Abstract—Observational studies have shown an increased lifetime risk of cardiovascular disease (CVD) in women who experienced a hypertensive disorder in pregnancy. This risk is related to the severity of the pregnancy-related hypertensive disease and gestational age at onset. However, it has not been investigated whether these differences in CVD risk factors are already present at postpartum cardiovascular screening. We evaluated postpartum differences in CVD risk factors in 3 subgroups of patients with a history of hypertensive pregnancy. We compared the prevalence of common CVD risk factors postpartum among 448 women with previous early-onset preeclampsia, 76 women with previous late-onset preeclampsia, and 224 women with previous pregnancy-induced hypertension. Women with previous early-onset preeclampsia were compared with women with late-onset preeclampsia and pregnancy-induced hypertension and had significantly higher fasting blood glucose (5.29 versus 4.80 and 4.83 mmol/L), insulin (9.12 versus 6.31 and 6.7 uIU/L), triglycerides (1.32 versus 1.02 and 0.97 mmol/L), and total cholesterol (5.14 versus 4.73 and 4.73 mmol/L). Almost half of the early-onset preeclampsia women had developed hypertension, as opposed to 39% and 25% of women in the pregnancy-induced hypertension and late-onset preeclampsia groups, respectively. Our data show differences in the prevalence of common modifiable CVD risk factors postpartum and suggest that prevention strategies should be stratified according to severity and gestational age of onset for the hypertensive disorders of pregnancy. (Hypertension. 2015;65:600-606. DOI: 10.1161/HYPERTENSIONAHA.114.04850.) • Online Data Supplement

Key Words: hypertension  ■  prevention

Cardiovascular disease (CVD) has gained interest in obstetrics in recent years because large observational studies revealed a remarkable increase in the long-term risk of CVD in women who experienced different types of gestational hypertensive disorders.1–3 These include pregnancy-induced hypertension (PIH) and preeclampsia, which affect 2% to 7% of all pregnancies worldwide.4

A review by Bellamy et al1 showed an increase of the postpartum risk of CVD events according to the severity of the hypertensive pregnancy disorder, with the highest risk in women who experienced early-onset preeclampsia. Women with a normal pregnancy have an advantage according to these results, but still develop CVD later in life. Currently, it is not possible to identify individual women who have the highest risk in developing CVD. In recent years, other studies did reveal that common modifiable risk factors such as fasting blood glucose and lipid levels are significantly elevated 6 months after a pregnancy complicated by early-onset preeclampsia.5–8 The dose–response relationship with the severity of a hypertensive pregnancy disorder and future CVD suggest that the differences in long-term CVD risk between women with a history of a hypertensive pregnancy may be dependent on variation in the underlying maternal CVD risk profiles. However, studies that compare cardiovascular risk factors between women with a previous pregnancy complicated by early-onset preeclampsia, late-onset preeclampsia, or PIH within the same population are lacking.

In this study, we compare CVD risk profiles ≥3 months postpartum between women with previous early-onset preeclampsia, term preeclampsia and term gestational hypertension. We hypothesize that there is a difference in the prevalence of modifiable CVD risk factors postpartum between women with a history of a hypertensive disorder of pregnancy. Identification of women at high risk of CVD at a relatively young age may provide an opportunity for early personalized follow-up and prevention.
Methods

Study Population
The study population consists of data from 2 cohorts: the Utrecht cohort and patients who participated in the Hypitat Risk Assessment Study (HyRAS). Both are discussed separately below.

Utrecht Cohort
All women delivered at the University Medical Center Utrecht between November 1994 and January 2012, with a pregnancy complicated by early-onset preeclampsia were asked to participate in a follow-up program starting ≥3 months postpartum. Patients with chronic hypertension, defined as known hypertension who required antihypertensive treatment before pregnancy, as well as chronic kidney disease and diabetes mellitus, were excluded. Characteristics of the study population and inclusion criteria have been published in detail elsewhere.13,15 For this analysis, women with an interval of >5 years between delivery and follow-up were excluded to ensure comparability with the HyRAS cohort.

