High Blood Pressure in Pregnancy and Coronary Calcification

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Abstract—A considerable proportion of pregnant women develop high blood pressure in pregnancy. Although it is assumed that this condition subsides after pregnancy, many of these women develop the metabolic syndrome later in life and are at increased risk to develop coronary heart disease. Atherosclerosis development is considered in between risk factors and occurrence of vascular symptoms. We set out to cross-sectionally study the relation of high blood pressure during pregnancy with risk of coronary calcification. The study population was composed 491 healthy postmenopausal women selected from a population-based cohort study. Information on high blood pressure during pregnancy was obtained using a questionnaire. Between 2004 and 2005, the women underwent a multidetector computed tomography (Philips Mx 8000 IDT 16) to assess coronary calcium. The Agatston score, volume, and mass measurements were used to quantify coronary calcium. A total of 30.7% of the women reported to have had high blood pressure in pregnancy. Body mass index (odds ratio [OR]: 1.05; 95% CI: 1.01 to 1.09) and diastolic blood pressure (OR: 1.03; 95% CI: 1.01 to 1.05) were significantly related to a history of high blood pressure in pregnancy. Age was significantly related to increased coronary calcification. Women with a history of high blood pressure during pregnancy had a 57% increased risk of having coronary calcification compared with those women without this condition (OR: 1.57; 95% CI: 1.04 to 2.37). After adjusting for age, the relation did not change (OR: 1.64; 95% CI: 1.07 to 2.53). We concluded that high blood pressure during pregnancy is associated with an increased risk of coronary calcification later in life. (Hypertension. 2007;49:1-5.)

Key Words: multidetector computed tomography (MDCT) • cardiovascular diseases (CVD) • coronary calcification • atherosclerosis • blood pressure

Hypertensive disorders are common complications of pregnancy and rank among the leading causes of maternal and perinatal morbidity and mortality worldwide.1-3 Depending on the definitions used and the populations studied, high blood pressure is reported to affect 2% to 35% of all pregnancies.4 In the various classification schemes proposed, hypertension specific for and secondary to pregnancy is referred to as gestational hypertension, pregnancy-induced hypertension, or, when proteinuria is observed as well, pre-eclampsia. Pre-eclampsia, in particular, is associated with an increased risk of adverse pregnancy outcome for both the mother and the fetus.

During the last decade, evidence has accumulated that hypertensive disorders of pregnancy, pre-eclampsia, in particular, are associated with future hypertension and cardiovascular events. Pre-eclampsia and cardiovascular disease (CVD) share chronic hypertension, increased total cholesterol, decreased insulin sensitivity, and increased body mass index as common risk factors.5 Large epidemiological studies have demonstrated that women who have had pre-eclampsia are at high (2-fold) risk to develop CVD in later life.6-11 Many of the women who have had pre-eclampsia in pregnancy and who have no signs of clinical disease after pregnancy exhibit the phenotype of the metabolic syndrome (overweight, latent hypertension, dyslipidemia, insulin resistance, and hyperhomocysteinemia) and impaired endothelial function at 3 to 12 months postpartum.12-15 Apparently, exposure of the women with this phenotype to the additional metabolic and cardiovascular challenges of pregnancy induces transient clinical disease (ie, pre-eclampsia) that subsides after pregnancy but is likely to re-emerge later in life as CVD.16-18 This knowledge has lead to the novel concept of pregnancy as a cardiovascular challenge test with the development of high blood pressure or pre-eclampsia as a marker of increased risk to develop atherosclerosis and vascular events in the future. To further expand on this notion toward the development of atherosclerosis, we studied the relation of high blood pressure during pregnancy with coronary atherosclerosis. Increased coronary calcium is indeed one of the strongest predictors of...
occurrence of coronary artery disease in the future and appears to be a better predictor of the risk of future events than conventional risk factors.\(^{19}\)

The use of coronary calcification as an end point in clinical studies is gaining interest. Arad et al\(^ {20}\) demonstrated that individuals with higher calcium scores (\(>160\)) were 35 times more likely to experience a cardiovascular event and that coronary artery calcification (CAC) measurements were more predictive of such events than were more traditional risk factors determinates. Guerci et al\(^ {21}\) found that the presence of coronary calcium was a “powerful predictor” of coronary artery disease regardless of other risk factors. In fact, recent evidence suggests that CAC quantification may be a better predictor of mortality than traditional Framingham risk factors, adding prognostic value when used in conjunction with traditional risk factor assessments.\(^ {22}\) There appears to be several valid indications for using CAC quantification as a screening test for CHD.\(^ {23}\)

