Pregnancy Complication History in 10-Year Cardiovascular Disease Risk Prediction: a Review of Recent Evidence

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Abstract

Purpose of Review Women with prevalent pregnancy complications (including preterm birth and preeclampsia) have twice the risk of later cardiovascular disease (CVD) compared to unaffected women. Current prevention guidelines recommend that reproductive history should be part of a woman's CVD risk assessment. This review synthesizes recent findings on the value of history of pregnancy complications in 10-year CVD risk prediction.

Recent Findings The associations between several pregnancy complications and CVD are still evident when conventional predictors are considered in middle age. However, comprehensive evaluation suggests that these associations translate into only minor, if any, clinically relevant improvements in prediction.

Summary Current evidence suggests that 10-year CVD risk prediction in women is not substantially improved by history of pregnancy complications. Future studies should identify subgroups to target with prevention efforts post-pregnancy. In the meantime, conventional models are appropriate for estimating 10-year CVD risk in women with a history of pregnancy complications.

Keywords Cardiovascular disease · Risk prediction · Preterm birth · Pregnancy · Preeclampsia · Women's health

Introduction

Women with pregnancy complications are also at higher risk of future cardiovascular disease (CVD), including myocardial infarction and stroke. In particular, women with history of hypertensive disorders of pregnancy (preeclampsia and gestational hypertension), preterm birth, or small for gestational age (SGA) offspring appear to have approximately twice the risk of future CVD compared to unaffected women [1–3]. A proportion of this risk is likely attributable to the suboptimal pre-pregnancy risk profile in women subsequently affected by pregnancy complications [4] but the risk of CVD in affected women

cannot solely be explained by hereditary preponderance for CVD or worse cardiometabolic status [5, 6]. In the predominating framework, pregnancy constitutes a “stress-test” of the maternal susceptibility to CVD [7], and pregnancy complication history could thus potentially improve CVD risk prediction in women [8]. A woman's reproductive history is currently included as a factor to consider in relevant clinical guidelines from the American Heart Association/American College of Cardiology [9] and European Society of Cardiology [10] but the statements are vague and offer little practical advice (Table 1) [3]. Studies comprehensively evaluating pregnancy complications in addition to existing 10-year CVD risk score models have only recently emerged. The aim of this narrative review is to synthesize the evidence on the additional value of pregnancy complication history in 10-year CVD risk prediction in women from these recent studies. We review prospective studies on the additional importance of pregnancy complications from a clinical perspective, focusing on the 10-year risk horizon commonly applied in treatment clinical guidelines for primary prevention [10]. Based on the recent advancements in the field, we also provide suggestions for future

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Table 1 Statement on reproductive history in current CVD prevention guidelines

Guideline	Year	Summary of the relevance of reproductive history
AHA guidelines for the prevention of cardiovascular disease in women [9]	2011	Healthcare professionals who meet women for the first time later in their lives should take a careful and detailed history of pregnancy complications with focused questions about a history of gestational diabetes mellitus, preeclampsia, preterm birth, or birth of an infant small for gestational age. History of preeclampsia, gestational diabetes, or pregnancy-induced hypertension classified as a major risk factor for CVD.
AHA guidelines for the prevention of stroke in women [11]	2014	Consider evaluating all women starting 6 months to 1 year post-partum, as well as those who are past childbearing age, and document their history of preeclampsia/eclampsia as a risk factor.
ESC guidelines on CVD prevention in clinical practice [10]	2016	Pre-eclampsia and pregnancy-related hypertension increase CVD risk (RR 1.5–2.5 and 1.9–2.5 respectively) but the degree to which the increased CVD risk occurs independent of conventional CVD risk factors is unknown. Information on whether female-specific conditions improve risk classification in women is unknown.
Dutch multidisciplinary evidence-based guideline on CVD risk after reproductive and pregnancy-related disorders [12]	2016	Follow-up and risk factor screening is recommended for women with a history of preeclampsia. For all reproductive and pregnancy-related disorders optimization of modifiable cardiovascular risk factors is recommended to reduce the risk of future CVD.

