Endothelial Function and Circulating Biomarkers Are Disturbed in Women and Children After Preeclampsia

Anne Stine Kvehaugen, Ralf Dechend, Heidi Bente Ramstad, Rebecca Troisi, Drude Fugelseth, Anne Cathrine Staff

Abstract—Preeclampsia is a long-term cardiovascular risk factor for the mother and possibly the offspring. Preeclampsia and cardiovascular diseases share common pathophysiological features, including endothelial dysfunction. We explored whether endothelial function, measured noninvasively, as well as circulating biomarkers reflecting lipid metabolism, angiogenesis, and inflammation, differed in paired mothers and offspring 5 to 8 years after delivery. Twenty-six mother and child pairs after pregnancies complicated by preeclampsia were compared with 17 mother and child pairs after uncomplicated pregnancies. In addition, we assessed whether concentrations of maternal circulating biomarkers at delivery predicted findings 5 to 8 years postpartum. We also included an assessment of early onset preeclampsia and specifically addressed the effects of small for gestational age. Endothelial function was significantly reduced in both mothers and children after preeclampsia when combined with a small-for-gestational-age infant compared with mothers and children after pregnancies without a small-for-gestational-age infant (mothers: $P<0.001$; children: $P<0.05$). Postpartum maternal soluble fms-like tyrosine kinase 1 ($P=0.05$) and high-sensitivity C-reactive protein ($P=0.02$) were elevated in the preeclampsia group compared with controls. High concentrations of these maternal biomarkers both at delivery and 5 to 8 years postpartum were also more frequent in preeclampsia compared with controls ($P<0.05$). The novelty of our study is the parallel finding of reduced endothelial function in mother and child pairs 5 to 8 years after small-for-gestational-age preeclamptic pregnancies, accompanied by increased inflammatory and antiangiogenic maternal biomarkers. This finding supports the concept of transgenerational risk of cardiovascular disease after preeclampsia.

Key Words: preeclampsia ■ biomarkers ■ cardiovascular diseases ■ risk factors ■ endothelium

Preeclampsia (PE) is a vascular-related disorder of pregnancy, which presents clinically after 20 weeks of gestation as newly recognized hypertension and proteinuria. The etiology of PE remains unclear; however, defective placentation is the underlying pathology in many cases, especially in early onset disease. The defective placentation results in a dysfunctional uteroplacental circulation and augmented placental oxidative stress. Women having undergone pregnancies complicated by PE, and possibly offspring of PE pregnancies, exhibit an increased risk of cardiovascular diseases (CVDs) later in life. Low birth weight, which frequently occurs in PE as a result of fetal growth restriction or preterm birth, is also associated with increased risk of cardiovascular events in adulthood. The mechanisms linking PE with future cardiovascular health are unknown but may include preexisting common risk factors. Alternatively, the metabolic and vascular alterations that occur during a complicated pregnancy may persist after delivery and increase the risk of cardiovascular sequelae later in life. Endothelial dysfunction is an important indicator for subsequent CVD and is a regular feature in PE pregnancies. Several functional studies have shown reduced maternal endothelial function for months or even years after a PE pregnancy, but corresponding studies of children are lacking. Few studies have investigated whether circulating biochemical markers, in particular, those reflecting angiogenesis and inflammation, could be involved in mediating endothelial dysfunction and PE development, as well as increased risk for CVD in women with previous PE.

We tested whether such biomarkers and endothelial function differ between mothers and their offspring after PE pregnancies compared with mothers and offspring after uncomplicated pregnancies. Because the risk of future cardiovascular morbidity and mortality increases with more severe PE, we also included an assessment of prematurity in PE and assessed the effects of small for gestational age (SGA).

Received March 7, 2011; first decision March 28, 2011; revision accepted May 5, 2011.

From the Departments of Obstetrics and Gynecology (A.S.K., A.C.S.), Pediatrics (H.B.R.), and Neonatal Intensive Care (D.F.), Oslo University Hospital, Ulleval, Oslo, Norway; Faculty of Medicine (A.S.K., A.C.S., D.F.), University of Oslo, Oslo, Norway; Experimental and Clinical Research Center (R.D.), Max-Delbrück Center and Charité Medical Faculty, Franz-Volhard Clinic, HELIOS Klinikum Berlin, Berlin, Germany; National Cancer Institute (R.T.), National Institutes of Health, US Department of Health and Human Services, Bethesda, MD.

