Maternal Cardiovascular Risk Profile After Placental Abruption

Jan H.W. Veerbeek, Janine G. Smit, Maria P.H. Koster, Emiel D. Post Uiterweer, Bas B. van Rijn, Steven V. Koenen, Arie Franx

Abstract—The prevalence of premature cardiovascular diseases (CVD) is increased in women with a history of maternal placental syndromes, including pregnancy-associated hypertensive disorders (eg, preeclampsia), fetal growth restriction, and placental abruption. Whereas previous studies have shown a high prevalence of CVD risk factors after pregnancies complicated by preeclampsia, this has not been studied for women with a history of placental abruption. To explore the association of placental abruption with CVD risk factors after delivery, we compared 75 women with a history of placental abruption with a control group of 79 women with uneventful pregnancies at 6 to 9 months postpartum for the presence of common CVD risk factors. In a subanalysis, data were stratified according to the presence or absence of concomitant hypertensive disease and further adjusted for potential confounders. Women with previous placental abruption had significantly higher mean systolic blood pressure, body-mass index, fasting blood glucose, C-reactive protein, total cholesterol, high-density lipoprotein-cholesterol, and low-density lipoprotein-cholesterol as compared with controls with only uneventful pregnancies. In the subanalysis, all differences remained significant for women with a history of placental abruption only (ie, without concomitant gestational hypertension), except for the associations with low-density lipoprotein-cholesterol and diastolic and systolic blood pressure. Most likely, the identified CVD risk factors predispose to placental abruption and development of premature CVD later in life. (Hypertension. 2013;61:1297-1301.)

Key Words: cardiovascular risk factors ■ dyslipidemia ■ placental abruption ■ pregnancy ■ prevention

Several large-scale population studies have found a strong link between pregnancy-specific disorders linked to abnormal development of the placental bed, such as preeclampsia, Hemolysis, Elevated Liver enzymes and Low Platelet count syndrome (HELLP), gestational hypertension, placental abruption, placental infarction, and fetal growth restriction, also known as maternal placental syndromes (MPS), and subsequent maternal risk of premature cardiovascular disease (CVD).1–4 MPS may be considered as a cluster of pregnancy-related disorders that appear when the cardiovascular system fails to adapt to the increased metabolic, inflammatory, and hemodynamic demands during pregnancy and represent the first manifestation of compromised cardiovascular health of the mother.5,6

Placental abruption, the separation of the placenta before delivery, is a serious complication of pregnancy, associated with a high morbidity and mortality for both mother and child. Placental abruption complicates ≈1% of pregnancies.7 The precise pathogenesis of placental abruption is unclear, although recent studies suggest an important role for defective development remodeling of uterine spiral arteries. This may lead to inadequate blood and nutrient supply to the placenta in the first and second trimesters of pregnancy preceding subsequent placental abruption data. From placental bed biopsy studies obtained in women with placental abruption show a higher prevalence of abnormal spiral artery remodeling, decidual thrombosis, inflammation, and intimal and subintimal thickening (so-called acute atherosis lesions) than that observed in normal pregnancy.7–11 Although the pathophysiology of these characteristic vascular abnormalities is not well understood, intriguing similarities exist in the vascular biology of early-stage atherosclerosis preceding most CVD.12

For preeclampsia and fetal growth restriction, previous studies on postpartum CVD risk factors revealed a higher prevalence of multiple modifiable risk factors for CVD within the first year after delivery.5,13,14 However, to date this has not been separately studied for women with previous placental abruption. In this study, we assessed common CVD risk factors in women with a history of placental abruption at 6 to 12 months after delivery, in comparison with a control group of women with a history of only uneventful pregnancies.

