Preeclampsia

Severe Preeclampsia With and Without HELLP Differ With Regard to Placental Pathology

Marie-Therese Vinnars, Liliane C.D. Wijnaendts, Magnus Westgren, Annemieke C. Bolte, Nikos Papadogiannakis, Josefine Nasiell

Abstract—The aim of the present study was to evaluate the histopathology in placentas from patients with severe preeclampsia with and without hemolysis, elevated liver enzymes, and low platelets (HELLP) syndrome. An additional aim was to compare the prevalence of infants born small for gestational age in the 2 groups. The study is retrospective and includes 178 women who have been diagnosed at the Karolinska University Hospital Huddinge or at the Free University Medical Center between 2000 and 2005 with severe preeclampsia. A total of 96 women had severe preeclampsia without signs of HELLP (preeclampsia group), whereas 82 fulfilled the criteria for having HELLP syndrome (HELLP group). Infarction ($P=0.014$), intervillus thrombosis ($P<0.001$), and abruption ($P=0.002$) were more common in the preeclampsia group than in the HELLP group. There was no statistically significant difference in the frequency of accelerated villous maturation ($P=0.61$), decidual arteriopathy ($P=0.27$), or choioamnionitis ($P=0.61$). Furthermore, there was a higher mean placental weight, adjusted for gestational age, in the Swedish HELLP material than in the preeclampsia group ($P<0.001$). Finally, mothers in the preeclampsia group gave birth significantly more often to small for gestational age babies than mothers suffering from HELLP syndrome ($P<0.001$). The histopathologic profile and the range of placental lesions were partly different in the preeclampsia and HELLP patients. Considering the central role that placenta seems to have in preeclampsia, the present result might suggest that different underlying pathogenetic mechanisms and courses can be in play in patients with preeclampsia and HELLP syndrome.

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Key Words: eclampsia ■ gestational hypertension ■ pregnancy hypertension ■ preeclampsia ■ proteinuria ■ women

Preeclampsia (PE) affects 2% to 7% of healthy nulliparous women and is a major cause of maternal and fetal morbidity and mortality. It is further subclassified into late-onset and early onset PE, severe and mild PE, and into a maternal and fetal syndrome. The syndrome is characterized by hypertension and proteinuria, and a common fetal feature is intrauterine growth restriction.

Common pathological features in PE include small placentas with decidual arteriopathy, infarcts in central portions of the placenta, abruption placentae, and intervillus thrombosis. Arteriopathy is commonly found in PE, as well as intrauterine growth restriction, whereas the other findings are nonspecific.

Hemolysis, elevated liver enzymes, and low platelets (HELLP) occurs in 20% of severe PE. The pathogenesis of this complication is not clear. Involvement of the coagulation system is seen in HELLP patients, which is not present in PE patients without HELLP. Symptoms include malaise, right upper quadrant tenderness, nausea, vomiting, edema, relative or absolute hypertension, and a varying degree of proteinuria. Although the classical severe PE with manifest hypertension is more common in an African population, the HELLP syndrome is more frequent in white women.

Because PE and HELLP have different clinical manifestations, our hypothesis was that the histopathology and the underlying pathophysiology in severe PE with and without HELLP might differ. The purpose of this study was to investigate and characterize in detail the histopathologic profile in placentas from patients with severe PE with and without HELLP syndrome. Furthermore, we have compared the prevalence of children born small for gestational age (SGA) in these 2 populations.

Materials and Methods

Study Population

This retrospective study includes 178 women who were diagnosed with severe PE at the Karolinska University Hospital Huddinge (n=117) or at the Free University Medical Center (n=61) between...
Table. Patient Demographics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>PE Group (n=96)</th>
<th>HELLP Group (n=82)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternal age, mean, y</td>
<td>32</td>
<td>30</td>
<td>0.12</td>
</tr>
<tr>
<td>Previous PE/HELLP, %</td>
<td>13.7</td>
<td>7.4</td>
<td>0.18</td>
</tr>
<tr>
<td>Hypertensive medication during pregnancy, %</td>
<td>71.9</td>
<td>79.3</td>
<td>0.25</td>
</tr>
<tr>
<td>Sectlo, %</td>
<td>82.3</td>
<td>90.2</td>
<td>0.13</td>
</tr>
<tr>
<td>Nulliparity, %</td>
<td>66.7</td>
<td>75.6</td>
<td>0.19</td>
</tr>
<tr>
<td>Stillborn fetus, %</td>
<td>5.2</td>
<td>3.7</td>
<td>0.73</td>
</tr>
<tr>
<td>Early onset (&lt;34 wk), %</td>
<td>62.5</td>
<td>74.4</td>
<td>0.09</td>
</tr>
<tr>
<td>Week of diagnosis, mean</td>
<td>33</td>
<td>31</td>
<td>0.05</td>
</tr>
<tr>
<td>Week of partus, mean</td>
<td>34</td>
<td>32</td>
<td>0.004</td>
</tr>
<tr>
<td>Weeks between diagnosis and partus, mean</td>
<td>1.3</td>
<td>0.7</td>
<td>0.06</td>
</tr>
<tr>
<td>Blood flow class (flow in umbilical artery), n</td>
<td>60</td>
<td>52</td>
<td>0.07</td>
</tr>
<tr>
<td>Class 0 (normal flow), %</td>
<td>58.3</td>
<td>51.9</td>
<td></td>
</tr>
<tr>
<td>Class 1 (PI &gt; mean + 2 SD and &lt;mean + 3 SD), %</td>
<td>8.3</td>
<td>21.2</td>
<td></td>
</tr>
<tr>
<td>Class 2 (PI &gt; mean + 3 SD), %</td>
<td>26.7</td>
<td>13.5</td>
<td></td>
</tr>
<tr>
<td>Class 3 (AEDF or REDF), %</td>
<td>6.7</td>
<td>13.5</td>
<td></td>
</tr>
</tbody>
</table>

PI indicates pulsatile index; AEDF, absent end diastolic flow; REDF, reversed end diastolic flow.

