Assessment of Cardiovascular Disease after Hypertensive Pregnancy Disorders

Visser, V.S.

2015

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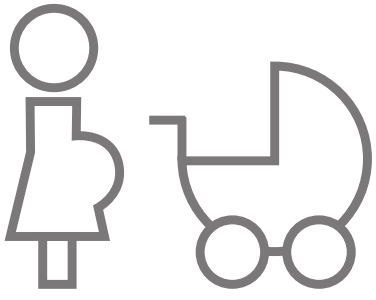
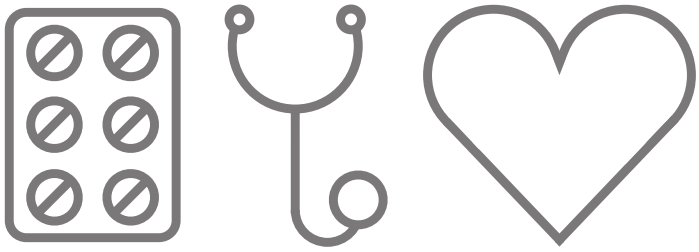


CHAPTER 10

Discussion



In this thesis we present several studies concerning cardiovascular disease risk after hypertensive pregnancy disorders. The ultimate goal of research in this area is to increase women's healthy aging by reducing cardiovascular event risk in those women with pregnancies complicated by hypertension. Recent literature demonstrates that these women are at increased risk to develop cardiovascular events at early age (**figure 1**). The first part of this thesis considers markers after hypertensive pregnancy disorders to gain insight in the pathogenesis of cardiovascular disease in women with a pregnancy complicated by hypertension. In the second part we first focused on prediction models of cardiovascular disorders to gain insight into prevention, and subsequently we examined barriers towards prevention of cardiovascular disease by investigating awareness of gynecologists and protocols of hypertensive pregnancy disorders. In this chapter we discuss implications of our research with finally suggestions for future research.

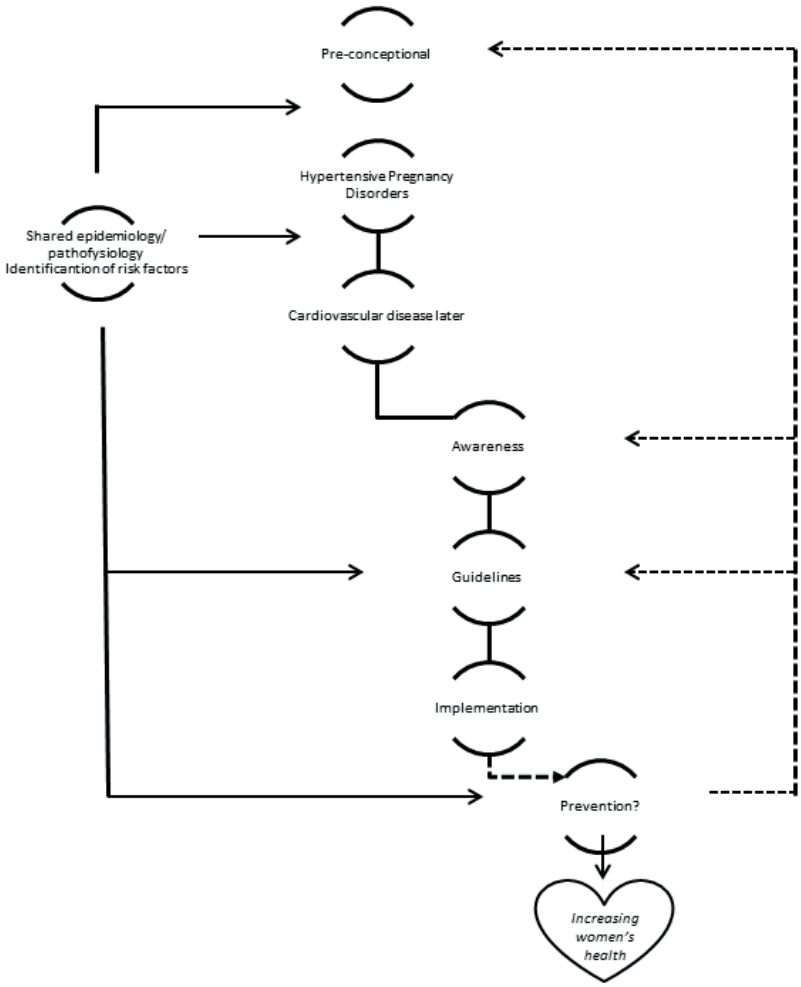


Figure 1.

