliseerd screeningsprogramma ontwikkeld worden op basis van een multimarker model, waarop preventieve therapieën kunnen worden afgestemd.

DOELGROEP

De doelstelling van dit proefschrift is onze kennis te vergroten in de cardiovasculaire determinanten, die het risico vergroten op het ontstaan van cardiovasculaire aandoeningen in vrouwen met pre-eclampsie. De vrouwen, die wij hebben onderzocht, zijn jong en hebben geen herkenbare of klassieke cardiovasculaire symptomen. Deze vrouwen komen grotendeels uit de regio oost-midden Nederland, die gezien de demografie vergelijkbaar is met de rest van Nederland.

INNOVATIE

De bevindingen van dit proefschrift tonen aan welke veranderingen er in het hart tijdens de zwangerschap plaatsvinden en welke aanhouden of verdwijnen tijdens de postpartum

periode. Het belicht belangrijk hartfalen stadium B, een stadium waarbij er al wel veranderingen in het hart zijn, maar nog geen symptomen. Één op de vier vrouwen heeft een aantal jaar na de gecompliceerde zwangerschap dit stadium van hartfalen al. Maar wat belangrijk is, is dat er ook een verschuiving is in prevalentie. Er zijn vrouwen die 1 jaar na de zwangerschap nog *geen* hartfalen stadium B hebben, maar dit *wel* na 4 jaar hebben ontwikkeld. Dit onderstreept het belang dat er ook na een aantal jaar een follow-up echografie belangrijk is.

Door inzicht te krijgen in de factoren, zoals endotheelfunctie en plasma volume, die een rol spelen in de etiologie van hartfalen, zullen preventieprogramma's daar beter op ingericht kunnen worden.

IMPLEMENTATIE, PLANNING EN REALISATIE

De eerder genoemde factsheet, waarop to the point resultaten vermeld zijn, is toepasbaar op de individuele patiënt en wordt gepubliceerd bij de hart voor HELLP stichting. Deze stichting zet zich in voor meer begrip, (h)erkenning en acceptatie voor vrouwen, die pre-eclampsie en/of het HELLP syndroom hebben gehad. Door het publiceren van de factsheet zal ten eerste voor de patiënt zelf inzichtelijk worden gemaakt met welke onderzoeken we ons momenteel bezighouden, welke uitkomsten daaruit komen en welke klinische consequenties deze kunnen hebben. Daarnaast zorgt het ook weer voor een reactivatie in het bewustzijn van zowel patiënt als hulpverlener en maatschappij. Door scherper intermediaire ziekte-maten te bestuderen hopen we veel beter de zorg te verleggen naar zij die het nodig hebben en de anderen juist in een vroeger stadium te kunnen geruststellen.

Verder geven de bevindingen van dit proefschrift aan, dat in de eerste decade na zwangerschap vrouwen niet eenmalig onderzocht moeten worden, maar in een gestructureerde follow-up terecht zouden moeten komen, waarbij om de paar jaar een uitgebreide cardiovasculaire screening verricht wordt. Vanuit deze structuur kunnen we in de zorg doelmatigheidsvragen beantwoorden, om zo de zorg voor deze groep veilig te personaliseren.

Tot slot is er op basis van de bevindingen een logische interventie trial in ontwikkeling, ter behandeling van subklinisch hartfalen.

REFERENTIES

1. Benjamin EJ, Virani SS, Callaway CW, Chamberlain AM, Chang AR, Cheng S, Chiuve SE, Cushman M, Delling FN, Deo R, de Ferranti SD, Ferguson JF, Fornage M, Gillespie C, Isasi CR, Jimenez MC, Jordan LC, Judd SE, Lackland D, Lichtman JH, Lisabeth L, Liu S, Longenecker CT, Lutsey PL, Mackey JS, Matchar DB, Matsushita K, Mussolino ME, Nasir K, O'Flaherty M, Palaniappan LP, Pandey A, Pandey DK, Reeves MJ, Ritchey MD, Rodriguez CJ, Roth GA, Rosamond WD, Sampson UKA, Satou GM, Shah SH, Spartano NL, Tirschwell DL, Tsao CW, Voeks JH, Willey JZ, Wilkins JT, Wu JH, Alger HM, Wong SS and Muntner P. Heart Disease and Stroke Statistics-2018 Update: A Report From the American Heart Association. *Circulation*. 2018;137:e67-e492.
2. Mosca L, Barrett-Connor E and Wenger NK. Sex/gender differences in cardiovascular disease prevention: what a difference a decade makes. *Circulation*. 2011;124:2145-54.
3. Nederlandse Hartstichting. Onderzoeksagenda Hartstichting. https://www.hartstichting.nl/wetenschappelijk-onderzoek/onderzoeksagenda-hartstichting.
4. Mosca L, Benjamin EJ, Berra K, Bezanson JL, Dolor RJ, Lloyd-Jones DM, Newby LK, Pina IL, Roger VL, Shaw LJ, Zhao D, Beckie TM, Bushnell C, D'Armiento J, Kris-Etherton PM, Fang J, Ganiats TG, Gomes AS, Gracia CR, Haan CK, Jackson EA, Judelson DR, Kelepouris E, Lavie CJ, Moore A, Nussmeier NA, Ofili E, Oparil S, Ouyang P, Pinn VW, Sherif K, Smith SC, Jr., Sopko G, Chandra-Strobos N, Urbina EM, Vaccarino V and Wenger NK. Effectiveness-based guidelines for the prevention of cardiovascular disease in women--2011 update: a guideline from the american heart association. *Circulation*. 2011;123:1243-62.
5. Brown MA, Lindheimer MD, de Swiet M, Van Assche A and Moutquin JM. The classification and diagnosis of the hypertensive disorders of pregnancy: statement from the International Society for the Study of Hypertension in Pregnancy (ISSHP). *Hypertension in pregnancy*. 2001;20:IX-XIV.
6. Bellamy L, Casas JP, Hingorani AD and Williams DJ. Pre-eclampsia and risk of cardiovascular disease and cancer in later life: systematic review and meta-analysis. *BMJ (Clinical research ed)*. 2007;335:974.
7. Jessup M, Abraham WT, Casey DE, Feldman AM, Francis GS, Ganiats TG, Konstam MA, Mancini DM, Rahko PS, Silver MA, Stevenson LW and Yancy CW. 2009 focused update: ACCF/AHA Guidelines for the Diagnosis and Management of Heart Failure in Adults: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines: developed in collaboration with the International Society for Heart and Lung Transplantation. *Circulation*. 2009;119:1977-2016.
8. Ammar KA, Jacobsen SJ, Mahoney DW, Kors JA, Redfield MM, Burnett JC, Jr. and Rodeheffer RJ. Prevalence and prognostic significance of heart failure stages: application of the American College of Cardiology/American Heart Association heart failure staging criteria in the community. *Circulation*. 2007;115:1563-70.
9. CBS-Statline. Geboorte; kerncijfers. https://opendata.cbs.nl/statline/#/CBS/nl/dataset/37422ned/table?ts=1560856985183. 6 maart 2020.
10. Roberts JM and Cooper DW. Pathogenesis and genetics of pre-eclampsia. *Lancet*. 2001;357:53-6.