ACC, American College of Cardiology; AHA, American Heart Association; CVD, cardiovascular disease; ESC, European Society of Cardiology; LDL, low-density lipoprotein; RR, relative risk

research on how to improve the primary prevention of CVD in women with history of pregnancy complications.

A History of Certain Pregnancy Complications Is Associated with Higher Risk of Future CVD

It has been repeatedly shown that preeclampsia, preterm birth, and SGA offspring are associated with higher risk of CVD, including ischemic heart disease and stroke, later in life [2]. Even though the higher relative risk of CVD in women with history of pregnancy complications might quantitatively decrease with age [6], it is still evident over five decades of follow-up [13]. Women with preeclampsia, preterm birth, and SGA offspring also have worse CVD risk profile post-pregnancy compared to women without these complications [14]. Women with preeclampsia [15] have worse endothelial function before, during, and after pregnancy [16]. Given that pregnancy complications might be manifestations of a cardiovascular phenotype prone to future CVD, such as worse endothelial function [16], a history of such complications might hold information that is not reflected in the established predictors

already included in CVD risk scores. Nevertheless, the absolute risk of CVD in women in their 30s is low, even in women with moderately increased risk on the relative scale. For clinical effectiveness, it is important to not only identify women with at high risk but also determine the appropriate time point for any intervention based on their absolute risk.

Methodological Considerations to Improve CVD Risk Prediction Models Using Pregnancy Complication History

Several excellent papers on CVD risk prediction describe the modeling process [17–19]. To evaluate the additional value of pregnancy complication history, a comprehensive analysis of the extent to which a new risk marker improves risk prediction [20, 21] is especially important. For reporting, the widely endorsed TRIPOD statement paper on the reporting of prediction models should be followed as appropriate [22]. Below we highlight aspects important to consider when evaluating pregnancy complications as potential predictors. Ten years is a common horizon in clinically implemented risk models [10,

[23], and it is also frequently used to define risk thresholds for pharmacological intervention in guidelines [10]. This follow-up period is thus suitable also for studies investigating the value of pregnancy complications in improving the prediction ability of current models. To assess the clinical relevance of a novel predictor, i.e., to study whether a predictor has the potential to enhance the clinical prediction of the outcome above and beyond the reference risk model, the reference model should be used in clinical practice or have equivalent performance to such models [24]. In contrast, to provide evidence *against* including a novel predictor in risk score models, all predictors in the reference model are arguably not needed. If the novel predictor does not improve risk prediction when adjusted for only a subset of reference model predictors, it is not likely to improve prediction when all risk factors are used.

To be potentially relevant from a modeling perspective, a novel predictor should be associated with CVD also when added to the reference model. To be clinically relevant, however, the addition of the new predictor should result in improved prediction—risk reclassification—as defined by relevant cut-offs for clinical decision making or other intervention. For example, for initiating statin therapy in US adults age 45–75 years, the optimal cutoff is likely between 5 to 10% 10-year predicted risk of atherosclerotic CVD [25]. If a novel predictor mainly improves risk prediction by increasing the risk estimate for individuals already at very high risk, or only lowers the risk estimate for individuals at already very low estimated risk, it does not affect the clinical decision to start an intervention or not. As a consequence, model evaluation should include categorical risk-reclassification across clinically relevant thresholds and present results for events and non-events separately. Mainly focusing on the receiver operating characteristic (ROC) curve and improvement of the c-index, or equivalent measure, does not directly translate to practical clinical relevance and should be avoided [26, 27].

The type of predictor added to the risk prediction model might also limit the potential improvement of the model. If the novel predictor is continuous it will potentially allow for a wide distribution of re-estimated risk. In contrast, if the predictor is dichotomous the updated risk calculation—compared to the original risk estimate—can only result in one of two counterfactual risk estimates for each individual depending on whether the individual is exposed or not. The prevalence of a risk factor in the target population is also important to consider. For example, preterm preeclampsia is a severe pregnancy complication and a strong relative risk factor for future CVD in young women, but only a small minority of pregnant women are affected by it (< 0.5%) [28]. Even under the assumption that preterm preeclampsia would improve CVD risk prediction on a statistical level, clinical implementation of such model might be hampered by the rarity of a positive response when asking women about reproductive history in the clinic. Risk factors that are linked to a particular high risk of CVD but have a

low prevalence are less relevant for primary risk score modeling and better suited to identify certain subgroups to target. For example, familial hypercholesterolemia is associated with a very high lifetime risk of CVD which motivates specific treatment guidelines in this particular group of patients [29].