Shared Pathogenesis of Hypertensive Pregnancy Disorders and later Cardiovascular Disease

Hypertension during pregnancy includes a broad spectrum of disease including pregnancy induced hypertension and preeclampsia. Especially for early hypertensive pregnancy disorders, disease before 34 weeks of pregnancy, etiology represents mostly processes of placentation.

Placentation is a process that starts in the first trimester of pregnancy [1]. One of the key steps in placentation is the remodeling of spiral arteries to obtain efficient blood supply through the placenta to the fetus [2]. In normal placentation, replacement of the endothelial cells in the lining of the blood vessels invading the uterine wall by cytotrophoblast cells results in a blood supply system with low resistance. It is widely accepted that abnormalities occurring in placentation eventually result in complications in late pregnancy such as preeclampsia. When the cytotrophoblast invasion is abnormal, decreased uteroplacental perfusion will result in ischemia. Abnormal placentation is likely to have a multifactorial etiology, but imbalanced angiogenesis is mentioned as one of the most important steps in its pathogenesis. Ischemia due to abnormal placentation will lead to release of factors that change maternal endothelial function [3]. Endothelial cells form the inner lining of vessels throughout the body and form an "organ" which influences vasoconstriction and dilatation and is responsible for the balance in several processes such as coagulation and anticoagulation functions.

Many markers of endothelial dysfunction have been described in women with pregnancies complicated by hypertension. This abnormal endothelial function is hypothesized to be responsible for the clinical manifestation of hypertension in pregnancy, especially in preeclampsia. Markers of endothelial dysfunction appear to be present in early pregnancies that will subsequently be complicated by hypertensive disorders, and this implies that endothelial dysfunction itself might play a role in the etiology of hypertensive pregnancy disorders (**figure 2**).

Women with a history of hypertensive pregnancy disorders have a higher risk of cardiovascular disease later in life [4]. Systematic review and meta-analyses demonstrate, next to a higher risk on cardiovascular disease, also an increased risk on cerebrovascular disease, peripheral arterial disease and cardiovascular mortality after preeclampsia [5].

It remains an interesting discussion whether women with a history of hypertensive pregnancy disorders experience this higher cardiovascular risk due to the complicated pregnancy or due to a pre-existing disturbance in endothelial function which leads to both hypertensive pregnancy disorders and cardiovascular disease later (**figure 3**) [6,7]. In addition, changes in the endothelial system occurring during hypertensive pregnancy disorders might accelerate or aggravate development of cardiovascular disease. Due to the heterogeneity of the disease, both theories might play a role.

In both hypertensive pregnancy disorders and cardiovascular disease several biomarkers differ from healthy women. By investigation of these biomarkers insight can be gained in the shared pathogenesis of cardiovascular disease after hypertensive pregnancy disorders. The shared biomarkers in hypertensive pregnancy disorders and cardiovascular disease contain both classic and nonclassic biomarkers (Chapter 2, **table 1**). The biomarkers are present or elevated as

