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Original Article

Coronary Calcification in Iraqi Middle-Aged Women With Previous Preeclampsia: A Cohort Study

Abdulameer Jasim Jawad al-Gburi[1*], MBChB;
Saba Ryadh Younis al-Obaidi[2], MBChB

ABSTRACT

Background: Both preeclampsia and coronary artery calcification (CAC) are associated with an increased cardiovascular risk. As CAC is race and ethnicity-dependent, we test it in a sample of Iraqi population. We compared the presence of CAC in a cohort of middle-aged women with and without previous preeclampsia.

Methods: This retrospective cohort study on middle-aged Iraqi women used logistic regression models to compare 100 women with and 100 women without a history of preeclampsia. Other cardiovascular risk factors were assessed as potential covariates. Between September 2020 and January 2022, the women underwent a multidetector computed tomography for the assessment of the presence of CAC.

Results: CAC was found in 22% of patients with previous preeclampsia compared with 11% in those without previous preeclampsia. Body mass index, systolic and diastolic blood pressures, lipid indices, glucose levels, and hypertension were significantly related to previous preeclampsia. Age, waist circumference, diastolic blood pressure, glucose levels, hypertension, and diabetes were significantly associated with the presence of CAC. Women with previous preeclampsia had a 128% greater risk of CAC than women without this condition (OR, 2.28; 95% CI, 1.04 to 5). Age adjustments had no discernible effect on the relationship (OR, 2.39; 95% CI, 1.07 to 5.31).

Conclusions: Women with previous preeclampsia were more likely to have CAC than women with normotensive pregnancies in their middle age even after adjustments for age. Cardiovascular screening may be beneficial for women with a history of preeclampsia.
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KEYWORDS: Pregnancy, Atherosclerosis, Cardiovascular disease, Blood pressure

[1] Department of Medicine, College of Medicine, al-Mustansiriyah University, Baghdad, Iraq.
[2] Department of Obstetrics and Gynecology, College of Medicine, al-Nahrain University, Baghdad, Iraq.

***Corresponding Author:** Abdulameer Jasim Jawad al-Gburi, MD; Department of Medicine, College of Medicine, al-Mustansiriyah University, Baghdad, Iraq.
Email: abdulamerjasim@gmail.com **Tel:** +9647733116661

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Cardiovascular disease (CVD) is the leading cause of death in women. Preeclampsia is a hypertensive pregnancy disease that affects between 3% and 5% of pregnancies in the developed world.[1] Preeclampsia is characterized by the development of elevated blood pressure and proteinuria, or the onset of elevated blood pressure and severe dysfunction of the end-organs, with or without proteinuria, in a previously normotensive woman after 20 weeks of pregnancy or postpartum.[2] Although symptoms diminish shortly after pregnancy, the condition has long-term health consequences.[3] Anomalies in the development of the uteroplacental circulation arise long before the appearance of the clinical symptoms of preeclampsia. In preeclampsia, the cytotrophoblast invades the decidual segment of the spiral arteries but not the myometrial segment, which is why abnormally small blood arteries do not grow in the placenta and ischemia and hypoperfusion ensue.[4] This process appears to be influenced by genetic, environmental, and immunological factors. Soluble fms-like tyrosine kinase 1 is a placental and vascular endothelial growth factor inhibitor.[5,6] It is secreted by a dysfunctional placenta and is a key moderator of the maternal signs and symptoms of preeclampsia.

Preeclampsia is linked with a 2 to 7-fold greater cardiovascular risk later in life in comparison with normal-pressure pregnancy.[7] The current belief is that this increased risk of CVD is the consequence of a predisposition to cardiovascular risk factors, such as high blood pressure, obesity, and high lipid, existing before pregnancy and contributing to the development of preeclampsia.[8,9] While some international guidelines recognize the elevated risk of CVD in women with previous preeclampsia, precise guidance for cardiovascular surveillance is absent.[10,11] Many women with previous preeclampsia may be considered at low risk when assessed by the current traditional risk score because of its age dependence. Pregnancy as a challenge test is a novel theory, with hypertension or preeclampsia development as a sign of an increased risk of developing future atherosclerotic vascular events. Women with a history of preeclampsia have modifiable cardiovascular risk factors, such as hypertension, dyslipidemia, and diabetes, 5 to 10 years sooner than women without such a history.[12]

There is extensive evidence that the coronary artery calcification (CAC) score has prognostic value in asymptomatic individuals, especially those at borderline and intermediate risk.[13,14] Prior research indicates that women with a history of preeclampsia are more likely to develop CAC than women who have normotensive pregnancies.[15–20] The included women were more than a decade older than the participants in our research and were mostly of white ethnicity in the western world. CAC differs by race and ethnicity as shown in the MESA study.[21]

To our knowledge, this research is the first to be conducted on the Iraqi population. The purpose of this study was to compare the presence of CAC in a cohort of middle-aged women with and without previous preeclampsia. We hypothesized that CAC was more prevalent in women with previous preeclampsia.