HyRAS Cohort
Between June 2008 and November 2010, 306 women who had participated in the Hypertension and Preeclampsia Intervention Trial at Term (HYPITAT) study were enrolled in the HyRAS study between 2 and 5 years postpartum. Details on inclusion criteria of this cohort have been published elsewhere.10 In short, women who have participated in the HYPITAT trial11 were consented for the HyRAS study, a cardiovascular follow-up 2 to 5 years after their pregnancy. The HYPITAT study evaluated if induction of labor between 36+0 and 41+6 weeks of gestation improved maternal outcome in women with late-onset preeclampsia and PIH. Exclusion criteria of the HYPITAT study included: diabetes mellitus, gestational diabetes mellitus needing insulin treatment, renal disease, heart disease, previous caesar- ean section, hemolysis elevated liver enzymes and low platelets syndrome, oliguria of <500 mL/24 h, pulmonary edema or cyanosis, HIV seropositivity, use of antihypertensive drugs before pregnancy, fetal anomalies, suspected intrauterine growth restriction, abnormalities detected during fetal heart rate monitoring, and postpartum preeclampsia. Seventy-six of these women had late-onset preeclampsia and 230 women had PIH; all women were ≥18 and delivered between 36+0 and 41+6 weeks of gestation. Women with a history of preeclampsia were excluded from the PIH group. The patient selection of this study is represented in Figure S1 in the online-only Data Supplement.

Definitions
Preeclampsia was defined as the presence of PIH and concomitant proteinuria in the second half of the pregnancy. PIH 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/or systolic blood pressure >140 mm Hg, measured on ≥2 separate occasions ≥4 hours apart. Proteinuria was diagnosed with urinary protein was >300 mg/24 h or ≥2 at dipstick urinalysis.12

Homeostasis Model Assessment score (fasting plasma glucose [mmol/L]×fasting insulin levels [mU/L]/22.5) was used as a measurement for insulin sensitivity, where higher values correspond with higher insulin resistance.15

Small for gestational age offspring was defined as birth weight below the 10th percentile according to the most recent growth charts used in the Netherlands.14 Hypertension at inclusion was defined as systolic blood pressure ≥140 mm Hg or diastolic blood pressure ≥90 mm Hg or taking antihypertensive drugs as described in The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure.15

Metabolic syndrome was defined according to the International Diabetes Foundation as body mass index (BMI) >30 kg/m² and ≥2 of the following: triglycerides ≥1.7 mmol/L, high-density lipoprotein cholesterol <1.3 mmol/L, systolic blood pressure ≥130 mm Hg or diastolic blood pressure ≥85 mm Hg, and fasting plasma glucose levels ≥5.6 mmol/L.16 The cutoff points total cholesterol >6.2 mmol/L, low-density lipoprotein cholesterol >1.8, and high-sensitivity C-reactive protein (hsCRP) >2.0 mg/mL were based on the Adult Treatment Panel III guidelines and Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER) trial.17,18

Assessment of Classic CVD Risk Factors
The 3 study groups were compared for baseline characteristics, pregnancy outcome, and CVD risk factors postpartum, including BMI, blood pressure, plasma lipids, glucose, insulin, Homeostasis Model Assessment score, hsCRP, smoking status, and current hypertension or diabetes mellitus. In all groups, breastfeeding was stopped 26 weeks before inclusion.

Both the assessment of risk factors in the early-onset preeclampsia group as well as in the late-onset preeclampsia and PIH group have been described in detail elsewhere.1–10 Study protocols on assessment of risk factors were the same in both hospitals. In summary, BMI was calculated using measured height and weight at inclusion. A trained research nurse measured blood pressure by auscultatory sphygmomanometry, using an aneroid sphygmomanometer, 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.

Interassay Variations
After centrifuging the blood samples at the local center, samples were sent to the routine clinical chemistry laboratory of the Medical Center Haaglanden (late-onset preeclampsia/PIH groups) or University Medical Center Utrecht (early-onset preeclampsia group). Protocols for blood analysis used by the laboratories were comparable and all technicians were blinded for outcome. Details about the assays used and their mutual comparability are presented in Table S1. Results from the different assays were harmonized with the use of annual data from the Dutch Foundation for Quality Assessment in Clinical Laboratories (SKML) from 1994 to 2013. This independent foundation uses assays from different laboratories to measure the same samples during 6 annual measuring rounds. As a result, accordance between centers is assured and the quality of laboratory performance is monitored.

Outcome Measures
The primary outcome measure was the difference in modifiable classic cardiovascular risk factors, that is, blood glucose, insulin, cholesterol, triglycerides, and hsCRP. Secondary outcome measures were the presence of hypertension and use of antihypertensive drugs.

Statistical Methods
All statistical analyses were performed using PASW statistics 21.0, SPSS Inc.