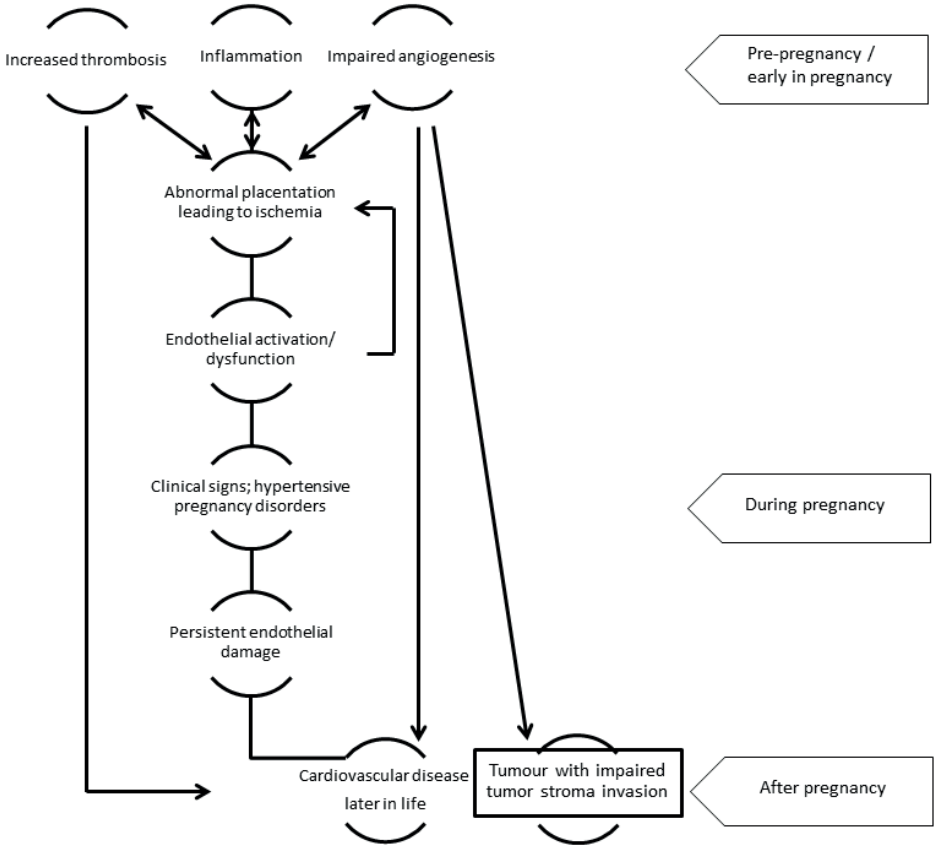


Figure 2.

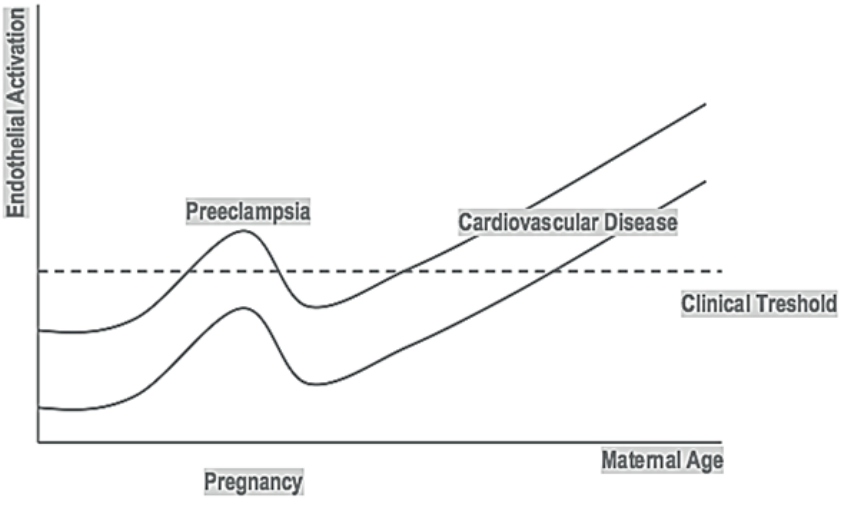


Figure 3.

Table 1. Cardiovascular markers in women after hypertensive pregnancy disorders

	Women with Hypertensive pregnancy disorders	Women with Cardiovascular Disease	Women with Cardiovascular Disease after Hypertensive Pregnancy
Clinical factors			
Age	+	+	+
Smoking	-	+	
Diabetes	+	+	
Family history	+	+	+ / -
Blood pressure	+	+	+
Classic Biomarkers			
Total cholesterol	-	+	+
HDL cholesterol	-	+	+
Glucose		+	+
Insulin		+	+
Triglyceride	+	+	+
Non Classic Biomarkers			
hsCRP	+		
homocysteine	+	+	+
inhibin A	+	+	-
soluble endoglin	+	+	

sign of increased thrombosis, inflammation or impaired angiogenesis leading to clinical signs in both cases with hypertensive pregnancy disorders compared to normotensive pregnancy and in women with cardiovascular disease compared to those with no cardiovascular disease. Extensive research is performed on cardiovascular markers after hypertensive pregnancy disorders [8,9]. Investigation of these biomarkers for cardiovascular disease after hypertensive pregnancy disorders has been suggested to obtain insights in the pathophysiological processes operating in these women. Finally, these insights can be important for preventive or therapeutical interventions in women with a history of hypertensive pregnancy disorders.