METHODS

Population

We conduct this retrospective cohort study on middle-aged Iraqi women (100 patients with and 100 patients without a history of preeclampsia). The study was done in Ibn al-Bitar Specialized Center, Baghdad, Iraq, with the subjects referred from the gynecology and obstetrics clinic between September 2020 and January 2022. Women were asked about pregnancy history using a validated questionnaire.[22]

We included asymptomatic middle-aged women between 40 and 60 years with previous preeclampsia and compared their findings with those of women with a history of normotensive pregnancies. The exclusion criteria consisted of no history of pregnancy, oral contraceptive consumption, a pregnancy lasting less than 6 months, a history of myocardial infarction, a history of stroke, dementia, congestive heart failure, any type of malignancy, neurological conditions (eg, epilepsy), and autoimmune diseases (eg, multiple sclerosis and lupus). The study was approved by the institutional medical ethics committee, and informed consent was obtained from all the participants before enrolment.

Questionnaires were used to collect information on medication usage, diabetes, and smoking, as well as reproductive, cardiovascular, and general medical histories. Age was determined using the participant's date of birth and the date of participation. The height and weight of the participants were determined. Body mass index was determined by multiplying the weight by height squared. The circumference of the waist was measured. Blood pressure was determined in both arms using a calibrated and automated blood pressure instrument (Contec ABPM50, Contec Medical Systems Co, Ltd), with the participant seated. After an overnight fast of 8 hours, a venous blood sample was taken. The total cholesterol, triglycerides, and glucose levels in the plasma were determined using conventional enzymatic techniques. The direct method was applied to determine the high-density lipoprotein cholesterol level (inhibition and enzymatic). In women with triglycerides below 400 mg/dL, the Friedewald formula was used to calculate the low-density lipoprotein cholesterol level. Hypertension was defined by the use of antihypertensive medication or systolic blood pressure more than or equal to 130 mm Hg or diastolic blood pressure more than or equal to 80 mm Hg.[23]

Coronary Calcium Measurements

The individuals were assessed for CAC using a multidetector computed tomography examination (Brilliance 64, Philips Medical Systems). The subjects were positioned in the supine position within the gantry. With the use of 120 kVp, a 64-slice scanner was employed to acquire slices 3 mm in thickness. Through the use of prospective electrocardiogram-triggered scanning at 50% to 80% of the interval between successive R waves, cardiac images were collected during a single breath-hold from the bifurcation of the trachea to just below the heart's base.

A skilled reader, who was unaware of the women's obstetric history, manually picked just the calcifications within one of the coronary arteries. The Hounsfield unit (HU) for peak density and the area for each selected location were computed. CAC was measured using the Agatston methodology by multiplying the calcification area (>1 mm^2 with a density >130 HU)[24] by a weighting factor for density. The total CAC was calculated for the coronary arteries using a computed tomography (CT) dataset with a slice thickness of 3.0 mm. The presence of CAC was defined as an Agatston score of more than 0 (non-0).

Statistical Analysis

Logistic regression models were used to assess the association between possible confounding variables and a history of preeclampsia. The relationship between risk variables and CAC was also investigated similarly. Confounding variables were defined as those that had a substantial association with both preeclampsia and CAC. There was a distinction between variables that were not involved in the causative route and those that might have been involved. A logistic regression model was used to evaluate the association between previous preeclampsia and the outcome variable (CAC absent/present [binary]). Odds ratios (ORs)

with a 95% confidence interval (CI) were used to quantify the relationships. A *P* value of less than 0.05 was considered statistically significant. All the analyses were done on Windows using the Statistical Package for Social Sciences (SPSS) software version 26 (SPSS, Inc, Chicago, IL).