The measurement error of a novel predictor is important for effectiveness in a clinical setting. To utilize pregnancy complications for prediction post-pregnancy there are potential for uncertainty both at the time of pregnancy (e.g., an incorrect diagnosis or a correct diagnosis but inadequate communication with the patient) and at the time of prediction because of recall uncertainty if self-report is used to collect the information [30, 31]. If health care providers are to rely on women's own recall of pregnancy complication history, simple models utilizing few additional predictors are likely most effective. In contrast, with access to integrated medical records, in which the pregnancy complication history is readily available, prediction models with a higher level of complexity become clinically more feasible.

If the predictive performance of pregnancy-related factors is to be generalizable to the general population of women, and not only those parous, parity needs to be concomitantly considered. This needs special consideration in regression modeling as only parous women can report pregnancy complications occurring in later pregnancy. Stuart et al. [32•] addressed this problem of positivity by merging parity and hypertensive disorders of pregnancy (HDP, i.e., preeclampsia and gestational hypertension) history into several exclusive categories and comparing them to the reference model in aggregate.

Pregnancy Complication History to Improve CVD Risk Prediction

In Table 2, we show a summary of studies investigating the extent to which pregnancy complications improve 10-year CVD risk prediction above and beyond established CVD risk prediction models [32•, 33•, 34•, 36•]. All in all, the studies report no clinically meaningful improvement of CVD risk prediction models after the addition of pregnancy complication history. Parikh et al. investigated if reproductive risk factors for coronary heart disease (CHD) improved risk reclassification when added to models with conventional CHD risk factors [33•]. For this purpose they utilized data from the observational arm of the Women's Health Initiative. CHD was defined as physician-adjudicated fatal and non-fatal CHD, which included clinical myocardial infarction and coronary artery revascularization. The study showed that several reproductive factors, such as younger age at first birth, number of stillbirths, number of miscarriages, and lack of breastfeeding, were positively associated with CHD in postmenopausal women but only modestly improved CHD event

Table 2 Summary of studies evaluating pregnancy complication history to improve 10-year cardiovascular disease risk prediction in women

Study	Study design	Location	Sample size	Age at baseline	Exposures investigated	Reference model	Summary of main findings	Categorical net reclassification improvement compared to reference model*
Parikh et al., 2016 [33•]	Prospective observational cohort study. Outcome is CHD.	USA	72,982 parous women	63.2 (SD: 7.3) years	Parity, number of live births, age at menarche, menstrual irregularity, age at first birth, number of stillbirths, number of miscarriages, any reported history of infertility ≥ 1 year and breastfeeding.	No established prediction model used.	Early age at first birth, number of stillbirths and miscarriages, and lack of breastfeeding for ≥ 1 month are independently associated with postmenopausal CHD and very modestly improved postmenopausal CHD event discrimination over and beyond established risk factors.	Events: 0.007 (95% CI –0.003 to 0.018) Non-events: 0.002 (95% CI 0.0001 to 0.005)
Timpka et al., 2018 [34••]	Population-based prospective cohort study	Västerbotten County, Sweden	11,110 parous women	50 or 60 years	HDP and LBW offspring	“Lab based model” by Gaziano et al. [35]	Compared with conventional risk factors, history of pregnancy complications did not meaningfully improve 10-year CVD risk prediction in women aged 50 years or older. History of LBW offspring at age 50 years was the most informative predictor.	Results for women aged 50 years, utilizing information on LBW offspring. Events: 0.038, (95% CI 0.003 to 0.074) Non-events: –0.001 (95% CI –0.006 to 0.003)
Stuart et al., 2018 [32••]	Prospective observational cohort study	USA	67,406 women	47.2 (SD: 5.1)	Combination of HDP and parity	ACC/AHA Pooled cohort equation [23]	Additional inclusion of HDP and parity did not improve discrimination or reclassification.	Events: 0.004, (95% CI –0.002 to 0.010) Non-events: –0.0003 (95% CI –0.0005 to –0.0002)
Markovitz et al., 2019 [36••]	Population-based prospective observational cohort study	Nord-Trøndelag County, Norway	18,231 parous women	52 years (IQR: 46–59)	Preeclampsia, gestational hypertension, preterm birth, and SGA	NORRISK 2 [37]	Preeclampsia predicted CVD when added to the reference model. The inclusion of preeclampsia, gestational	Events: 0.02, (95% CI –0.002 to 0.05) Non-events: 0.004 (95% CI 0.002 to 0.006)