An example of a biomarker that is elevated in women with increased risk of thrombosis is homocysteine. Homocysteine is found to be elevated in women with hypertensive pregnancy disorders compared to women with normotensive pregnancies. These elevated levels of homocysteine support the hypothesis of a role for increased thrombosis in the pathophysiology of hypertensive pregnancy disorders [10]. Homocysteine is known as an independent risk factor for atherosclerosis and to be elevated in case of cardiovascular disease [11]. In Chapter 3 of this thesis we present a review and a cohort study that both showed higher homocysteine levels in women with a history of hypertensive pregnancy disorders compared to women with uncomplicated pregnancy at relatively young age (2 ½ years post partum). These higher homocysteine levels might suggest a sign that increased homeostasis plays an important role in the shared pathophysiology in hypertensive pregnancy disorders and cardiovascular disease (figure 2). It has been suggested that homocysteine, as markers for increased thrombosis, is already elevated preconceptional in women who subsequently develop hypertensive pregnancy disorders, but currently there is no evidence for this.

Prediction of cardiovascular disease after hypertensive pregnancy disorders

For the discussion we will make a tour through the clinical, classic and non-classical markers from those during pregnancy complicated by hypertensive disorders, to several years after complicated pregnancies and finally in women with manifest cardiovascular disease. Since it is stated that *prediction* of disease is an important step towards prevention of disease, extensive research is performed on prediction of both hypertensive pregnancy disorders and of cardiovascular disease (**table 1**).

Prediction of hypertensive pregnancy disorders

Different predictive models containing pregnancy related markers, clinical markers and biomarkers, are described for prediction of hypertensive pregnancy disorders. In these predictive models, the different markers are combined to calculate the risk for a pregnant woman to develop hypertensive pregnancy disorders. A review in 2015 described 38 prediction models for preeclampsia as hypertensive pregnancy disorder [12]. Pregnancy specific predictive markers include uterine artery Doppler and biochemical markers including pregnancy-associated plasma protein-A and placental growth factor. Other clinical markers described with predictive value for development of preeclampsia include advanced maternal age, higher body mass index, medical history (e.g. chronic hypertension or diabetes mellitus), and a positive family history of preeclampsia of the mother of patient. Biomarkers that were found predictive for preeclampsia are inhibin A and soluble endoglin.

Besides the risk models evaluated in the review, different individual markers (clinical, classic and nonclassic) are evaluated for their predictive value for hypertensive pregnancy disorders. Clinical markers like diabetes and increased blood pressure are also found to be predictive for an increased risk of development of hypertensive pregnancy disorders. Smoking is known to have a role in development of cardiovascular disease, but, surprisingly, smoking during the first trimester of pregnancy is suggested to have a preventive effect on development of hypertensive disorders during pregnancy [13]. However, the pathophysiology is unknown.

The classic biomarkers triglyceride and total cholesterol and HDL cholesterol have been investigated in women with hypertensive pregnancy disorders. Recent data described a relation of increased triglyceride with hypertensive pregnancy disorders, but no relation of increased cholesterol with hypertensive pregnancy disorders [14].

The nonclassic biomarkers with predictive value for hypertensive pregnancy disorders have been broadly investigated and described. Nonclassic markers that are described to have predictive value for hypertensive pregnancy disorders contain markers in the areas of inflammation, increased thrombosis and impaired angiogenesis [15,16]. In this thesis we focus on a nonclassic inflammatory biomarker (hsCRP) and a biomarker of increased haemostasis (homocysteine). hsCRP has been suggested to be a sensitive maker of inflammation [17]. hsCRP is elevated in women during hypertensive pregnancy disorders (preeclampsia) compared to women with normotensive pregnancy [18]. As stated above, homocysteine levels, a sensitive marker for increased haemostasis, is elevated in women with hypertensive pregnancy disorders compared to women with normotensive pregnancy. Although these two markers are found to be elevated in the first trimester of

pregnancy in women with subsequently hypertensive pregnancy disorders compared to women with subsequently normotensive pregnancy, the predictive value of these individual nonclassic biomarkers is limited (**table 1**) [19].