RESULTS

Patient Characteristics

Our study included 100 women with previous preeclampsia and compared them with a control group of 100 women. Women in both groups were on average 49 years old at the time of CAC imaging. CAC, defined as an Agatston score of 1 or more, was identified in 22% of the patients with previous preeclampsia compared with 11% of the patients with a history of normotensive pregnancies. The median Agatston score was 12. Table 1 summarizes the characteristics of the participants.

The relationship between general characteristics and a history of preeclampsia and CAC is shown in Table 2. Increased body mass indices, systolic and diastolic blood pressures, total cholesterol levels, low and high-density lipoprotein levels, glucose levels, and hypertension were significantly related to previous preeclampsia. Age was significantly associated with CAC (OR, 1.07; 95% CI, 1.008 to 1.148). Increased waist circumference, diastolic blood pressure, glucose levels, and the existence of hypertension and diabetes were all associated with the presence of CAC in a significant way. Based on this information, overweight parameters and blood pressure, glucose levels, and the existence of hypertension may be regarded as possible confounders; however, these factors may also be considered intermediary parameters in the causation pathway.

As is shown in Table 3, prior preeclampsia was significantly associated with the presence of CAC in an unadjusted model. Compared with women without a history of preeclampsia, the risk was elevated by 128% (OR, 2.28; 95% CI, 1.04 to 5). Age adjustments had no significant influence on the relationship (OR, 2.39; 95% CI, 1.07 to 5.31). When the association was adjusted for factors that could be considered intermediate factors in the causal pathway from preeclampsia to atherosclerosis pathogenesis, such as body mass index, diastolic blood pressure, waist circumference, glucose levels, and the presence of hypertension, the relationship weakened and did not reach statistical significance.

Table 1: General characteristics of the study population

General Characteristics	Previous Preeclampsia (n=100)	No Previous Preeclampsia (n=100)	*P* value
Age, y	49.32	49.67	0.684
BMI, kg/m^2	27.48	24.59	<0.001
WC, cm	79	78	0.175
SBP, mm Hg	131.59	109.06	<0.001
DBP, mm Hg	82.22	72.63	<0.001
Hypertension, %	85	18	<0.001
Total cholesterol, mg/dL	198.50	181	<0.001
LDL cholesterol, mg/dL	124.21	100.73	<0.001
HDL cholesterol, mg/dL	49.38	60.14	<0.001
Triglycerides, mg/dL	122.14	114.12	0.125
Glucose, mg/dL	99.71	95.09	0.002
Diabetes diagnosis, %	5	2	0.248
Smoking, %	5	4	0.733
Presence of coronary calcification, %	22	11	0.036

DBP, Diastolic blood pressure; HDL, High-density lipoprotein; LDL, Low-density lipoprotein; WC, Waist circumference; SBP, Systolic blood pressure

Table 2: Relationship between characteristics and previous preeclampsia

Risk Factors	Previous Preeclampsia, OR (95% CI)	Coronary Calcification, OR (95% CI)*
Age, y	0.99 (0.94-1.03)	
BMI, kg/m^2	1.09 (1.03-1.14)	1.00 (0.94-1.07)
Waist circumference, cm	1.03 (0.98-1.09)	1.19 (1.09-1.30)
SBP, mm Hg	1.09 (1.06-1.12)	0.99 (0.97-1.01)
DBP, mm Hg	1.09 (1.05-1.12)	1.03 (1.00-1.07)
Cholesterol, mg/dL	1.04 (1.02-1.06)	1.00 (0.99-1.02)
LDL, mg/dL	1.05 (1.03-1.07)	0.99 (0.96-1.01)
HDL, mg/dL	0.93 (0.90-0.95)	1.02 (0.99-1.06)
Triglycerides, mg/dL	1.00 (0.99-1.01)	0.99 (0.98-1.00)
Glucose, mg/dL	1.04 (1.01-1.08)	1.04 (1.01-1.08)
Current or former smoking, %	1.26 (0.32-4.84)	2.88 (0.65-12.67)
Hypertension, %	25.81 (12.20-54.61)	2.79 (1.22-6.34)
Diabetes diagnosis, n (%)	2.57 (0.48-13.61)	4.92 (1.02-23.74)

BMI, Body mass index; DBP, Diastolic blood pressure; HDL, High-density lipoprotein; LDL, Low-density lipoprotein; WC, Waist circumference; SBP, Systolic blood pressure