Average missing rates per variable were 15% in women with early-onset preeclampsia (95% confidence interval, 1%–28%), 5% (95% confidence interval, 2%–11%) in women with late-onset preeclampsia, and 5% (95% confidence interval, 2%–12%) in PIH, respectively. To avoid any potential bias that may occur in complete-case analysis, we used a previously described multiple imputation method (10×) using the observed patient characteristics.19,20 Missing data were imputed using a logistic regression model that included the following variables: follow-up time, group, smoking, maternal age, BMI, nul- liparity, blood pressure, glucose, insulin, hsCRP, triglycerides, and cholesterol.

For all parameters, mean and SE or numbers and percentages were calculated. Baseline characteristics were compared using ANOVA for continuous variables and χ² tests for categorical variables. Generalized linear models were used to compare the cardiovascular risk factors between early-onset preeclampsia, late-onset preeclampsia, and PIH. Variables were adjusted for age, BMI, and nulliparity. P<0.017 were considered to indicate statistical significance and were adjusted with the Bonferroni correction for multiple testing.
Ethical Approval

Results
Baseline characteristics are shown in Table 1. Maternal age, percentage of non-whites, gestational age, and birth weight were significantly lower in women who had early-onset preeclampsia when compared with women with late-onset preeclampsia and PIH. Furthermore, nulliparity and percentage of small for gestational age offspring were lower when women with early-onset preeclampsia were compared with PIH. BMI was higher in women with a history of PIH compared with women who experienced early-onset preeclampsia during pregnancy. Follow-up time was significantly different between the Utrecht cohort (mean, 213 days [SE, 10.4]) and HyRAS cohort (late-onset preeclampsia: mean, 919 days [SE, 19.7] and PIH: mean, 921 days [SE, 11.1]).

The percentage of women with hypertension at time of screening varied from 25% in the late-onset preeclampsia group to 39% in PIH and 45% in the early-onset preeclampsia group, respectively. Use of antihypertensive drugs varied from 9% to 16% and 21% in women with late-onset preeclampsia, PIH, and early-onset preeclampsia, respectively. However, the difference between late-onset preeclampsia and PIH was nonsignificant for the use of hypertensive drugs.

CVD Risk Factors
A generalized linear model was used to compare mean and SDs in the 3 study groups after adjustment for maternal age, BMI, and nulliparity (Table 2). Blood pressure, glucose, Homeostasis Model Assessment scores, triglycerides, and total cholesterol were significantly different between the early-onset preeclampsia and late-onset preeclampsia groups (P<0.017). All parameters were significantly different between women with early-onset preeclampsia and PIH, except for diastolic blood pressure and hsCRP. Significant differences in the late-onset preeclampsia and PIH groups were only seen in blood pressures and high-density lipoprotein levels.

Metabolic Syndrome and CVD Cutoff Points
The prevalence of metabolic syndrome was the same in all the 3 groups (Table 3). Several individual components of the metabolic syndrome, however, were significantly different between the groups. Glucose levels >5.6 mmol/L occurred in 16% of women with previous early-onset preeclampsia, compared with 5% and 6% in women with late-onset preeclampsia and PIH, respectively (P<0.001). A BMI>30 was present in 21% to 29% of the women, but was only significantly different between early-onset preeclampsia and PIH (21% versus 29%, P<0.001). Blood pressures measured ≥3 months postpartum did not differ between women with early-onset preeclampsia and PIH.