Table 2 (continued)

Study	Study design	Location	Sample size	Age at baseline	Exposures investigated	Reference model	Summary of main findings	Categorical net reclassification improvement compared to reference model*
							hypertension, preterm delivery and SGA in aggregate made only small improvements to the CVD prediction performance.	

CHD, coronary heart disease; CVD, cardiovascular disease; CI, confidence interval; HDP, hypertensive disorders of pregnancy; IQR, interquartile range; LBW, low birth weight; SD, standard deviation; SGA, small for gestational age

*Results for risk reclassification across three similar risk categories (approximately 0–5%, 5–10%, and > 10% predicted 10-year CVD risk) are used for comparison between studies. Following multiplication by 100, the presented results can be interpreted as percentage reclassified in each category

discrimination. Net reclassification of CHD was not materially improved by the addition of reproductive factors to established risk factors. For the purpose of early identification of women with high risk of CVD following pregnancy, limitations of the study include the relatively old age of women (mean age 63 years), the outcome was limited to CHD, and the lack of data on common pregnancy complications such as preeclampsia and preterm birth.

Timpka et al. studied to which extent including a history of HDP or delivering low birth weight (LBW; < 2500 g) offspring would improve CVD risk prediction above and beyond conventional predictors [34••]. The study leveraged data from population-based prevention visits in primary care for women aged 50 or 60 years in a county in northern Sweden in combination with registries of births and CVD events. CVD was defined as myocardial infarction, angina, stroke, and TIA based on International Classification of Diseases (ICD) diagnosis codes. The authors used a reference model developed by Gaziano et al. [35] and investigated the incremental value of incorporating the pregnancy complication history to the conventional predictors. History of LBW offspring was associated with increased risk of CVD in women 50 years of age but not at age 60 years. CVD prediction was not further improved by information on LBW offspring, except that a slightly greater proportion of the women who developed CVD were assigned to a higher risk category. History of HDP was not associated with CVD when adjusted for reference model predictors and the authors concluded that a history of pregnancy complications could identify women with increased risk of CVD mid-life but did not meaningfully improve 10-year CVD risk prediction in women age 50 years or older. Limitations of the study include the age-restricted sample of Scandinavian women age 50 and 60 years and no available data on preterm birth.

Stuart et al. [32••] studied if the inclusion of HDP and parity in an established CVD risk score (pooled cohort equation) [23] improved the prediction of CVD events women 40 years or older who were at an overall lower risk for CVD. To do so, the authors utilized data from the Nurses' Health Study II, a questionnaire-based prospective study of female nurses in the US. Preeclampsia history was determined by self-report in middle age and CVD events (myocardial infarction, angina, stroke, or TIA) were collected either through self-reported—subsequently verified against medical records when possible—or death records. HDP and parity were associated with 10-year CVD risk independent of established CVD risk factors, overall and at ages 40 to 49 years and improved model fit at ages 40 to 49 years. However, the inclusion of HDP and parity in the risk prediction model did not improve discrimination or risk classification. Limitations of the study include self-report of pregnancy complications and the convenience-based sample of female nurses.