*Age-adjusted relationship between coronary calcification and the subjects' characteristics

Table 3: Relationship between previous preeclampsia and coronary calcification

Previous Preeclampsia	Coronary Calcification, OR (95% CI)
Previous preeclampsia	2.28 (1.04-5.00)
Previous preeclampsia adjusted for age	2.39 (1.07-5.31)
Previous preeclampsia adjusted for age, WC, and DBP	1.58 (0.62-4.01)
Previous preeclampsia adjusted for age, WC, BMI, and DBP	1.52 (0.59-3.93)
Previous preeclampsia adjusted for age, WC, BMI, DBP, glucose, and HT	0.67 (0.20-2.25)

BMI, Body mass index; DBP, Diastolic blood pressure; HDL, High-density lipoprotein; LDL, Low-density lipoprotein; WC, Waist circumference; SBP, Systolic blood pressure; HT, Hypertension

DISCUSSION

To our knowledge, this is the first study to demonstrate a link between previous preeclampsia and CAC in Iraqi women. CAC differs by race and ethnicity as was shown in the MESA study.[21] This study reveals that asymptomatic women with a history of preeclampsia had a higher risk of CAC and more cardiovascular risk factors than those without previous preeclampsia.

Previous research has found that women with previous preeclampsia have a 1.6 to 3.5-fold increased chance of CAC than those with normotensive pregnancies.[15–18] These studies used small samples and included older women who were about a decade older than the participants in our research. Nonetheless, the frequency of CAC was consistently greater in women with a history of preeclampsia than in women without a history of preeclampsia over the age of 60 years. Our findings contribute significantly to this body of evidence by demonstrating a similar effect in previously preeclamptic women at a younger age and in Iraqi women, unlike other studies which mainly included Western women. Even though cardiovascular risk factors contribute to the increased risk of CAC, the association is still significant after adjustments for age. The precise mechanisms

by which cardiovascular risk factors, CAC, and preeclampsia interact remain unknown. They may be related genetically, or preeclampsia may predispose to vascular wall injury.

Many years ago, it was reported that preeclamptic women had atherosclerotic risk factors at an earlier age or might have a higher risk before pregnancy.[25] Subsequent population-based investigations established that these women do, in fact, experience CVD about 5 years sooner than women without previous preeclampsia.[26] Conventional cardiovascular risk factors may account for up to 90% of CVD risks.[27] Previous research has also demonstrated that preeclamptic women have an elevated cardiovascular risk immediately after delivery.[12,28,29] A recent investigation found an early onset of subclinical CVD among women with a history of preeclampsia before the age of 45.[20] Most women at this age will be premenopausal and will benefit most from primary prevention.

The majority of cardiovascular prevention guidelines are ambiguous about the method and timing of cardiovascular follow-up in women with previous preeclampsia.[10,30–33] A lengthy follow-up period is essential in outcome studies to determine the potential impact of early screening and treatment. This is prohibitively expensive and, thus, unlikely to be implemented. As a result, we suggest that cardiovascular surveillance of these women begin earlier. Additionally, we believe that early risk factor treatment may be important to avert the development of irreversible CAC and later CVD.

The current study recruited relatively young participants; consequently, data on cardiac events and the implications of CAC were unavailable. Still, we presume that these women were at a higher risk of CVD since prior research has demonstrated a significant correlation between the presence of CAC and cardiovascular events.[34,35]

Some of our study's limitations must be addressed. In addition to CAC, there are many cardiovascular risk factors, such as genetic inheritance. We did not include a time measurement for the onset of CAC. The observational nature of this research precludes causal inference and does not rule out the possibility of residual confounding. We gathered information regarding preeclampsia history using a questionnaire rather than a well-established medical record system. Nevertheless, the questionnaire had been evaluated in a prior study.[22] This might have resulted in misclassification and recall bias. (Subjects with hypertension at baseline may remember having experienced preeclampsia "better" than those who are normotensive.) Our study's relatively small sample size limits the accuracy of the estimates. Further investigations with larger populations are required to confirm or refute our findings. The strengths of the present study include its population-based design and meticulous CAC measurements. The multidetector CT technique for the identification of CAC, employed in the current investigation, is extremely accurate and reproducible.