Table 1. Baseline Characteristics of the Study Population

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Early-Onset PE</th>
<th>Late-Onset PE</th>
<th>PIH</th>
<th>Early vs Late</th>
<th>Early vs PIH</th>
<th>Late vs PIH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Characteristics at postpartum screening</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, y</td>
<td>31.5 (0.23)</td>
<td>34.2 (0.63)</td>
<td>33.5 (0.34)</td>
<td>&lt;0.001*</td>
<td>&lt;0.001*</td>
<td>0.271</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>26.2 (0.26)</td>
<td>26.6 (0.72)</td>
<td>28.0 (0.35)</td>
<td>0.565</td>
<td>&lt;0.001*</td>
<td>0.045</td>
</tr>
<tr>
<td>White</td>
<td>425 (94.9%)</td>
<td>69 (90.7%)</td>
<td>202 (90.2%)</td>
<td>0.014*</td>
<td>&lt;0.001*</td>
<td>1.000</td>
</tr>
<tr>
<td>Smoking</td>
<td>72 (16.1%)</td>
<td>11 (14.5%)</td>
<td>30 (13.4%)</td>
<td>0.865</td>
<td>0.355</td>
<td>0.841</td>
</tr>
<tr>
<td>Hypertension</td>
<td>201 (44.9%)</td>
<td>19 (25.0%)</td>
<td>88 (39.3%)</td>
<td>0.002*</td>
<td>0.017*</td>
<td>0.016*</td>
</tr>
<tr>
<td>Antihypertensive medication</td>
<td>94 (20.9%)</td>
<td>7 (9.2%)</td>
<td>35 (15.6%)</td>
<td>0.017*</td>
<td>0.023</td>
<td>0.085</td>
</tr>
<tr>
<td>Time interval pregnancy-screening, d</td>
<td>213 (10.4)</td>
<td>919 (19.7)</td>
<td>921 (11.1)</td>
<td>&lt;0.001*</td>
<td>&lt;0.001*</td>
<td>0.935</td>
</tr>
<tr>
<td>No. of women with pregnancies between index and screening</td>
<td>6 (1.3%)</td>
<td>24 (31%)</td>
<td>63 (28%)</td>
<td>&lt;0.001*</td>
<td>&lt;0.001*</td>
<td>0.661</td>
</tr>
<tr>
<td>Pregnancy (index)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nulliparity</td>
<td>374 (83.5%)</td>
<td>59 (77.6%)</td>
<td>164 (73.2%)</td>
<td>0.251</td>
<td>0.002*</td>
<td>0.544</td>
</tr>
<tr>
<td>Gestational age, d</td>
<td>206.5 (0.84)</td>
<td>272.8 (1.11)</td>
<td>276.4 (0.55)</td>
<td>&lt;0.001*</td>
<td>&lt;0.001*</td>
<td>0.002*</td>
</tr>
<tr>
<td>Birth weight, kg</td>
<td>1042 (19.5)</td>
<td>3146 (54.7)</td>
<td>3482 (34)</td>
<td>&lt;0.001*</td>
<td>&lt;0.001*</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>SGA</td>
<td>123 (27.5%)</td>
<td>12 (15.8%)</td>
<td>16 (7.1%)</td>
<td>0.033</td>
<td>&lt;0.001*</td>
<td>0.038</td>
</tr>
</tbody>
</table>

Data are presented as mean (SE) unless otherwise indicated. BMI indicates body mass index; PE, preeclampsia; PIH, pregnancy-induced hypertension; and SGA, small for gestational age.

*Significant.
Besides the cutoff points defined in the metabolic syndrome, we also chose to compare other clinically relevant cutoff points for total cholesterol and hsCRP (Table 2). Again the results showed significantly altered lipid levels in women with early-onset preeclampsia versus PIH. However, total cholesterol >6.21 mmol/L was nonsignificant between women with early-onset preeclampsia and late-onset preeclampsia. Significantly higher levels of hsCRP were found in women with early-onset preeclampsia and PIH compared with late-onset preeclampsia. The main findings are summarized in Figure S2.

### Discussion

This study provides evidence that the number and levels of postpartum modifiable CVD risk factors differ between the different hypertensive disorders of pregnancy; early-onset preeclampsia, late-onset preeclampsia, or PIH. Women with a previous early-onset preeclampsia showed an overall less favorable CVD risk profile, compared with women with late-onset preeclampsia and PIH, particularly reflected in glucose and lipid levels. Hypertension postpartum is observed in almost half of the patients with a history of early-onset preeclampsia and PIH. Furthermore, we showed that blood pressure was significantly higher in women who experienced early-onset preeclampsia and PIH compared with late-onset preeclampsia. These results support the hypothesis that the CVD risk profile after pregnancy may reflect the risk of CVD later in life, in particular, the risk of chronic hypertension.

Large observational studies have shown that there is an increased risk of future CVD for women who experienced hypertensive pregnancy complications, such as early-onset preeclampsia, late-onset preeclampsia, and PIH. For instance,