Correspondence to Anne Cathrine Staff, Departments of Obstetrics and Gynecology, Oslo University Hospital, PO Box 4950 Nydalen, 0424 Oslo, Norway. E-mail annetteine.staff@ulleval.no

Hypertension is available at http://hyper.ahajournals.org

DOI: 10.1161/HYPERTENSIONAHA.111.172387
Previously analyzed maternal biomarkers at delivery were also evaluated to assess persisting longitudinal biomarker dysregulations.

**Methods**

Patients were drawn from a study of ~150 women who were included previously in a pregnancy biobank at Oslo University Hospital in 2001–2004. The women were assessed in terms of PE, diabetes mellitus, or uncomplicated pregnancies. In 2008–2009, we invited these women and their offspring from the index pregnancy to a clinical follow-up study described previously in more detail.15 Sixty-three women agreed to participate, of which 20 followed a diabetic pregnancy, who are not reported in the present study. Twenty-six women and their children were included in the present study because they had a history of PE. Seventeen women with uncomplicated pregnancies and their children served as a control group. In the PE group, 17 women (65%) were prematurely delivered before gestational week 34, and 12 women (46%) delivered an SGA infant. Ten of these 12 women were also prematurely delivered before week 34. SGA was defined according to a Norwegian population-based ultrasound-based growth percentile chart using the fifth percentile as a cutoff.16 None of the control women had a PE pregnancy before or after the index pregnancy, and none of the children in the control group were born premature or SGA. In the PE group, 3 women had preexisting diabetes mellitus type 1 in the index pregnancy. Two control women were not examined because of current pregnancy or lactation, but their children were included. The Regional Committee for Medical and Health Research Ethics in Southeastern Norway approved the study, and written, informed consent was obtained from the mothers.

Blood was drawn from an antecubital arm vein in mothers and children after fasting overnight. Serum (lacking for 10 children, of which 6 were in the PE group) and EDTA plasma (lacking for 10 children, of which 6 were in the PE group) were collected and stored in a −80°C freezer.17,18 Comparisons of the index pregnancy biomarker results at delivery for the larger PE and control study groups from the pregnancy biobank have been published previously.15,17,19,20 Maternal results were used in the present longitudinal analyses comparing findings for the index pregnancy with those at 5 to 8 years postpartum in the present study subjects.

We used an ELISA to measure the antiangiogenic factors soluble endoglin (sEng) and soluble fms-like tyrosine kinase 1 (sFlt1) and the proangiogenic factors vascular endothelial growth factor (VEGF) and placental growth factor (PIGF; R&D Systems, Minneapolis, MN) in plasma. We defined the lowest detectable PIGF and VEGF concentrations as the lowest standard of the kit, namely, 15.6 and 31.2 pg/mL, respectively, and concentrations below the detection limit were assigned these values.19 Plasma calprotectin, a protein involved in several inflammatory processes (eg, inflammatory diseases and autoimmune diseases), was analyzed in duplicate by ELISA, as described previously.19 Serum concentrations of high-sensitivity C-reactive protein (hsCRP) were determined by an immunoturbidimetric method with a detection limit of 0.03 mg/L (Roche Diagnostics).17 Serum total cholesterol, triglycerides, and high-density lipoprotein cholesterol were determined using automated methods. Low-density lipoprotein cholesterol was determined by the Friedewald formula.

To reflect endothelial function, we relied on the reactive hyperemia peripheral arterial tonometry (PAT) device (EndoPAT-2000; Itamar Medical Ltd). The apparatus consists of pneumatic probes with biosensors that are attached to the distal index finger of each hand. The biosensors record digital pulse wave amplitude at baseline (preocclusion) and changes during reactive hyperemia. Reactive hyperemia was induced by occlusion of the brachial artery by inflating a blood pressure cuff to suprasystolic levels for 5 minutes. The blood pressure cuff was placed on the participant’s nondominant arm, whereas the contralateral arm served as a control, enabling correction for systemic endothelial-independent vascular changes. The examinations were done in thermo-neutral and quiet surroundings. The reactive hyperemia-PAT index (RHI), a standardized postocclusion/preocclusion ratio, is the final result of test and is calculated by the EndoPAT software.21 The measurements were not possible to perform in 1 woman and 2 offspring in the PE group. All of the other participants successfully completed the measurements.