Prediction of cardiovascular disease

Cardiovascular risk assessment is widely believed to play a crucial role in prevention of cardiovascular disease. Therefore, a lot of research is performed in the area of prediction of cardiovascular disease. Cardiovascular disease contains a spectrum of diseases of heart and blood vessels including coronary heart disease, heart failure, peripheral arterial disease and cerebrovascular events that are responsible for the majority of morbidity and mortality in women in the Western world [20]. For prediction of cardiovascular disease, clinical, classic and nonclassic markers are combined in risk assessment models that have been widely recommended in international and national guidelines. The most cited risk model used is the sex specific Framingham risk score that includes clinical markers and biomarkers in prediction of cardiovascular events over the following 10 years [21]. The clinical factors include age, smoking, diabetes and blood pressure; the biomarkers include total cholesterol and HDL cholesterol. In 2012 the American Heart Association compared the Framingham risk score with the latter designed Reynolds risk score in multiethnic women [22]. Conclusion of this independent validation cohort showed a better discrimination of the Reynolds risk score in women. The Reynolds risk score included the biomarker high sensitive C-reactive protein (hsCRP) and the clinical markers of a positive family history on heart attack before the age of 60 to the markers included in the Framingham risk score in prediction of a cardiovascular event in the following 10 years.

Besides to the cardiovascular risk models, which focus on clinical markers and classic biomarkers, extensive research is performed in the areas of nonclassic biomarkers that might play a role in the pathogenesis of cardiovascular disease. Nonclassic biomarkers elevated in women with cardiovascular disease are broadly described, but their roll in prediction of cardiovascular disease remains unclear. Two recent reviews on biomarkers of cardiovascular disease in specifically women state that hsCRP has been improved in prediction of cardiovascular disease in women [23.24]. Another nonclassic biomarkers frequently mentioned in research on prediction of cardiovascular disease is homocysteine. As stated above, homocysteine is an independent risk factor for atherosclerosis (**table 1**).

Prediction of cardiovascular disease after hypertensive pregnancy disorders

In this thesis we found predictive value for cardiovascular disease of several clinical factors relatively shortly *after* hypertensive pregnancy disorders. This knowledge of an increased risk on cardiovascular disease early in life opens a window of opportunities for preventive strategies. Clinical factors with predictive value that we found include higher maternal age, lower education, negative family history on hypertensive pregnancy disorders, higher BMI at booking, higher diastolic blood pressure in early pregnancy and higher systolic blood pressure during at pregnancy. In earlier work we found elevated classic biomarkers after hypertensive pregnancy disorders which can be used in prediction of cardiovascular disease [25]. The classic biomarkers that were described are glucose, insulin, total cholesterol, triglycerides, HDL cholesterol.

In literature nonclassic biomarkers are described extensively. Therefore we chose to focus on a few biomarkers that are well investigated. Nonclassic biomarkers for prediction of cardiovascular disease contain markers in areas of inflammation, increased thrombosis and impaired angiogenesis. In the review in this thesis (Chapter 2) we focus on a selection of nonclassic biomarkers in these areas. In individual articles biomarkers in the areas of inflammation and of impaired angiogenesis are described to be elevated but meta-analyses of the articles showed no significant increased levels of these biomarkers in women with a history of hypertensive pregnancy disorders compared to women with a history of normotensive pregnancy [9]. In the area of increased thrombosis, a significant higher level of homocysteine is discovered in women with a history of hypertensive pregnancy disorders compared to women with a history of normotensive pregnancy 2½ years postpartum.

In earlier work we studied nonclassic biomarkers for cardiovascular disease in women with a history of hypertensive pregnancy disorders and found higher levels of hsCRP. In this thesis we report an increased level of homocysteine after hypertensive pregnancy disorders (Chapter 3, **table 1**).

To our knowledge there is no predictive model for cardiovascular events specific for women with hypertensive pregnancy disorders. For the development of such risk models we suggest that the predictive clinical factors, classic and nonclassic biomarkers described in this thesis are to be considered.