### Table 2. Determinants of Cardiovascular Risk in Early-Onset PE, Late-Onset PE, and PIH

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Early-Onset PE</th>
<th>Late-Onset PE</th>
<th>PIH</th>
<th>Early vs Late</th>
<th>Early vs PIH</th>
<th>Late vs PIH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic blood pressure, mmHg</td>
<td>128 (0.80)</td>
<td>119 (1.49)</td>
<td>124 (0.94)</td>
<td>&lt;0.001*</td>
<td>0.006*</td>
<td>0.004*</td>
</tr>
<tr>
<td>Diastolic blood pressure, mmHg</td>
<td>82 (0.61)</td>
<td>79 (1.26)</td>
<td>82 (0.67)</td>
<td>0.007*</td>
<td>0.952</td>
<td>0.003*</td>
</tr>
<tr>
<td>Fasting glucose, mmol/L</td>
<td>5.29 (0.04)</td>
<td>4.80 (0.09)</td>
<td>4.83 (0.05)</td>
<td>&lt;0.001*</td>
<td>&lt;0.001*</td>
<td>0.754</td>
</tr>
<tr>
<td>Fasting insulin, uIU/L</td>
<td>9.12 (0.32)</td>
<td>6.31 (0.08)</td>
<td>6.17 (0.43)</td>
<td>&lt;0.001*</td>
<td>&lt;0.001*</td>
<td>0.786</td>
</tr>
<tr>
<td>HOMA score</td>
<td>2.19 (0.08)</td>
<td>1.37 (0.18)</td>
<td>1.37 (0.11)</td>
<td>&lt;0.001*</td>
<td>&lt;0.001*</td>
<td>0.93</td>
</tr>
<tr>
<td>hsCRP, mg/L</td>
<td>4.83 (0.52)</td>
<td>3.85 (0.69)</td>
<td>4.46 (0.42)</td>
<td>0.197</td>
<td>0.546</td>
<td>0.414</td>
</tr>
<tr>
<td>Triglycerides, mmol/L</td>
<td>1.32 (0.04)</td>
<td>1.02 (0.08)</td>
<td>0.97 (0.05)</td>
<td>0.004*</td>
<td>&lt;0.001*</td>
<td>0.629</td>
</tr>
<tr>
<td>Total cholesterol, mmol/L</td>
<td>5.14 (0.05)</td>
<td>4.73 (0.11)</td>
<td>4.73 (0.06)</td>
<td>0.002*</td>
<td>&lt;0.001*</td>
<td>0.937</td>
</tr>
<tr>
<td>HDL, mmol/L</td>
<td>1.36 (0.02)</td>
<td>1.34 (0.04)</td>
<td>1.44 (0.02)</td>
<td>0.627</td>
<td>0.002*</td>
<td>0.012*</td>
</tr>
<tr>
<td>LDL, mmol/L</td>
<td>3.19 (0.04)</td>
<td>2.93 (0.1)</td>
<td>2.85 (0.06)</td>
<td>0.048</td>
<td>&lt;0.001*</td>
<td>0.432</td>
</tr>
</tbody>
</table>

Data are presented as mean (SE), adjusted for age, BMI, and nulliparity. BMI indicates body mass index; HDL, high-density lipoprotein; HOMA, Homeostatic Model Assessment; hsCRP, high-sensitive C-reactive protein; LDL, low-density lipoprotein; PE, preeclampsia; and PIH, pregnancy-induced hypertension.

### Table 3. Cutoff Values Used in Metabolic Syndrome, ATP III Guidelines and JUPITER Trial in Early-Onset PE, Late-Onset PE, and PIH

<table>
<thead>
<tr>
<th>Cutoff Values</th>
<th>Early-Onset PE</th>
<th>Late-Onset PE</th>
<th>PIH</th>
<th>Early vs Late</th>
<th>Early vs PIH</th>
<th>Late vs PIH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metabolic syndrome</td>
<td>n=448 (%)</td>
<td>n=76 (%)</td>
<td>n=224 (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMI &gt;30 kg/m²</td>
<td>69 (15)</td>
<td>11 (14)</td>
<td>36 (16)</td>
<td>0.873</td>
<td>0.846</td>
<td>0.755</td>
</tr>
<tr>
<td>Systolic BP &gt;130</td>
<td>209 (47)</td>
<td>22 (29)</td>
<td>95 (42)</td>
<td>0.006*</td>
<td>0.395</td>
<td>0.042</td>
</tr>
<tr>
<td>Diastolic BP &gt;85</td>
<td>202 (45)</td>
<td>23 (30)</td>
<td>108 (48)</td>
<td>0.009*</td>
<td>0.406</td>
<td>0.008*</td>
</tr>
<tr>
<td>Glucose &gt;5.6 mmol/L</td>
<td>70 (16)</td>
<td>4 (5)</td>
<td>11 (5)</td>
<td>0.024</td>
<td>0.004*</td>
<td>0.858</td>
</tr>
<tr>
<td>Triglycerides &gt;1.7 mmol/L</td>
<td>88 (20)</td>
<td>8 (11)</td>
<td>18 (8)</td>
<td>0.065</td>
<td>&lt;0.001*</td>
<td>0.540</td>
</tr>
<tr>
<td>LDL cholesterol &gt;1.8 mmol/L</td>
<td>430 (96)</td>
<td>74 (97)</td>
<td>213 (95)</td>
<td>0.629</td>
<td>0.580</td>
<td>0.458</td>
</tr>
<tr>
<td>ATP III guidelines and JUPITER trial</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HDL cholesterol &lt;1.29 mmol/L</td>
<td>200 (45)</td>
<td>36 (47)</td>
<td>79 (35)</td>
<td>0.748</td>
<td>0.020</td>
<td>0.081</td>
</tr>
<tr>
<td>Total cholesterol &gt;6.21 mmol/L</td>
<td>62 (14)</td>
<td>4 (5)</td>
<td>14 (6)</td>
<td>0.050</td>
<td>0.005*</td>
<td>0.840</td>
</tr>
<tr>
<td>hsCRP &gt;2 mg/mL</td>
<td>249 (56)</td>
<td>27 (36)</td>
<td>126 (56)</td>
<td>0.006*</td>
<td>0.873</td>
<td>0.002*</td>
</tr>
</tbody>
</table>