Statistical analyses were performed using the Statistical Package for the Social Sciences (version 15.0, SPSS Inc, Chicago, IL). Pairwise comparisons of central tendency between study groups were analyzed using the parametric Student t test if data were normally distributed (reporting mean and SD) and the nonparametric Mann-Whitney U test if data were skewed (reporting median and interquartile range). χ² statistics tested differences in proportions between groups. Correlations were investigated using the Spearman correlation coefficient. Linear regression analyses were conducted to adjust for potential confounders; if necessary, dependent variables were log transformed. Statistical significance for all of the tests was defined as P<0.05.

**Results**

Demographic information is given in Table 1. At inclusion 5 to 8 years postpartum, women in the PE group were slightly younger and had a slightly higher systolic blood pressure and mean arterial pressure compared with controls. Median body mass index (BMI) did not differ significantly between the women study groups. Median parity at follow-up was 2 in younger and had a slightly higher systolic blood pressure and mean arterial pressure compared with controls. Median body mass index (BMI) did not differ significantly between the women study groups. Median parity at follow-up was 2 in

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>C</th>
<th>PE</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y†</td>
<td>40.5 (±4.2)</td>
<td>37.2 (±4.4)</td>
<td>0.02 *</td>
</tr>
<tr>
<td>Primipara/</td>
<td>13</td>
<td>35</td>
<td>0.2</td>
</tr>
<tr>
<td>multipara, %‡</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>24.6 (21.5 to 27.7)</td>
<td>25.3 (21.6 to 30.0)</td>
<td>0.4</td>
</tr>
<tr>
<td>SBP, mm Hg</td>
<td>115 (110 to 118)</td>
<td>120 (115 to 130)</td>
<td>0.01*</td>
</tr>
<tr>
<td>DBP, mm Hg†</td>
<td>69.7 (±6.2)</td>
<td>73.8 (±8.0)</td>
<td>0.1</td>
</tr>
<tr>
<td>MAP, mm Hg†</td>
<td>84.4 (±5.2)</td>
<td>90.1 (±8.9)</td>
<td>0.03*</td>
</tr>
<tr>
<td>Children</td>
<td>n=17</td>
<td>n=26</td>
<td></td>
</tr>
<tr>
<td>Age, y</td>
<td>6.0 (6.0 to 7.0)</td>
<td>6.0 (6.0 to 6.2)</td>
<td>0.08</td>
</tr>
<tr>
<td>Age, mo†</td>
<td>83.6 (±7.5)</td>
<td>77.2 (±9.8)</td>
<td>0.03*</td>
</tr>
<tr>
<td>SGA, %‡</td>
<td>0</td>
<td>46</td>
<td>0.001</td>
</tr>
<tr>
<td>Sex, male/</td>
<td>47/53</td>
<td>46/54</td>
<td>1.0</td>
</tr>
<tr>
<td>female, %‡</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMI, kg/m²†</td>
<td>16.6 (±1.4)</td>
<td>16.4 (±2.0)</td>
<td>0.7</td>
</tr>
<tr>
<td>SBP, mm Hg</td>
<td>98.2 (±5.7)</td>
<td>99.8 (±6.7)</td>
<td>0.4</td>
</tr>
<tr>
<td>DBP, mm Hg†</td>
<td>60.0 (55.0 to 60.0)</td>
<td>60.0 (55.0 to 64.0)</td>
<td>0.7</td>
</tr>
<tr>
<td>MAP, mm Hg†</td>
<td>71.4 (±4.6)</td>
<td>72.2 (±5.2)</td>
<td>0.6</td>
</tr>
</tbody>
</table>

Table 1. Clinical Characteristics of Women and Children 5 to 8 Y Postpartum

C indicates control; PE, preeclampsia; BMI, body mass index (kg/m²); SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure. All of the data except MAP have been published previously for the same cohort, also describing blood pressure measurement methods.15 Minor deviations from the previously reported findings are attributed to minor alterations in the classification of study groups in the present study.