Awareness, from doctor to patient

From prediction of cardiovascular disease in women with a history of hypertensive pregnancy disorders to subsequent preventive interventions, the crucial first step is awareness (**figure 1**) [26]. This is the *awareness* of women on their increased risk and the interventions that might prevent cardiovascular disease. Awareness is defined as the level of consciousness on a particular subject. To create awareness in women with a history of hypertensive pregnancy disorders, it is important that doctors inform their patients on this subject as well as women are informed by newspapers, patients organizations, social media and so on. In Chapter 7 we focus on the awareness of the doctors, which will increase the awareness for their patients. In area of cardiovascular disease risk after hypertensive pregnancy disorders, several doctors are involved including general practitioners, gynecologists or obstetricians, midwifes and the internal medicine doctors. During pregnancy, the gynecologist or obstetrician is the attending doctor, but after pregnancy in case of cardiovascular risk assessment and possible even treatment the general practitioner or the doctor of internal medicine is mainly in the lead. We argue that awareness should exist throughout doctors working in these specialties and that they should work together in achieving the best awareness in and care for these women besides other social media options. Awareness of the doctor is achieved by adequate protocols and *guidelines* on a subject transfer of knowledge about this topic in general and specific about each women [37]. In case of management and prevention of cardiovascular disease after hypertensive pregnancy, a multidisciplinary guideline available for all health care workers in this field should be aimed towards.

Future Perspectives

Research up till now, including research presented in this thesis, yielded important insight in the

prediction of cardiovascular disease after hypertensive pregnancy disorders. As stated before, this prediction is an important step towards prevention of cardiovascular disease. In earlier work we have shown cost effectiveness of prevention of cardiovascular disease after hypertensive disease in pregnancy. In the sequence from prediction of cardiovascular disease after hypertensive pregnancy disorders toward decreasing cardiovascular events, the proof of effectiveness of preventive interventions for cardiovascular disease in these women is still missing (**figure 1**).

Different strategies for *prevention* of cardiovascular disease include lifestyle adjustments and pharmacotherapeutic options [28,29]. To our knowledge no randomized controlled trial has been performed in this specific group of women with an increased cardiovascular risk in comparing the effect of different preventive measurements. An effect of life style interventions after hypertensive pregnancy disorders is described to be effective in decreasing cardiovascular risk, but further research in this area is definitely recommended [30]. In general population most recommendations on effectiveness of preventive measurements are based on research performed in men [31]. For instance studies that claim a significant effect in reduction of cardiovascular events by aspirin included mostly men [32]. When results were divided due to different sex, the beneficial effects of aspirin seemed modest in women.

Studies show that cardiovascular disease in women is mainly a result of hypertension [33]. Therefore, preventive measurements for cardiovascular disease in women should focus on reduction of hypertensive risk. This is described to be accomplished by maintaining healthy body weight through diet and exercise, reduce sodium intake, stop smoking and reduce alcohol intake in women. Therefore, these lifestyle interventions are interesting to examine in the specific group of women with a history of hypertensive pregnancy disorders for their effect on reduction of cardiovascular disease risk. Further, since we found that homocysteine levels are significantly increased in women after hypertensive pregnancy disorders, this could open therapeutic options. Although homocysteine-lowering interventions did not show any significant effect on myocardial infarction, stroke or death by any cause when compared to a placebo in general population, this is an opportunity for research [34].

In addition it is important to investigate which form of preventive interventions are achievable and preferred by this group of women. Women should be questioned about this issue. Then we suggest a randomized controlled trial comparing different strategies in preventive interventions for cardiovascular disease in women with a history of hypertensive pregnancy disorders. Results of research on preventive measurements in women more general should be taken in account to define preventive strategies to be compared. We propose an intervention trial that will include women with a history of hypertensive pregnancy disorders who will be randomized in either intervention group, these women will be provided a tailor made lifestyle changing program or the control group using "care as usual". In the Netherlands, several studies have been performed using a tailor made lifestyle program for lifestyle changes to reduce cardiovascular risk factors that might be useful for designing intervention program for this trial [35,36]. The first step for women in the intervention group should be a personal risk assessment and feasibility study to study the willingness for life style changes in order to develop a tailor made program that preferable will start several months after pregnancy. Besides the contribution of the patient, the program should

be carried out in close collaboration with the patient's general practitioner and supported by computer-tailored advice modules. For the women in the control group normal procedures post partum should be followed. To indicate the effectiveness of the intervention program, a 10-year cardiovascular risk assessment estimated with the Framingham risk function can be used [21]. Since we expect a low Framingham risk score due to the low maternal age, we propose an extrapolation of risk at age of 60 years will indicate if a difference in cardiovascular risk is achieved.

When this final step is completed, and an effective preventive strategy for cardiovascular disease is discovered for women with a history of hypertensive pregnancy disease, we feel that the cascade from prediction of cardiovascular disease after hypertensive pregnancy disorders towards improvement of women's health is completed.

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