Data are presented as number and percentage. BMI indicates body mass index; BP, blood pressure; HDL, high-density lipoprotein; hsCRP, high-sensitive C-reactive protein; JUPITER, Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin; LDL, low-density lipoprotein; PE, preeclampsia; and PIH, pregnancy-induced hypertension.

*Significant.
women who experienced preeclampsia have a 2.28 higher risk of developing CVD according to a recent meta-analysis on this subject. Only few articles have addressed the changes in risk for developing CVD between different hypertensive pregnancy complications. In the study of Wikström et al, the risk for developing ischemic heart disease was significantly higher in women with severe preeclampsia compared with PIH and mild preeclampsia similar to the study of Lykke et al. Women with mild preeclampsia had an ≈4-fold increased risk of subsequent hypertension later in life. However, the risk increased to 5- and 6-fold in women with a history of PIH and severe preeclampsia, respectively. Although we acknowledge that stratification in early versus late preeclampsia is not the same as mild and severe preeclampsia, we observed similar patterns in mean blood pressure, usage of antihypertensive medication and the presence of hypertension with the highest incidence in early-onset preeclampsia followed by PIH and late-onset preeclampsia. It is striking that 25% to 45% of women in this relatively young population has hypertension compared with 8% in the Dutch female population aged 30 to 39 years. Even more, the use of antihypertensive drugs was only 2% in this age category compared with the 9% to 21% in our cohort.

Patterns of maternal vascular remodeling and responsiveness show a distinct vascular adaptation between early and late preeclampsia. It has also been shown that women with early preeclampsia show high total vascular resistance and women with late preeclampsia have low total vascular resistance 1 year postpartum. Increased vascular resistance might lead to systolic and diastolic dysfunction and could be a possible mechanism in the development of chronic hypertension. This also supports the theory that pregnancy is a stress test for cardiovascular health and that hypertensive disorders unmask the patients more prone to develop CVD later in life. However, we cannot exclude the reverse: more severe endothelial damage and inflammatory stress in early-onset preeclampsia cause (more) permanent vascular damage as opposed to the milder late-onset preeclampsia and PIH. These differences in permanent vascular damage may contribute to the pathogenesis of CVD later in life and explain the seemingly gliding scale in differences in CVD prevalence between the hypertensive pregnancy disease early-onset preeclampsia and late-onset preeclampsia, PIH.

Up to now, PIH has not been included in postpartum research as a separate clinical entity. Our data show that the postpartum biochemical CVD risk factors do not differ between late-onset preeclampsia and PIH. Although significant differences were found between early-onset preeclampsia on the one hand and late-onset preeclampsia and PIH on the other hand. Fasting blood glucose, insulin, Homeostasis Model Assessment score, triglycerides, and total cholesterol were significantly higher than in women with a history of late-onset preeclampsia and PIH. BMI seemed not to relate to this difference hence the fact that BMI was only significantly higher in the PIH group when compared with the early-onset preeclampsia group.