*Data are statistically significant at P<0.05.
†Mean value ±SD is reported and t test is performed.
‡χ² statistics are performed, otherwise median value with interquartile range is reported and Mann-Whitney U test is performed.
pertinent drugs. The median time from index pregnancy to this follow-up study was slightly lower in the PE group than in the control group (77 versus 84 months). Therefore, children from PE pregnancies were slightly younger than children from uncomplicated pregnancies. There were no significant group differences in sex, BMI, systolic or diastolic blood pressures, or mean arterial pressure between the children study groups 5 to 8 years after birth.

The maternal blood biomarker concentrations at 5 to 8 years postpartum are shown in Table 2. The concentrations of hsCRP and sFlt1 were elevated in the PE group as compared with controls (Table 2). Adjustment for differences in age increased the difference in hsCRP and sFlt1 between the study groups (P<0.01 and P=0.02, respectively). Further adjustment for BMI as a potential confounder attenuated the differences but did not alter the main group findings (P=0.19 and P=0.02, respectively). Furthermore, we found that sFlt1 and hsCRP were positively correlated (R=0.40; P=0.01). The majority of women had a PIGF concentration below the lowest detection limit, and concentrations of sEng, VEGF, calprotectin, and serum lipids did not differ significantly between formerly preeclamptic women and controls (Table 2).

Blood biomarker concentrations in children at ages 5 to 8 years are shown in Table 3. Children from preeclamptic pregnancies had significantly higher median serum concentrations of total cholesterol compared with children from uncomplicated pregnancies (Table 3). No significant differences in angiogenic or inflammation biomarkers were found between these 2 groups (Table 3).

There were no significant differences in maternal endothelial function (RHI) 5 to 8 years postpartum between the total PE group and the control group (mean and SD: 2.13±0.64 and 2.18±0.45, respectively; P=0.7). However, the subgroup of women who delivered an SGA infant (11 of 25 in the PE group) had a significantly lower RHI (blunted response) compared with all of the women (all of the controls and remaining PEs) who did not deliver an SGA infant (Figure 1A). A significantly lower RHI was also found in the SGA PE group compared with the remaining subjects (14 of 25) in the non-SGA PE group (Figure 1A) and when compared with the control group separately (Figure 1A). Endothelial function in the prematurely delivered PE subgroup did not differ compared with the control and the remaining nonprematurely delivered PE group (data not shown).

For the children study groups, there were no significant differences in endothelial function testing (RHI) between the total PE group versus controls at 5 to 8 years of age (median and interquartile range: 1.21 [1.13 to 1.43] and 1.21 [1.10 to 1.41] for PE and control, respectively; P=0.8). Similar to the maternal findings, a lower RHI was detected in children who were born SGA (11 of 24 in the PE group) compared with children (all controls and remaining PE) who were not born SGA (Figure 1B) and when compared with the remaining subjects (13 of 24) in the non-SGA PE study group (Figure 1B). However, when compared with the control group separately, the difference in RHI did not reach statistical significance (Figure 1B). Endothelial function in the subgroup of children born premature after PE pregnancies did not differ from the control and the remaining nonprematurely born children in the PE group (data not shown).

Maternal and offspring RHI were positively correlated both in the total study cohort (PE + control: R=0.35, P=0.03), as well as in the PE study group (R=0.49, P=0.02). There were no significant correlations between the RHI and the blood biomarkers, BMI or blood pressures, for the women or children postpartum (data not shown). These variables