Our findings may have consequences for women who have already had preeclampsia. An organized follow-up of women who have been diagnosed with preeclampsia should be undertaken. New follow-up methods and risk factor management for previously preeclamptic women must be developed and studied for their benefits in preventing future CVD.

CONCLUSIONS

In the present study, previously preeclamptic middle-aged Iraqi women had more cardiovascular risk factors and were more likely to develop CAC than their counterparts with a history of normotensive pregnancies. Age-adjusted associations remained largely unchanged. As a result,

women who have had preeclampsia may benefit from periodic cardiovascular testing and management before reaching this age.

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REFERENCES

1. Ananth CV, Keyes KM, Wapner RJ. Pre-eclampsia rates in the United States, 1980-2010: age-period-cohort analysis. BMJ 2013; 347:f6564.

2. Gestational Hypertension and Preeclampsia: ACOG Practice Bulletin, Number 222. Obstet Gynecol 2020; 135:e237-e260.

3. Mol BWJ, Roberts CT, Thangaratinam S, Magee LA, Groot CJM de, Hofmeyr GJ. Pre-eclampsia. The Lancet 2016; 387:999–1011.

4. Garrido-Gomez T, Dominguez F, Quiñonero A, Diaz-Gimeno P, Kapidzic M, Gormley M, et al. Defective decidualization during and after severe preeclampsia reveals a possible maternal contribution to the etiology. Proc Natl Acad Sci U S A 2017; 114:E8468-E8477.

5. Burke SD, Zsengellér ZK, Khankin EV, Lo AS, Rajakumar A, DuPont JJ, et al. Soluble fms-like tyrosine kinase 1 promotes angiotensin II sensitivity in preeclampsia. J Clin Invest 2016; 126:2561–74.

6. Dvorak HF. Vascular permeability factor/vascular endothelial growth factor: a critical cytokine in tumor angiogenesis and a potential target for diagnosis and therapy. J Clin Oncol 2002; 20:4368–80.

7. Cirillo PM, Cohn BA. Pregnancy complications and cardiovascular disease death: 50-year follow-up of the Child Health and Development Studies pregnancy cohort. Circulation 2015; 132:1234–42.

8. 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.

9. Theilen LH, Fraser A, Hollingshaus MS, Schliep KC, Varner MW, Smith KR, et al. All-Cause and Cause-Specific Mortality After Hypertensive Disease of Pregnancy. Obstet Gynecol 2016; 128:238–44.

10. Bushnell C, McCullough L. Stroke prevention in women: synopsis of the 2014 American Heart Association/American Stroke Association guideline. Annals of Internal Medicine 2014; 160:853–7.

11. Grundy SM, Stone NJ, Bailey AL, Beam C, Birtcher KK, Blumenthal RS, et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Circulation 2019; 139:e1082-e1143.

12. Behrens I, Basit S, Melbye M, Lykke JA, Wohlfahrt J, Bundgaard H, et al. Risk of post-pregnancy hypertension in women with a history of hypertensive disorders of pregnancy: nationwide cohort study. BMJ 2017; 358:j3078.

13. Budoff MJ, Young R, Burke G, Jeffrey Carr J, Detrano RC, Folsom AR, et al. Ten-year association of coronary artery calcium with atherosclerotic cardiovascular disease (ASCVD) events: the multi-ethnic study of atherosclerosis (MESA). European Heart Journal 2018; 39:2401–8.

14. Erbel R, Möhlenkamp S, Moebus S, Schmermund A, Lehmann N, Stang A, et al. Coronary risk stratification, discrimination, and reclassification improvement based on quantification of subclinical coronary atherosclerosis: the Heinz Nixdorf Recall study. Journal of the American College of Cardiology 2010; 56:1397–406.

15. Cassidy-Bushrow AE, Bielak LF, Rule AD, Sheedy PF, Turner ST, Garovic VD, et al. Hypertension during pregnancy is associated with coronary artery calcium independent of renal function. J Womens Health (Larchmt) 2009; 18:1709–16.

16. Beckman JP, Camp JJ, Lahr BD, Bailey KR, Kearns AE, Garovic VD, et al. Pregnancy history, coronary artery calcification and bone mineral density in menopausal women. Climacteric 2018; 21:53–9.

17. Sabour S, Franx A, Rutten A, Grobbee DE, Prokop M, Bartelink M-L, et al. High blood pressure in pregnancy and coronary calcification. Hypertension 2007; 49:813–7.