**Methods**

**Population**

We used data from a cross-sectional study among 573 postmenopausal healthy women. These women were selected from participants of the Predictors of Response to Cardiac Resynchronization Therapy (PROSPECT) Study, 1 of the 2 Dutch cohorts participating in the European Prospective Investigation into Cancer and Nutrition.\(^ {24}\) In PROSPECT, 17,357 healthy participants of a nationwide population-based breast cancer screening program, aged 49 to 70 years, living in Utrecht and surroundings, were enrolled between 1993 and 1997. Between October 2002 and April 2004, a re-examination was planned in a sample to investigate the prognostic value of age at menopause on CVD risk. For this purpose, 6,612 women of the total of 17,357 were excluded because of death, further participation in PROSPECT or in other studies, absence of written informed consent, or emigration. Other reasons for exclusion were premenopausal state (n=1309), missing data on menopausal status (n=2105), or use of oral contraceptives or postmenopausal hormone therapy in the year before or after the last menstruation (n=1487), because age at menopause cannot be estimated precisely then. Of 5844 eligible women, a random selection of 1996 women was invited by a personal letter from the principal investigator of PROSPECT, and 1000 (50.1\%) answered positively. Of these 1000 women, 573 women were randomly selected for CAC measurement. In 5 women, no calcium scores could be obtained. Furthermore, information on a history of high blood pressure in pregnancy was missing in 77 women, so the final study population was composed of 491 women.

The medical ethical committee of the University Medical Center Utrecht approved the study, and written informed consent was obtained from all of the participants before enrollment.

At the baseline examination of the PROSPECT Study, women had been asked, “Did you suffer from high blood pressure during pregnancy?” If confirmative, we regarded women to have had a hypertensive disorder of pregnancy. At the re-examination visit, smoking behavior and family history of CVD were assessed by a questionnaire. Age was calculated from birth date and date of investigation. Height and weight were measured, and body mass index was calculated as weight divided by height squared (kilograms per meter squared). Waist:hip ratio was assessed. Systolic and diastolic blood pressures were measured at both arms with an automated and calibrated blood pressure device (DINAMAP XL, Critikon, Johnson & Johnson) with the subject in the supine position. A venous blood sample was drawn after an overnight fast of \(\geq 8\) hours. Plasma total cholesterol, plasma triglycerides, and plasma glucose were measured using standard enzymatic procedures. High-density lipoprotein cholesterol was measured by the direct method (inhibition, enzymatic). Low-density lipoprotein cholesterol was calculated using the Friedewald formula. We defined hypertension as either using antihypertensive therapy or a systolic blood pressure \(>140\) mm Hg or a diastolic blood pressure \(>90\) mm Hg.

**Coronary Calcium Measurements**

At a second visit between 2004 and 2005, the participants underwent a multidetector computed tomography examination (Mx 8000 IDT 16, Philips Medical Systems) for the assessment of CAC. Subjects were positioned within the gantry of the multidetector computed tomography scanner in supine position. A 16-slice scanner with 0.42-s rotation time was used to obtain 1.5-mm–thick sections. During a single breath hold, images of the heart, from the level of the tracheal bifurcation to below the base of the heart, were acquired using prospective ECG triggering at 50% to 80% of the RR interval, depending on the heart rate. Scan parameters were 16×1×5-mm collimation, 205-mm field of view, 0.42-s rotation time, 0.28-s scan time per table position, 120 kVP, and 40 to 70 mAs (patient weight <70 kg: 40 mAs; 70 to 90 kg: 55 mAs; >90 kg: 70 mAs). Scan duration was \(\sim 10\) s, depending on heart rate and patient size. Between the 2 scans, subjects sat upright and then lay down again. From the acquired raw data, 3-mm–thick sections were reconstructed. Quantification of coronary calcium was performed on a separate workstation with software for calcium scoring (Heartbeat-\(\text{CS, EBW, Philips Medical Systems.}\) All of the regions with a density \(>130\) Hounsfield units were identified as potential calcifications. After completing a training program, a trained scan reader, blinded for the obstetric history of the women, manually selected only the calcifications within 1 of the coronary arteries (left main, left anterior descending, left circumflex, right coronary artery, or posterior descending artery). To reduce the influence of noise, the minimum size of a calcified lesion was set at 0.5 mm\(^2\). The peak density in Hounsfield units and the area in millimeters squared of each selected region were calculated. The Agatston\(^ {26}\) calcium score was obtained by multiplying the area by a weighting factor that depends on the peak signal anywhere in the lesion. The scores of individual lesions were added to obtain the Agatston calcium score for the entire coronary tree. The total calcium volume was calculated by multiplying the area of the calcified lesion (measured in square millimeters) by section thickness (1.5 mm). The calcium volume for each coronary vessel was computed by summing the volumes of the lesions in that vessel for all of the sections. Finally, the total volume from all of the vessels became the calcium volume for a subject. The total coronary calcium mass uses volumetric, density information and a calibration phantom of hydroxyapatite to calculate the actual mass of the calcified plaques.