---

### Table 2. Circulating Biomarkers in Women 5 to 8 Y Postpartum

<table>
<thead>
<tr>
<th>Biomarkers</th>
<th>C (n=15)</th>
<th>PE (n=26)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>hs-CRP, mg/L</td>
<td>0.64 (0.47 to 0.97)</td>
<td>1.23 (0.71 to 5.09)</td>
<td>0.02*</td>
</tr>
<tr>
<td>Calprotectin, μg/L</td>
<td>572 (±169)</td>
<td>730 (±356)</td>
<td>0.06</td>
</tr>
<tr>
<td>sFlt-1, pg/mL†</td>
<td>70.9 (±11.2)</td>
<td>79.7 (±15.0)</td>
<td>0.05</td>
</tr>
<tr>
<td>sEng, ng/mL†</td>
<td>4.33 (3.92 to 4.85)</td>
<td>4.12 (3.88 to 5.11)</td>
<td>0.9</td>
</tr>
<tr>
<td>VEGF, pg/mL</td>
<td>353 (227 to 559)</td>
<td>266 (125 to 458)</td>
<td>0.2</td>
</tr>
<tr>
<td>PIGF &lt;15.6, pg/mL, %†</td>
<td>87</td>
<td>77</td>
<td></td>
</tr>
<tr>
<td>TAG, mmol/L</td>
<td>0.93 (0.75 to 1.31)</td>
<td>0.89 (0.67 to 1.49)</td>
<td>0.8</td>
</tr>
<tr>
<td>Tot chol, mmol/L†</td>
<td>5.18 (±0.89)</td>
<td>5.31 (±1.31)</td>
<td>0.8</td>
</tr>
<tr>
<td>HDL, mmol/L†</td>
<td>1.45 (±0.32)</td>
<td>1.50 (±0.38)</td>
<td>0.6</td>
</tr>
<tr>
<td>LDL, mmol/L</td>
<td>3.41 (1.89 to 4.52)</td>
<td>2.89 (1.62 to 7.23)</td>
<td>0.8</td>
</tr>
</tbody>
</table>

C indicates control; PE, preeclampsia; TAG, triglycerides; HDL, high-density lipoprotein cholesterol; LDL, low-density lipoprotein cholesterol; Tot chol, total cholesterol; hs-CRP, high-sensitivity C-reactive protein; sFlt-1, soluble fms-like tyrosine kinase 1; sEng, soluble endoglin; VEGF, vascular endothelial growth factor; PIGF, placental growth factor.

*Data are statistically significant at P<0.05.
†Mean value±SD is reported and t test is performed.
‡χ² statistics are performed, otherwise median value with interquartile range is reported and Mann-Whitney U test is performed.

### Table 3. Circulating Biomarkers in Children 5 to 8 Y Old

<table>
<thead>
<tr>
<th>Biomarkers</th>
<th>C (n=14)</th>
<th>PE (n=19 to 206)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>hs-CRP, mg/L</td>
<td>0.63 (0.27 to 0.93)</td>
<td>0.46 (0.23 to 0.91)</td>
<td>0.8</td>
</tr>
<tr>
<td>Calprotectin, μg/L</td>
<td>646 (490 to 950)</td>
<td>878 (454 to 1084)</td>
<td>0.5</td>
</tr>
<tr>
<td>sFlt-1, pg/mL†</td>
<td>92.1 (±14.9)</td>
<td>93.6 (±14.1)</td>
<td>0.8</td>
</tr>
<tr>
<td>sEng, ng/mL†</td>
<td>5.13 (±0.72)</td>
<td>5.42 (±0.83)</td>
<td>0.3</td>
</tr>
<tr>
<td>VEGF, pg/mL</td>
<td>266 (±146)</td>
<td>266 (±191)</td>
<td>1.0</td>
</tr>
<tr>
<td>PIGF, pg/mL</td>
<td>18.4 (15.6 to 20.0)</td>
<td>16.5 (15.6 to 21.2)</td>
<td>0.8</td>
</tr>
<tr>
<td>PIGF &lt;15.6, pg/mL, %†</td>
<td>40</td>
<td>48</td>
<td>0.3</td>
</tr>
<tr>
<td>TAG, mmol/L</td>
<td>0.58 (0.53 to 0.82)</td>
<td>0.60 (0.53 to 0.73)</td>
<td>0.9</td>
</tr>
<tr>
<td>Tot chol, mmol/L</td>
<td>4.43 (4.00 to 5.00)</td>
<td>5.01 (4.44 to 5.39)</td>
<td>0.04*</td>
</tr>
<tr>
<td>HDL, mmol/L†</td>
<td>1.41 (±0.34)</td>
<td>1.60 (±0.31)</td>
<td>0.1</td>
</tr>
<tr>
<td>LDL, mmol/L</td>
<td>1.53 (1.12 to 2.26)</td>
<td>1.81 (1.20 to 2.42)</td>
<td>0.3</td>
</tr>
</tbody>
</table>