18. White WM, Mielke MM, Araoz PA, Lahr BD, Bailey KR, Jayachandran M, et al. A history of preeclampsia is associated with a risk for coronary artery calcification 3 decades later. Am J Obstet Gynecol 2016; 214:519.e1-519.e8.

19. Zoet GA, Benschop L, Boersma E, Budde RPJ, Fauser, Bart C J M, van der Graaf Y, et al. Prevalence of Subclinical Coronary Artery Disease Assessed by Coronary Computed Tomography Angiography in 45- to 55-Year-Old Women With a History of Preeclampsia. Circulation 2018; 137:877–9.

20. Benschop L, Brouwers L, Zoet GA, Meun C, Boersma E, Budde RPJ, et al. Early Onset of Coronary Artery Calcification in Women With Previous Preeclampsia. Circ Cardiovasc Imaging 2020; 13:e010340.

21. McClelland RL, Chung H, Detrano R, Post W, Kronmal RA. Distribution of coronary artery calcium by race, gender, and age: results from the Multi-Ethnic Study of Atherosclerosis (MESA). Circulation 2006; 113:30–7.

22. Diehl CL, Brost BC, Hogan MC, Elesber AA, Offord KP, Turner ST, et al. Preeclampsia as a risk factor for cardiovascular disease later in life: validation of a preeclampsia questionnaire. Am J Obstet Gynecol 2008; 198:e11-3.

23. Whelton PK, Carey RM, Aronow WS, Casey DE, Collins KJ, Dennison Himmelfarb C, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Hypertension 2018; 71:e13-e115.

24. Agatston AS, Janowitz WR, Hildner FJ, Zusmer NR, Viamonte M, Detrano R. Quantification of coronary artery calcium using ultrafast computed tomography. Journal of the American College of Cardiology 1990; 15:827–32.

25. Sattar N, Greer IA. Pregnancy complications and maternal cardiovascular risk: opportunities for intervention and screening? BMJ 2002; 325:157–60.

26. Mongraw-Chaffin ML, Cirillo PM, Cohn BA. Preeclampsia and cardiovascular disease death: prospective evidence from the child health and development studies cohort. Hypertension 2010; 56:166–71.

27. Yusuf S, Hawken S, Ôunpuu S, Dans T, Avezum A, Lanas F, et al. Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case-control study. The Lancet 2004; 364:937–52.

28. Engeland A, Bjørge T, Klungsøyr K, Skjærven R, Skurtveit S, Furu K. Preeclampsia in pregnancy and later use of antihypertensive drugs. Eur J Epidemiol 2015; 30:501–8.

29. Stuart JJ, Tanz LJ, Missmer SA, Rimm EB, Spiegelman D, James-Todd TM, et al. Hypertensive Disorders of Pregnancy and Maternal Cardiovascular Disease Risk Factor Development: An Observational Cohort Study. Annals of Internal Medicine 2018; 169:224–32.

30. Heida KY, Bots ML, Groot CJ de, van Dunné FM, Hammoud NM, Hoek A, et al. Cardiovascular risk management after reproductive and pregnancy-related disorders: A Dutch multidisciplinary evidence-based guideline. European Journal of Preventive Cardiology 2016; 23:1863–79.

31. Piepoli MF, Hoes AW, Agewall S, Albus C, Brotons C, Catapano AL, et al. 2016 European Guidelines on cardiovascular disease prevention in clinical practice: The Sixth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of 10 societies and by invited experts)Developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR). European Heart Journal 2016; 37:2315–81.

32. Visseren FLJ, Mach F, Smulders YM, Carballo D, Koskinas KC, Bäck M, et al. 2021 ESC Guidelines on cardiovascular disease prevention in clinical practice. European Heart Journal 2021; 42:3227–337.

33. World Health Organization. WHO recommendations for prevention and treatment of pre-eclampsia and eclampsia, 2011.

34. Detrano R, Guerci AD, Carr JJ, Bild DE, Burke G, Folsom AR, et al. Coronary calcium as a predictor of coronary events in four racial or ethnic groups. New England Journal of Medicine 2008;358:1336–45.

35. Genders TSS, Pugliese F, Mollet NR, Meijboom WB, Weustink AC, van Mieghem CAG, et al. Incremental value of the CT coronary calcium score for the prediction of coronary artery disease. European Radiology 2010; 20:2331–40.