Methods

Study Population

All women with a pregnancy complicated by placental abruption who delivered at the University Medical Center Utrecht, The Netherlands, between November 1994 and December 2009 were considered to...
be eligible for inclusion. Placental abruption was diagnosed as the following: retroplacental bleeding or clots at cesarean section, sonographic visualization of abruption, or a combination of abdominal pain or vaginal bleeding accompanied by a nonreassuring fetal heart rate trace, uterine hypertonicity, or as evident signs of placental abruption on histopathologic examination.11 Patients with chronic hypertension, that is, using antihypertensive treatment for known chronic hypertension before pregnancy and patients with traumatic injury before hospital admission were excluded. Preeclampsia was defined as the presence of gestational hypertension and concomitant proteinuria in the second half of pregnancy. Gestational hypertension was defined according to the criteria of the International Society for the Study of Hypertension in Pregnancy as diastolic blood pressure ≥90 mm Hg and systolic blood pressure ≥140 mm Hg, measured on ≥2 separate occasions ≥24 hours apart. Proteinuria was diagnosed with urinary protein ≥300 mg per 24 hour or ≥2+ at dipstick urinalysis.12 Infants were considered small-for-gestational age if the birth weight was below the fifth centile based on standardized Dutch population charts.16 Women with abruption were divided into 2 groups: abruption with or without concomitant MPS in the index pregnancy or obstetric history. The control group was recruited from the same background population as cases and consisted of healthy women who had experienced only uncomplicated pregnancies. Control women were randomly selected and asked to participate by the research team in collaboration with the low-risk primary care antenatal clinic of the University Medical Center Utrecht and at a local midwifery practice nearby, within the same referral population as the cases to prevent selection bias. Control subjects were recruited according to the same inclusion protocol, were enrolled by the same research team, and were subject to identical sample handling and laboratory procedures as the cases. None of the women had a subsequent pregnancy at screening, and all stopped breastfeeding ≥6 weeks before screening. The study was approved by the Institutional Review Board of the University Medical Center Utrecht, and all participants provided written informed consent.

Assessment of Classic CVD Risk Factors
CVD risk factors were assessed 6 to 9 months after delivery. Breast feeding and vitamin or folic acid supplements were discontinued ≥6 weeks before the risk assessment. The presence of diabetes mellitus and smoking were recorded, and body-mass index (BMI) was calculated, using self-reported height and measured weight at inclusion. A trained research nurse measured blood pressure by auscultatory sphygmomanometer, using an aneroid sphygmomanometer with normal cuff size, in sitting position. Diastolic blood pressure values were determined using the fifth Korotkoff sound. Where appropriate, cuff sizes were adjusted to arm circumference. The mean value of 2 separate measurements 30 minutes apart was used for analysis. All fasting venous blood samples were immediately centrifuged and analyzed directly for lipid markers, glucose, and triglyceride levels by standard operating procedures at the routine Clinical Chemistry Laboratory of our hospital. A detailed description of measurements and laboratory procedures was previously published elsewhere.5 Briefly, fasting total cholesterol, high-density lipoprotein (HDL)-cholesterol, triglycerides, and glucose were determined using a Vitros950 dry-chemistry analyzer (Johnson & Johnson, Rochester, NY). Low-density lipoprotein (LDL) cholesterol was calculated using the Friedewald formula. The Homeostatic Model Assessment (HOMA) score was used to calculate the level of insulin resistance with the following equation: (fasting glucose × fasting insulin)/22.5. Within-run variation coefficients were 1.7% for total cholesterol, 2.3% for HDL-cholesterol, 1.9% for triglycerides, and 4.3% for fasting glucose levels. Technicians were blinded for outcome.

Statistical Methods
Statistical analyses were performed using Statistical Package for the Social Sciences (version 17.0 SPSS Inc, Chicago, IL). Baseline variables in the group with and without a previous abruption were expressed as means with 95% confidence intervals, or number and percentage. Statistical comparison was performed using generalized linear models. In the original data set, several women had missing data, and for some variables selective missing may have occurred. Average missing rate per variable was 17% in controls (confidence interval, 10–25) and 20% in cases (confidence interval, 10–35). To avoid any potential bias that may occur in complete-case analysis, multiple imputations (20x) were applied using observed patient characteristics.13-19 Missing data were imputed using a logistic regression model that included the following variables: maternal age, BMI, nul- liparity, blood pressure, glucose, insulin, high sensitive C-reactive protein, triglycerides, and cholesterol. Generalized linear models were used to analyze the data in each imputation set separately, before pooling the data using Rubin’s rules.20