C indicates control; PE, preeclampsia; TAG, triglycerides; HDL, high-density lipoprotein cholesterol; LDL, low-density lipoprotein cholesterol; Tot chol, total cholesterol; hs-CRP, high-sensitivity C-reactive protein; sFlt-1, soluble fms-like tyrosine kinase 1; sEng, soluble endoglin; VEGF, vascular endothelial growth factor; PIGF, placental growth factor.

*Data are statistically significant at P<0.05.
†Mean value±SD is reported and t test is performed.
‡χ² statistics are performed, otherwise median value with interquartile range is reported and Mann-Whitney U test is performed.
§n=20 plasma samples.
were, therefore, not regarded as potential confounders for the observed differences in the maternal or offspring RHI between the SGA and non-SGA study groups. We identified no correlations between the maternal biomarkers measured at delivery and the corresponding biomarkers measured 5 to 8 years postpartum (data not shown). However, we observed an inverse correlation between maternal PlGF at delivery and sFlt1 5 to 8 years later ($R^2 = 0.48$; $P = 0.01$). Compared with controls, a higher proportion of women in the PE group (as well as in the PE subgroups) also had persistently high concentrations of antiangiogenic and inflammatory proteins from delivery to 5 to 8 years postpartum. However, significant differences were only seen for sFlt1 and hsCRP (Figure 2). At both time points, a high biomarker concentration was defined as the upper quartile cutoff value derived from the distribution of the control group.

**Discussion**

The data presented here provide evidence that endothelial function in women and children of preeclamptic, SGA pregnancies are impaired several years subsequent to the pregnancy. In addition, high concentrations of circulating antiangiogenic and inflammatory proteins persist from delivery to 5 to 8 years postpartum in the mother with a history of PE compared with women with a history of uncomplicated pregnancy. Endothelial dysfunction may represent the mechanistic link between PE and subsequent CVD risk. Several biomarkers are typically dysregulated in PE, including inflammatory markers, circulating lipids, and antiangiogenic factors. These markers have also been associated with CVD.

An association between low birth weight and signs of endothelial dysfunction has been observed in newborns. Furthermore, this association has been demonstrated in children in the first decade of life and in young adults (20 to 28 years), unrelated to or before the development of any classic CVD risk factors. A study showed that the association between low birth weight and endothelial dysfunction was attributable to SGA rather than to preterm birth alone. In accordance with this notion, we found reduced endothelial function, as indicated by a lower RHI in children born SGA after a PE pregnancy compared with children who were not born SGA or compared with non-SGA children of PE pregnancies. In contrast, we did not observe a significant difference in RHI between all of the children who were born prematurely and those born at term. Interestingly, RHI was lower in PE mothers who delivered an SGA infant, compared with those who did not, also within the PE group alone. However, the observation did not hold between the total group of mothers who were prematurely delivered and those who delivered at term. Yinon et al recently showed a reduced flow-mediated dilation (FMD) in women whose pregnancies were complicated by fetal growth restriction, but without PE, as well as in women whose pregnancies were complicated by early onset PE combined with fetal growth...
Diameter by ultrasound scan. Despite these discrepancies, macrovascular function as the change in brachial artery pulse wave amplitude, whereas the FMD technique evaluates ratio is calculated. These methods differ, however, in site of measurement. The EndoPAT technique evaluates microvascular endothelial function by assessing changes in finger pulse wave amplitude, whereas the FMD technique evaluates macrovascular function as the change in brachial artery diameter by ultrasound scan. Despite these discrepancies, the RHI result of the EndoPAT has been shown to correlate well with brachial artery FMD and is correlated with coronary endothelial dysfunction.

The main advantages of the EndoPAT analysis are that it is noninvasive and little influenced by interoperator and intraoperator variability. The EndoPAT-2000 device has been shown to be a feasible and reproducible method in children and adolescents.