Markovitz et al. [36••] evaluated whether history of pregnancy complications (preeclampsia, gestational hypertension,

preterm delivery, or SGA improved CVD risk prediction in women 40 years or older using NORRISK2 as the reference model [37]. Data on pregnancy complications were collected from a comprehensive birth registry and data from the population-based Nord-Trøndelag Health (HUNT) studies were used to capture conventional CVD risk factors in middle age. Incident CVD (first non-fatal MI, fatal CHD, or non-fatal or fatal stroke) was based on medical records from the two primary hospitals in the county and subsequently validated by a cardiologist. Preeclampsia was found to independently predict CVD after controlling for established predictors. Including all pregnancy complications made only small improvements to CVD prediction and the improvement was driven by inclusion of preeclampsia. Regardless, the observed differences compared to the reference model were small and unlikely to be clinically meaningful.

Current Gap of Knowledge

As we review above, the current evidence suggests that adding pregnancy complication history to general population CVD risk models do not translate into clinically meaningful improvements of CVD prediction models in women. Still, there are significant gaps of knowledge to address both regarding risk prediction modeling and how to best leverage information available at pregnancy to improve primary prevention of CVD in women. Little evidence exists on the extent to which specific pregnancy complication history interact with age and other pregnancy complications in the prediction of CVD, which might offer an opportunity to improve and refine conventional 10-year CVD risk prediction models. All studies on pregnancy complications and risk prediction included in this review predominantly include white women, and two are based on data from Scandinavia. Little evidence exists regarding the improvement of CVD risk scores in young women in their 30s by including pregnancy complications, but as the absolute risk of CVD in this group is low, investigators need to consider the theoretical potential of any candidate predictor to improve prediction modeling *a priori*. Still, the time between pregnancy and overt CVD development should indeed be regarded as a “window of opportunity” for primary prevention [38]. Though including pregnancy complication history in risk score modeling *per se* might not be effective, pregnancy still has great potential as a period to identify and modify a woman’s risk of future CVD. With increased use of integrated medical records, information on pregnancy complication history will become more readily available to all clinicians over the next decade. However, it is important to not only focus on the occurrence of pregnancy complications for the prevention of CVD. Women with obesity or hypertension might also be at a relative risk of CVD that is comparable [39, 40], or higher, to the doubled risk reported for women with pregnancy complications. A

recent study suggested that blood pressure in early pregnancy is strongly related to worse cardiovascular profile, including hypertension, 6 years post-pregnancy [41]. There is also evidence suggesting that overweight and obesity is especially detrimental for women with history of HDP, resulting in high risk of chronic hypertension and type 2 diabetes [42, 43]. Thus, for effective primary prevention at the time of, or following, maternity care it is important that all risk factors for CVD are considered and not only those directly pregnancy-related. Dam et al. [44] investigated the performance of three commonly used CVD risk prediction models (SCORE, Framingham risk score, and Pooled Cohorts Equation) in women with a history of HDP and compared the performance to women with only normotensive pregnancies. They found the predictive performance of all models to be similar regardless of HDP history. The SCORE model, which predicts CVD mortality, had the best calibration and discrimination without recalibration. A limitation of the study was that the HDP history was self-reported and 26.7% of women reported such history, which is two to three times higher than most studies. For example, Markovitz et al. reported < 10% women to have preeclampsia or gestational hypertension based on comprehensive birth registry data [36•]. The extent to which non-traditional pregnancy-related predictors available post-partum predict CVD, or its intermediates, in comparison to traditional risk scores in women with pregnancy-related complications is unknown and should be studied.

Conclusions

Women with a history of HDP, preterm birth, or SGA offspring have increased risk of future CVD and also develop certain risk factors at an earlier age compared to unaffected women. However, current available evidence suggests that traditional CVD risk score models are not meaningfully improved by including information on women’s history of these pregnancy complications. Instead, women affected by pregnancy complications might be regarded as a high-risk group for CVD to target with screening for traditional risk factors and intervene as appropriate. Still, the number of studies available, as well as the racial/ethnic diversity of study samples, is low. In order to further elucidate the value of pregnancy complications and reproductive history in CVD risk prediction, investigators should especially consider the prevalence of the candidate risk factor in the target population, define clinically relevant risk thresholds to analyze risk reclassification, and present analyses that allow for easy comparison with established risk prediction models. To improve the primary prevention of CVD in young women in general, future studies should focus on how, and when, to best leverage all information potentially available to health care providers caring for pregnant or post-partum women, regardless whether this information is derived from pregnancy or not.

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Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by the author.

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