For subgroup analyses, the patient population was stratified into abruption without additional MPS (ie, preeclampsia/HELLP, gestational hypertension, or small-for-gestational age) and abruption with additional MPS. Where appropriate, variables were adjusted for potential confounders that were identified in the baseline comparison. P<0.05 were considered statistically significant. In addition, several parameters were dichotomized using the common cutoff values for metabolic syndrome, or those described in the JUPITER trial, and were subsequently compared between the groups by χ2 test.21

Results
Seventy-five women with placental abruption and 79 population-based controls were included in the analysis. Baseline characteristics are presented as mean and 95% confidence interval. BMI indicates body mass index; HDL, high-density lipoprotein; HOMA, Homeostatic Model Assessment; hsCRP, high sensitive C-reactive protein; and LDL, low-density lipoprotein.

Table 1. Baseline Patient Characteristics of Controls and Placental Abruption Cases

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Control Group</th>
<th>Placental Abruption</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>n=79</td>
<td>n=75</td>
</tr>
<tr>
<td>Age, years</td>
<td>33.1 (32.9–33.4)</td>
<td>30.9 (30.7–31.1)*</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>22.8 (21.8–23.7)</td>
<td>25.7 (24.8–26.7)*</td>
</tr>
<tr>
<td>White, %</td>
<td>79 (100)</td>
<td>73 (97.3)</td>
</tr>
<tr>
<td>Nulliparity, %</td>
<td>47 (59.5)</td>
<td>58 (77.3)*</td>
</tr>
<tr>
<td>Smoking, %</td>
<td>14 (17.7)</td>
<td>18 (24)</td>
</tr>
<tr>
<td>Pregnancy outcome</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gestational age at delivery (days)</td>
<td>282 (7.5)</td>
<td>207 (37.8)*</td>
</tr>
<tr>
<td>Infant's birth weight</td>
<td>3592 (467)</td>
<td>1024 (619)*</td>
</tr>
<tr>
<td>Small-for-gestational age, %</td>
<td>1 (1.3)</td>
<td>22 (29.3)*</td>
</tr>
<tr>
<td>Gestational hypertension, %</td>
<td>—</td>
<td>11 (14.7)</td>
</tr>
<tr>
<td>Preeclampsia, %</td>
<td>—</td>
<td>31 (41.3)</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>113 (110–116)</td>
<td>122 (117–126)*</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>75 (72–77)</td>
<td>80 (76–83)</td>
</tr>
<tr>
<td>Fasting glucose, mmol/L</td>
<td>4.11 (3.9–4.3)</td>
<td>5.09 (4.9–5.3)*</td>
</tr>
<tr>
<td>Fasting insulin, uIU/L</td>
<td>12.35 (9.2–15.4)</td>
<td>10.75 (9.4–12.1)</td>
</tr>
<tr>
<td>HOMA score</td>
<td>1.97 (1.5–2.5)</td>
<td>2.43 (2.2–2.7)</td>
</tr>
<tr>
<td>hsCRP, mg/L</td>
<td>1.59 (0.6–2.6)</td>
<td>4.36 (1.6–7.1)</td>
</tr>
<tr>
<td>Triglycerides, mmol/L</td>
<td>1.08 (0.9–1.3)</td>
<td>1.2 (1.1–1.4)</td>
</tr>
<tr>
<td>Cholesterol, mmol/L</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total cholesterol</td>
<td>3.76 (3.5–4.0)</td>
<td>5.01 (4.7–5.3)*</td>
</tr>
<tr>
<td>HDL</td>
<td>1.22 (1.1–1.3)</td>
<td>1.44 (1.1–1.3)*</td>
</tr>
<tr>
<td>LDL</td>
<td>2.06 (1.8–2.3)</td>
<td>3.00 (2.8–3.2)*</td>
</tr>
<tr>
<td>Cholesterol/HDL ratio</td>
<td>3.40 (3.0–3.8)</td>
<td>3.71 (3.4–4.1)</td>
</tr>
</tbody>
</table>

Data are presented as mean and 95% confidence interval. BMI indicates body mass index; HDL, high-density lipoprotein; HOMA, Homeostatic Model Assessment; hsCRP, high sensitive C-reactive protein; and LDL, low-density lipoprotein.