Interestingly, mean hsCRP levels did not differ between the groups. However, when the cutoff value of 2 mg/mL was used, there was a significant difference in prevalence when early-onset preeclampsia and PIH were compared with the late-onset preeclampsia group. The role of hsCRP as a predictor for CVD is controversial and several reports have questioned its usefulness. Nonetheless, recent data from a large cohort reconfirmed the associations found in the JUPITER trial. Our results show that women with early-onset preeclampsia or PIH in their medical history are more prone to hypertension than late-onset preeclampsia. This difference is also reflected in hsCRP cutoff levels. Recent data show that elevated prepregnancy CRP predisposes to recurrent preeclampsia in women with a history of early-onset preeclampsia, which might explain the higher incidence of hypertension as well. Further research and follow-up are needed to confirm the relationship between hsCRP and subsequent hypertension after complicated pregnancy.

Some limitations of this study need to be addressed. First, women in the early-onset preeclampsia were significantly younger than women with previous late-onset preeclampsia or PIH. Advanced age is associated with an increased risk of CVD. However, in this relatively young population of women, the effect of a few years difference is estimated to be small. Besides, data were corrected for age and showed no effect on the associations found. Second, data were obtained from 2 different cohorts. However, population differences between both cohorts are highly unlikely due the fact that the HyRAS cohort was based on a national study, including the Utrecht region. Although almost identical in design, some inclusion criteria were different with follow-up time being the most notable. The follow-up time within the groups was not correlated with any of the other variables tested. Besides, several articles have shown that early as 6 to 7 weeks serum lipid levels rapidly decrease to normal values. Therefore, it is unlikely that the differences between groups have confounded importantly by a difference in follow-up time. The exception would be the number of intervening pregnancies that was lower in the early-onset preeclampsia group. However, there is no proper data available that indicate that multiple pregnancies would further increase the risk on CVD later in life. Finally one of the limitations of this study is the lack of prepregnancy values of the measured CVD risk factors. It is possible that women with early-onset preeclampsia exhibit more risk factors simply because there is a difference in prepregnancy values. Nonetheless, this does not detract from our main conclusion that these pregnancy-related diseases present an opportunity for early detection of CVD risk factors in young women.

In conclusion, our study showed that early-onset preeclampsia, late-onset preeclampsia, and PIH differ significantly on the levels of postpartum biochemical CVD risk factors and the presence of hypertension. Women with a previous early-onset preeclampsia show an overall less favorable risk profile compared with late-onset preeclampsia and PIH, in particular, for glucose and lipid levels. The high prevalence of hypertension in both early-onset preeclampsia and PIH compared with late-onset preeclampsia may be of benefit for the development of targeted prevention programs. With high rates of hypertension found in our study, it seems justified to assess the CVD risk profile within 1 year after pregnancy routinely. Specific follow-up strategies may be required for the different hypertensive disorders of pregnancy.
Perspectives

Hypertension increases the risk for a variety of CVDs, including stroke, coronary artery disease, heart failure, and peripheral vascular disease. Of great interest is the gliding scale of prevalence of hypertension postpartum. In early-onset pre-eclampsia, the prevalence is the highest followed by PIH and late-onset preeclampsia. Furthermore, the women with previous early-onset preeclampsia have the most deviant risk profile compared with late-onset preeclampsia and PIH in terms of glucose levels and lipid profile. Our results not only emphasize on early prevention programs for these high-risk women but also suggest that physicians should stratify for the different hypertensive pregnancy complications to further personalize preventive strategies.

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Disclosures

None.

References


**Novelty and Significance**

**What Is New?**

- This is the first study that compared the cardiovascular risk profile ≥3 months postpartum between women with a history of early onset preeclampsia, late-onset preeclampsia, and pregnancy-induced hypertension.
- Women with previous early onset preeclampsia have the most deviant risk profile compared with late-onset preeclampsia, and pregnancy-induced hypertension in terms of glucose levels and lipid profile.

**What Is Relevant?**

- Our findings emphasizes the need for awareness on hypertensive pregnancy-related complications and future cardiovascular health. Physicians should stratify for the different hypertensive pregnancy complications to further personalize preventive strategies.

**Summary**

Differences in the prevalence of common modifiable cardiovascular disease risk factors postpartum suggests that prevention strategies could be stratified according to severity and gestational age of onset for the hypertensive disorders of pregnancy.
Cardiovascular Disease Risk Factors After Early-Onset Preeclampsia, Late-Onset Preeclampsia, and Pregnancy-Induced Hypertension
Jan H.W. Veerbeek, Wietske Hermes, Anath Y. Breimer, Bas B. van Rijn, Steven V. Koenen, Ben W. Mol, Arie Franx, Christianne J.M. de Groot and Maria P.H. Koster

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CARDIOVASCULAR DISEASE RISK FACTORS AFTER EARLY-ONSET PREECLAMPSIA, LATE-ONSET PREECLAMPSIA AND PREGNANCY INDUCED HYPERTENSION.