Evidence also suggests that women who themselves were born SGA have an increased risk of giving birth preterm and of delivering an SGA infant. Furthermore, it has been shown that being born SGA increases the risk of severe PE, independent of whether the woman was exposed to PE during her own fetal development. On the other hand, intrauterine exposure to PE may augment the risk for both mild and severe PE in the offspring later in life. Possibly, an increased risk for both adult CVD and (in female offspring) placental dysfunction could be established already in utero because of maternal placental dysfunction, with resulting fetal programming of adult disease. However, a genetic or (another) environmental common disposition may also exist.

In the studies of Yinon et al and Germain et al, no group differences in angiogenic factors or inflammation markers were observed. In contrast, our study showed a persistent elevation of maternal hsCRP at 5 to 8 years postpartum in the PE group compared with controls. Moreover, when potential confounders such as maternal age and BMI were taken into account, the results remained unaltered. This observation is in line with a study that showed elevated hsCRP in women having undergone eclamptic seizures even 30 years after the event compared with control women. Our findings of persistently increased hsCRP and not of calprotectin after a PE pregnancy may have been precluded by power limitations but may also suggest that these markers represent different aspects of inflammation. The absence of a (elevated) circulating inflammatory marker does not necessarily reflect the absence of inflammatory processes because of the many systems and processes that may be involved to various extents. A recent study showed that the proinflammatory markers interleukin 6 and tumor necrosis factor-α were still elevated in women with previous PE 12 to 14 weeks postpartum. In contrast, a study investigating inflammatory markers in women 20 years postpartum failed to demonstrate increased levels of interleukin 6, tumor necrosis factor-α, and C-reactive protein in formerly preeclamptics compared with controls. On the other hand, this study detected an increased interleukin 6:interleukin 10 ratio in women with a history of PE, suggesting an elevated proinflammatory state. Thus, although the inflammatory markers investigated in women after PE differ between studies and results are somewhat inconsistent, our study adds to the understanding that a proinflammatory state may persist or perhaps even reappear several years after PE.

We found that sFlt1 was marginally elevated in women with a history of PE compared with controls. More women in the PE subgroups (PE complicated by premature delivery or an SGA infant) also had persistently high concentrations of sFlt1 between the index deliveries to 5 to 8 years postpartum compared with controls. This observation may indicate that women with previous PE and evidence of placental dysfunction are more likely to have a persistent antiangiogenic profile in the circulation. To our knowledge, this is the first report showing elevated sFlt1 in women as late as 5 to 8 years after recovery from PE. However, our findings are supported by measurements made 7 days and 18 months after delivery. We are not aware of correlations between circulating angiogenic proteins in PE pregnancies and later CVD risk. The role of angiogenesis in CVD pathophysiology and its prediction remains unclear. Interestingly, elevated PIGF levels measured in the nonpregnant state have been shown to (modestly) predict coronary heart disease in healthy women, as well as to predict a new cardiovascular event in patients with acute coronary syndrome. In contrast, reduced PIGF in pregnancy correlates with development of PE (hypertension and proteinuria) in pregnancy, which is a predictor for later CVD. A possible explanation for this apparent discrepancy could be that more PIGF is produced by an activated endothelium through inflammatory processes in women at risk for CVD, whereas low maternal PIGF in pregnancy reflects an excess placenta production of sFlt1. The sFlt1 binds and reduces free circulating PIGF and VEGF molecules. The hypertensive and proteinuric effects of elevated sFlt1, low PIGF, and reduced VEGF in pregnancy may be because of endothelial cell impairment of VEGF-dependent endothelial NO synthase activation. At present, no kits can reliably measure the very low free VEGF concentrations in pregnancy; therefore, free VEGF has not proven valuable as a biomarker or predictor for PE. Longitudinal and larger studies are needed to conclude whether a persistent antiangiogenic situation 5 to 8 years postpartum is associated with future development of CVD.

Total cholesterol concentration was elevated in children of PE pregnancies compared with controls. Dietary factors may contribute to variation in cholesterol levels. We have previously published data from the same cohort regarding dietary intake 5 to 8 years after birth but did not detect any major differences in dietary intake between PE offspring and controls. Feeding during early infancy may also affect cholesterol levels later in life, because evidence suggests an inverse association between breastfeeding and cholesterol concentrations in adulthood. Premature delivery may negatively affect the success of breastfeeding, and a large proportion of children in our PE group were prematurely born SGA.
delivered. However, because we have insufficient information regarding infant feeding patterns in our study, we can only speculate as to whether differences in the success of breastfeeding could have contributed to the differences in cholesterol levels observed.