We performed reproducibility studies in which 199 scans were read in duplicate, showing intraclass correlation coefficients of \(>0.95\) for the duplicate readings. A reproducibility study in which in 73 women a duplicate multidetector computed tomography scan was made showed intraclass correlation coefficients between repeat scans of \(>0.90\) for all of the estimates of coronary calcification (volume, mass, and Agatston score; unpublished observations).

**Data Analysis**

First, the relation between potential confounding factors and a history of high blood pressure in pregnancy was examined using logistic regression models. In a similar manner, the relation of risk factors with coronary calcification in 1.5-mm–slice thicknesses was examined. Factors that showed significant relations with both a history of high blood pressure in pregnancy and coronary calcification were considered as confounders. Distinction was between factors not in the causal pathway and those potentially in the causal pathway. The relation between a history of high blood pressure in pregnancy with the outcome variable (coronary calcium absent/present) was investigated using logistic regression models. The relations were quantified by odds ratios with corresponding 95% confidence limits. Data analysis was performed using SPSS for Windows version 12.0.

Because the information on a history of high blood pressure in pregnancy was collected at the baseline examination of the
TABLE 1. General Characteristics of Study Population (N=491)

<table>
<thead>
<tr>
<th>General Characteristics</th>
<th>Mean</th>
<th>SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>66.8</td>
<td>5.4</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>26.8</td>
<td>4.5</td>
</tr>
<tr>
<td>WHR</td>
<td>0.84</td>
<td>0.06</td>
</tr>
<tr>
<td>SBP, mm Hg</td>
<td>136.9</td>
<td>20.1</td>
</tr>
<tr>
<td>DBP, mm Hg</td>
<td>72.3</td>
<td>9.2</td>
</tr>
<tr>
<td>Use of blood pressure-lowering drugs, %</td>
<td>24.6</td>
<td></td>
</tr>
<tr>
<td>Hypertension, %</td>
<td>32.3</td>
<td></td>
</tr>
<tr>
<td>Total cholesterol, mmol/L</td>
<td>5.97</td>
<td>0.89</td>
</tr>
<tr>
<td>LDL cholesterol, mmol/L</td>
<td>4.21</td>
<td>0.91</td>
</tr>
<tr>
<td>HDL cholesterol, mmol/L</td>
<td>1.37</td>
<td>0.36</td>
</tr>
<tr>
<td>Triglycerides, mmol/L</td>
<td>1.24</td>
<td>0.62</td>
</tr>
<tr>
<td>Glucose, mmol/L</td>
<td>4.28</td>
<td>0.90</td>
</tr>
<tr>
<td>Current smoking, %</td>
<td>12.0</td>
<td></td>
</tr>
<tr>
<td>Former smoking, %</td>
<td>43.7</td>
<td></td>
</tr>
<tr>
<td>Previous CVD, %</td>
<td>4.0</td>
<td></td>
</tr>
<tr>
<td>Pregnancy-induced hypertension, %</td>
<td>30.7</td>
<td></td>
</tr>
<tr>
<td>Family history of CHD in either parent, %</td>
<td>11.2</td>
<td></td>
</tr>
</tbody>
</table>

BMI indicates body mass index; CHD, coronary heart disease; DBP, diastolic blood pressure; LDL, low-density lipoprotein; HDL, high-density lipoprotein; SBP, systolic blood pressure; WHR, waist:hip ratio.

PROSPECT Study (long after the last pregnancy), those with chronic hypertension might recall high blood pressure in pregnancy better than those women who, at baseline, did not suffer from hypertension (ie, recall bias). To examine this, we repeated the analyses after subjects with hypertension at baseline were excluded (n=104).

Results

Information on a history of high blood pressure in pregnancy was present in 491 women. Women who had never been pregnant and those who reported an onset of hypertension before the age of 45 years were excluded. The general characteristics of the study population are given in Table 1. In our study population, the prevalence of a history of high blood pressure in pregnancy was 30.7% (n=151). The high prevalence is most likely a consequence of the fact that our measurement of “hypertension in pregnancy” includes women with not only brief and modest elevation of blood pressure during pregnancy but also women with (pre)eclampsia. Coronary calcium, that is, an Agatston score of ≥1, was found in 62.9% of our study population (n=305). The median Agatston score was 9.90. (interquartile range: 0 and 93.1).

Table 2 shows the relations of general characteristics with a history of high blood pressure in pregnancy. Increased body mass index, systolic blood pressure, diastolic blood pressure, and presence of hypertension were significantly related to a history of high blood pressure in pregnancy. Increased age, waist:hip ratio, systolic blood pressure, diastolic blood pressure, and presence of smoking were significantly related to presence of CAC. Based on this information, a parameter of overweight and of blood pressure may be considered as potential confounders, although one may also argue these factors are intermediate parameters in the causal pathway.