CVD risk factors after hypertensive disorders of pregnancy

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Supplemental table S1. Assays used in assessment of endocrine and cardiometabolic profile per center

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Medical Center Haaglanden</th>
<th>University Medical Center Utrecht</th>
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<tbody>
<tr>
<td></td>
<td>Date</td>
<td>Assay</td>
</tr>
<tr>
<td>Insulin (mIU/L)</td>
<td>*</td>
<td>Immulite platform</td>
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<td></td>
<td></td>
<td></td>
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<tr>
<td>Glucose (mmol/L)</td>
<td>*</td>
<td>Roche Modular P800</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HsCRP mg/L</td>
<td>*</td>
<td>Roche Modular P800</td>
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<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lipids (mmol/L)</td>
<td>*</td>
<td>Roche Modular P800</td>
</tr>
<tr>
<td>Total-C, TG, LDL-C, HDL-C</td>
<td></td>
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</tbody>
</table>

For insulin the results of assays were internally adjusted according to the standards of the last used assay. This internal correction was derived from the quality controls performed by the Dutch Foundation for Quality Assessment in Clinical Laboratories (SKML) using a reference sample used in all laboratories in the Netherlands to ensure comparability nation wide. This way no “between center conversion factor” needed to be applied to ensure between center homogeneity. Glucose, HsCRP and lipids did not differ between the platforms tested so no conversion formula was needed. These were again meticulously tested 6 times a year by the SKML as part of routine care in the Netherlands.

* assay used during entire study period, # conversion factor not applicable.

Beckman Dxi system, Unicell DxC 800, AU 5811: Beckman Coulter, Woerden, Netherlands
Roche Modular E170, Roche Modular P800: Roche Diagnostics Almere, Netherlands
Immulite platform, Immulite 1000, Immulite 2000, RIA DPC: Diagnostics Products Corporation Breda, Netherlands
VITROS Chemistry System: Ortho-Clinical Diagnostics, Strasbourg, France

In house RIA: in house developed extraction RIA.
Supplemental figure S1. Flowchart of patient selection. A total of 748 women enrolled after excluding >5 year follow-up time and women with a history of PE in the PIH group. EOPE: early-onset preeclampsia; LOPE: late-onset preeclampsia; PIH: pregnancy induced hypertension.
**Supplemental figure S2.** Summary of main findings between the three groups studied. A. Systolic and diastolic blood pressures (mean and SD); B. Fasting glucose levels (mean and SD); C. Total cholesterol (mean and SD); D. Triglycerides (mean and SD); E. Percentage of women with HsCRP >2mg/ml (%); F. Percentage of women with hypertension at screening (%). PE: preeclampsia; PIH: pregnancy induced hypertension. * Significant versus early onset PE, # Significant versus PIH.
Cardiovascular Disease Risk Factors After Early-Onset Preeclampsia, Late-Onset Preeclampsia, and Pregnancy-Induced Hypertension

Jan H.W. Veerbeek, Wietse Hermes, Anath Y. Breimer, Bas B. van Rijn, Steven V. Koenen, Ben W. Mol, Arie Franx, Christianne J.M. de Groot, Maria P.H. Koster

Observational studies have reported a higher incidence of cardiovascular disease in women with a history of preeclampsia. The association between preeclampsia and subsequent cardiovascular disease is not well understood. We aimed to determine the risk factors for cardiovascular disease in women with a history of preeclampsia.

Methods: We conducted a retrospective cohort study of women with a history of preeclampsia and compared them with women without a history of preeclampsia. We analyzed data on age, parity, smoking status, body mass index, blood pressure, and other risk factors for cardiovascular disease.

Results: Women with a history of preeclampsia had a higher risk of cardiovascular disease compared to women without a history of preeclampsia. The risk was increased for women with a history of preeclampsia who were older, had a higher body mass index, and had higher blood pressure.

Conclusions: Women with a history of preeclampsia are at increased risk of cardiovascular disease. Further research is needed to identify the underlying mechanisms and to develop strategies to reduce the risk.

(Hypertension. 2015;65:600-606.)