Traditional CVD risk factors, such as lipids and BMI, did not correlate with early signs of endothelial dysfunction in mothers or children in our study. On the other hand, lifestyle interventions focusing on caloric intake, nutritional composition of the diet, and physical activity have shown to be effective in improving endothelial function in patients with established CVD and in individuals with CVD risk factors, including obesity. Whether changes in such variables could modify the concomitant endothelial dysfunction shown in the subgroup of preeclamptic women with evidence of placental disease is uncertain. Nevertheless, a reduction in total CVD risk factors in these women, as well as their children, could possibly affect the overall risk for actually developing CVD.

Our study should be viewed as a pilot study, because the results may have been affected by power limitations because of a small participant number. Therefore, the findings must be interpreted with caution. In particular, some true associations may not have reached statistical significance because of lack of power. However, a major advantage of the study is the longitudinal design for mother and offspring along with the comprehensive registration of both clinical characteristics and biomarker patterns.

We defined an SGA infant as a birth weight for gestational age below the fifth percentile. Because of the small study cohort, stricter criteria, such as a cutoff below the 2.5th percentile, would result in very few cases in the SGA study group, further impairing statistical power. SGA could result from other causes than PE, such as fetal malformations and ethnic variations. In our study, all mothers except 8% in the PE group and 6% in the control group were of Norwegian (white) origin, and no children had malformations. Ideally, we could have categorized the pregnancies as the failure of a fetus to achieve its full growth potential, linking the small infant to restricted fetal growth as evidenced by longitudinal pregnancy findings. All of the women in the PE group had fetal growth assessed; however, most were delivered before the 2-week observation time necessary to identify a fetus that is not gaining weight appropriately in utero. Using the SGA group as a proxy for placental dysfunction is appropriate in our setting, where other causes of SGA than placental dysfunction are unlikely.

Perspectives

The parallel findings of reduced endothelial function in mother and child pairs 5 to 8 years after SGA preeclamptic pregnancies support previous studies demonstrating transgenerational risk of CVD after PE and a higher risk after placental dysfunction with delivery of an SGA child. Whether our finding of persistent high concentrations of antiangiogenic factors and inflammatory markers from delivery to several years postpartum is associated with future development of CVD is unknown and needs further investigation. Prophylactic lifestyle measures or even early pharmacological therapy could be offered to reduce cardiovascular risk in this group of high-risk persons. We believe that studying PE patients and their offspring as a “unit” is a unique approach to this problem.

Acknowledgments

We are grateful for the assistance of Lise Levy, Tone Haug, and Marie Jeanette Le, all Oslo University Hospital, in patient recruitment to the CHASE study (Cardiovascular health in mother and offspring after pregnancy complicated by preeclampsia or diabetes mellitus) (L.L., T.H., and M.J.L.) and biobank work (L.L. and M.J.L.), as well as the CHASE clinical follow-up (M.J.L.).

Sources of Funding

The CHASE study (Cardiovascular health in mother and offspring after pregnancy complicated by preeclampsia or diabetes mellitus) has received research funding from the South-Eastern Norway Regional Health Authorities. A.C.S. has received funding from Oslo University Hospital.

Disclosures

None.

References


Endothelial Function and Circulating Biomarkers Are Disturbed in Women and Children After Preeclampsia

Anne Stine Kvehaugen, Ralf Dechend, Heidi Bente Ramstad, Rebecca Troisi, Drude Fugelseth and Anne Cathrine Staff

Hypertension. 2011;58:63-69; originally published online May 23, 2011;
doi: 10.1161/HYPERTENSIONAHA.111.172387
Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2011 American Heart Association, Inc. All rights reserved.
Print ISSN: 0194-911X. Online ISSN: 1524-4563

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://hyper.ahajournals.org/content/58/1/63

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Hypertension can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Hypertension is online at:
http://hyper.ahajournals.org//subscriptions/