Table 3 shows that in an unadjusted model, a history of high blood pressure during pregnancy was significantly related to presence of CAC (Agatston score). We obtained the same results for volume and mass score. The risk increased by 57% compared with women without a history of high blood pressure during pregnancy (odds ratio: 1.57; 95% CI: 1.04 to 2.37). Adjustments for age did not substantially alter the association (odds ratio: 1.64; 95% CI: 1.07 to 2.37). When factors that may be regarded as intermediate factors in the causal pathway from a history of high blood pressure during pregnancy to atherosclerosis development, that is, body mass index, systolic blood pressure, diastolic blood pressure, and waist:hip ratio, the magnitude of the association attenuated and the relation did not reach statistical significance.
We repeated the analysis of a relation between a history of high blood pressure in pregnancy and CAC in participants without self-reported hypertension at baseline (n=387) to control for potential recall bias. The magnitude of the finding did not materially differ (age-adjusted odds ratio: 1.53; 95% CI: 0.88 to 2.64), although statistical significance was not reached.

Discussion

To the best of our knowledge, the present study is the first to show that a history of high blood pressure during pregnancy is related to coronary calcification later in life. Many of the women who have had pre-eclampsia exhibit the phenotype of the metabolic syndrome and impaired endothelial function at 3 to 12 months postpartum. In addition, observational studies demonstrated that pre-eclampsia is associated with an increased risk of cardiovascular events and death in later in life. Our finding is in line with these observations and expands the evidence to an increased risk of atherosclerosis. It has been well established that increased coronary calcification is a significant predictor of subsequent CVD and total mortality.

Based on our way of assessment of exposure, the increased risk appears not to be restricted only to those women with pre-eclampsia but also applies to those with nonproteinuric hypertension or mild elevation of blood pressure in pregnancy. Unfortunately, blood pressure levels during pregnancy of these women were not available.

High blood pressure in pregnancy usually subsides when the pregnancy is over. The accumulating evidence in the literature and our present findings support the concept of pregnancy as a cardiovascular challenge test, with hypertensive disorders in pregnancy as “positive test results,” marking those at increased risk of future CVD. These women might benefit from cardiovascular risk factor management starting soon after pregnancy, at an age where they are more likely to benefit from secondary prevention. At present, however, it is not clear whether and how risk factor management can be achieved in these women and what benefit may be expected from such a strategy. Studies addressing these issues are on their way.

Some limitations of our study need to be addressed. The information on history of high blood pressure during pregnancy was obtained by questionnaire when the participants were at or above middle age. This may have lead to misclassification. The question was not directed toward the more severe hypertensive disorder of pregnancy, that is, preeclampsia. So, milder variants of hypertension in pregnancy have been included too. Therefore, one might question its effect on the validity and magnitude of our findings. If only severe elevated blood pressure during pregnancy is related to increased risk of atherosclerosis, then the magnitude of our finding is clearly an underestimation of the truth. The direction of the relation is, however, valid. Despite the impossibility to precisely classify hypertension in pregnancy on the basis of this information, a positive history of high blood pressure was related to coronary calcification later in life. We, therefore, assume that the true relationship may be actually stronger than the one that we observed, rather than attenuated. Another aspect is that recall bias may have affected the relationship between high blood pressure in pregnancy and coronary calcification. Recall bias means that those with hypertension at baseline may recall having had a high blood pressure in pregnancy “better” than normotensive. Because hypertension is a determinant of CAC, the magnitude of the reported association may have been biased upward. Our stratified analysis shows, however, that the magnitude of the relation among normotensive women is similar to those of the entire group, and, therefore, the reported relation does not seem to be biased. The fact that the results of that stratified analyses are not statistically significant can most likely be attributed to the smaller sample size.

Furthermore, it can be asked whether the 781 exclusions (because of death) may have biased our results in any way. However, we do not believe such a selection through death may be an issue. Finally, the relatively small sample size in our study puts some restriction to the precision of the estimates. Future studies with a larger sample size are needed to support or refuse our findings. Strengths of the study are its population-based nature and the CAC measurements that were performed according to the highest standards. Multi-detector computed tomography for detection of CAC, which we have used in our study, has an excellent accuracy and reproducibility with an intra-class correlation coefficient of 0.99 and κ value of =0.90. In conclusion, we have shown that high blood pressure in pregnancy is associated with increased coronary calcification later in life.

Perspectives

Our finding may have important implications for the management of women who have had high blood pressure in pregnancy. Up to now it has been assumed that high blood pressure subsides after pregnancy, and there was no structured follow-up of the women who experienced it. This (lack of) policy needs reconsideration. Novel strategies of follow-up and cardiovascular risk factor reduction in women who have had hypertension in pregnancy must be developed and evaluated for their potential to reduce CVD in the future.

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Disclosures

None.

References


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