*P<0.05.
characteristics are summarized in Table 1. Women in the control group were slightly older compared with the cases, with a mean difference in age of 2.2 years. Placental abruption was associated with a 63% rate of concomitant gestational hypertension, preeclampsia, and intrauterine growth restriction (47 cases). Of the 28 women without MPS in the index pregnancy, 8 women were multiparous. None had MPS in their obstetric history. Women with previous placental abruption had significantly higher mean BMI, systolic blood pressure, fasting blood glucose, total cholesterol, HDL-cholesterol, and LDL-cholesterol than women in the control group (Table 1). No significant differences were found for diastolic blood pressure, cholesterol/HDL ratio, triglycerides, high sensitive C-reactive protein, and HOMA score.

Subgroup analysis between multiple determinants of CVD risk and a history of placental abruption is shown in Table 2. After adjustment for age, BMI, and nulliparity, the associations between increased systolic blood pressure, fasting blood glucose, total cholesterol, HDL-cholesterol, and LDL-cholesterol remained significant for both the subgroup of women with a placental abruption and concomitant MPS, as well as for women with placental abruption without concomitant MPS, except for blood pressure and LDL cholesterol (Table 2).

Table 3 shows stratified results according to clinical cutoff values used in the JUPITER trial and according to established criteria for components of the metabolic syndrome. Significant differences were observed for all CVD risk factors between women who experienced placental abruption with other concomitant MPS as compared with the control group. Similar, for placental abruption without MPS differences remained significant except for the difference in glucose levels.

**Discussion**

This study demonstrates an association between placental abruption and increased prevalence of CVD risk factors several months after delivery. Women with a history of placental abruption seem to have a different CVD risk profile compared with women with a history of only uncomplicated pregnancies. Blood pressure, BMI, fasting blood glucose, total cholesterol, and LDL-cholesterol are significantly higher in women after placental abruption compared with population-based controls. Previous studies have shown that preeclampsia and small-for-gestational age are associated with CVD risk factors early in life and an increased risk of future CVD.2,3,13,14,22 Even the 10-year CVD risk in women with a history preeclampsia is significantly higher with an odds ratio of 1.31 according to the Framingham risk score.23 Therefore, in our study, the presence of placental abruption seems to be an independent risk factor for CVD in the long term.
of concomitant MPS may be considered as a potential con-
founder for the association between placental abruption and subsequent CVD risk factor levels. However, with the excep-
tion of blood pressure and LDL cholesterol, subgroup analysis of cases in our study without concomitant MPS demonstrated a virtually unaltered significant difference in CVD risk profiles compared with healthy controls. This is also reflected in Table 3, where several cutoff points were used. Next to the meta-

bolism of placental spiral arteries in women who are already predisposed to CVD.4,5 Defective spiral artery remodeling is assumed to cause underperfusion of the placental bed with subsequent infarction and increased resistance of the placent-
tal vessels.11,24,25 Specific decidual vasculopathy like muscular thickening, thrombosis, and acute atherosclerosis lesions possibly arise as response to increased shear stress and are indeed seen more often in cases of placental abruption and other MPS.10,11 In this concept, pregnancy acts as a metabolic stress test revealing poor cardiovascular health in women with a pregnancy complicated by an MPS, such as placental abruption.6,26

Several studies have shown a strong correlation between placental lesions and placental abruption.9,10 It has been hypothesized that placental abruption results from poor vessel quality of placental spiral arteries in women who are already predisposed to CVD.4,5 Defective spiral artery remodeling is assumed to cause underperfusion of the placental bed with subsequent infarction and increased resistance of the placent-
tal vessels.11,24,25 Specific decidual vasculopathy like muscular thickening, thrombosis, and acute atherosclerosis lesions possibly arise as response to increased shear stress and are indeed seen more often in cases of placental abruption and other MPS.10,11 In this concept, pregnancy acts as a metabolic stress test revealing poor cardiovascular health in women with a pregnancy complicated by an MPS, such as placental abruption.6,26

Of note, HDL-cholesterol levels were mildly lower in the control group. Because HDL-cholesterol is shown to be inversely related to the CVD risk in several epidemiological studies, we expected levels to be lower in women with a his-
tory of placental abruption.27–30 It is difficult to explain this finding. HDL levels are known to be higher in women and show a temporal decline with increasing age; thus, one may speculate that increased HDL-cholesterol levels observed in women with previous placental abruption may (temporarily) protect them against early atherogenesis, despite alterations in other lipid parameters and metabolic disturbances.31

Some limitations of this study need to be addressed. First, controls were significantly older than women with previ-
ous placental abruption. However, this attenuates rather than explains the differences in CVD risk factors between cases and controls because advanced age is associated with an incre-

ment in CVD risk factor levels. We estimate this effect to be rather small because age-adjusted logistic regression models had virtually no effect on the observed associations. Second, although we aimed to create the first data set on CVD risk factors after placental abruption, for some outcomes in the stratified subanalysis, our sample size had limited power to draw any definitive conclusions. Third, our data were collected several months after delivery. It is not certain that abnormal risk profiles were already present before pregnancy in women who experienced placenta abruption. However, because the minimum delivery-to-assessment interval was 6 months, we assume that the levels of blood pressure and all biochemical risk factors had returned to prepregnancy val-

ues. Furthermore, there is no evidence that maternal weight decreases more or faster after normal pregnancy as compared with pregnancy complicated by placental abruption.

In spite of the higher prevalence of CVD risk factors in women with previous placental abruption, the estimated absolute CVD risk is low for most women during the first years after delivery. Nevertheless, this is mainly attributable to the young age of the study population masking the long-term impact of a positive history of placental abruption on CVD risk. Because the CVD risk profile is already significantly different in these young and apparently healthy women without known CVD shortly after delivery, the observed alterations in CVD risk profiles are likely to precede the appearance of clinically relevant metabolic abnormalities and signs of accelerated development of atherosclerosis in some of these women, leading to premature development of CVD later in life.1–4

Clinical Perspective
Evidence exist that CVD is largely preventable by early modi-
fication of CVD risk factors.32 However, the first presentation of CVD usually does not occur before menopause, making it difficult to identify women at risk for future CVD. The presence of modifiable risk factors in women with a history of multiple placental syndromes, including placental abruption, may therefore be of potential use for primary prevention programs. Currently, CVD follow-up of women with a history of placental abruption or other MPS is not routine practice in The Netherlands and is largely clinic dependent. At present, very few clinics worldwide have started such cardiovascular risk assessment programs.33,34 The American Heart Association updated the guideline for the prevention of CVD in women in 2011 in which they recognized preeclampsia, gestational diabetes mellitus, and pregnancy-induced hypertension as independent risk factors for CVD.35 The update emphasizes referring these women to a primary care physician or cardi-

ologist in the years after pregnancy. Recently, Spaan et al33 suggested a structured cardiovascular screening program for these women by multidisciplinary teams, including an obstetrician. Our findings suggest that such multidisciplinary rou-
tine assessment and reduction of CVD risk factors may also be offered to women with placental abruption in the future. However, as for the hypertensive disorders of pregnancy, the feasibility and clinical and cost-effectiveness of such a strategy of screening and preventive interventions in women who experienced placenta abruption must be evaluated before wide implementation in clinical practice.

Disclosures
None.

References
diovascular event risks for women who experienced hypertensive disor-

Novelty and Significance

What is New?

- In this study, we identified the association between placental abruption and a significantly altered cardiovascular disease risk factor profile post-partum compared with women with a history of uneventful pregnancies.
- Cholesterol is an important risk factor for cardiovascular disease, and in women with a history of placental abruption, the cholesterol levels are significantly higher.

What is Relevant?

- Our findings emphasize the need for awareness on pregnancy-related complications and future cardiovascular health: not only for preeclampsia, gestational diabetes mellitus, and pregnancy-induced hypertension, but also for placental abruption.

Summary

We demonstrated a strong association between placental abruption and the presence of cardiovascular risk disease factors after delivery.

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