2000 and 2005. All of the women in the study were diagnosed with severe PE without (PE group; n=96) or with HELLP syndrome (HELLP group; n=82).

PE was diagnosed according to American College of Obstetricians and Gynecologists criteria and defined as severe with systolic blood pressure >160 mm Hg and/or a diastolic blood pressure >110 mm Hg on 2 occasions ≥6 hours apart and/or proteinuria ≥5 g/L in a 24-hour period. Blood pressure was measured by well-trained observers using the auscultatory method with a Riva-Rocci cuff, size 14×37 cm, attached to a sphygmomanometer. The cuff was wrapped around the left arm, and the sounds of Korotkow were monitored through a stethoscope. The position of the arm was at heart level, and the patient was in a sitting position. In addition, PE was defined as severe when there was a presence of fetal growth restriction. HELLP was defined as hemolysis (based on low serum haptoglobin levels <0.24 g/L and/or elevated lactate dehydrogenase levels >600 U/L), elevated liver enzymes (alanine aminotransferase >70 U/L and/or aspartate aminotransferase >70 U/L), and low platelets (platelet count ≤100 000 /μL).^2

All of the patients had had an ultrasound examination in the first or second trimester, and estimated day of delivery was calculated according to measurements of the biparietal diameter. Data on umbilical flow, which were available on 60 PE patients and 52 HELLP patients, are presented in the Table.

The gestational age at delivery ranged from 23 to 42 weeks. Five stillborn fetuses were found in the PE group and 3 in the HELLP group. Where we had data concerning smoking, we found no difference in cigarettes usage among the patients (P>0.9), as 5.6% of the HELLP patients (n=71) and 6.3% of the PE patients (n=64) were smoking in gestational weeks 8 to 12. Patient demographic data and outcome are illustrated in the Table. Three patients in the PE group and 6 in the HELLP group suffered from diabetes mellitus. Moreover, 2 patients in the PE group had essential hypertension, 1 had SLE, and 1 had nephropathy.

We originally collected 96 PE patients and 21 HELLP patients at Karolinska University Hospital Huddinge. According to the present practice, all of the placentas from severe PE patients are routinely sent to pathological examination. The material in this study is composed of all of the placentas from severe PE sent to the Karolinska University Division of Pathology during this time period. However, placentas from multiple pregnancies were excluded.

Because the HELLP material was relatively small, we added HELLP patients from Free University Medical Center. Hence, the material from the Netherlands included only patients with HELLP, whereas the Swedish material consisted of severe PE patients both complicated and not complicated by HELLP syndrome. To exclude national differences, the 2 populations of HELLP patients were compared using statistical tests explained in the Statistical Analysis section (see below). Because the groups were homogeneous concerning relevant parameters, the populations were pooled to 1 group and compared with the solely Swedish PE group. Parameters considered relevant were maternal smoking, frequency of SGA infants, and histopathologic findings, such as accelerated villous maturation, decidua arteriopathy, infarction, intervillous thrombosis, and abruption. In the Netherlands, placentas were weighed fresh, whereas they were weighed formalin fixed in Sweden. Because placential weight changes after formalin fixation,^9,10 we could not pool the populations concerning this parameter. Therefore, only Swedish PE and HELLP cases were compared regarding placential weight.

Pathological Examination

At least 1 section from the umbilical cord and the membranes and 2 sections from macroscopically normal placenta were subjected to histopathologic examination according to standard procedures. Furthermore, all of the macroscopically detected focal changes in the placentas were sampled. Histological variables evaluated were villous maturation, decidua arteriopathy, infarction, intervillous thrombosis, abruption, thrombosis in fetal vessels, and chorioamnionitis. Other eventual findings were noted separately. Decidua arteriopathy was defined as fibrinoid necrosis of the artery wall, often with dilation of the vessels, with or without the presence of acute atherosclerosis, or lumen thrombosis. The extent of infarction and intervillous thrombosis was assessed during the macroscopic examination of the placenta. Infarction was diagnosed when more than 5% of the placental tissue was involved. The presence of ≥1 intervillous thrombosis was noted. Abruption was diagnosed clinically (acute abruption) and/or histopathologically (more often chronic abruption). The histopathologic diagnosis of abruption was based on the presence of a retroplacental hematoma.

The Swedish placentas were weighed formalin fixed after trimming of the cord and the membranes. A mean placential weight was adjusted for gestational age and compared between the Swedish PE and HELLP patients. The placential weight was also compared in relation to gestational age, as low (<10th centile), normal, or high (>90th centile), according to reference tables of placential weight standards (DR Genest, DJ Roberts, unpublished data, 2001).

Birth Weight Evaluation

Newborns were diagnosed as SGA if the adjusted birth weight deviation exceeded −2 SDs according to Scandinavian growth curves^11 or Dutch growth curves,^12 respectively.

Statistical Analysis

Statistical analyses were made using logistic regression, ANCOVA, χ2 tests, Fisher’s exact test, Mann–Whitney U test, and t test, depending on the parameter investigated. When gestational age was shown to affect the result, gestational week was included in the analyses as a covariate. A local ethics committee approved this study, and informed consent was obtained from the women included in the study.

Results

Histopathologic Results

In the PE group there were significantly more placentas with >5% infarction (P=0.014), intervillous thrombosis (P<0.001), and abruption (P=0.002) than in the HELLP...
group (PE: 41.7%, 45.3%, 29.2%; HELLP: 23.5%, 11.9%, 9.9%, respectively). The placentas in both groups showed high frequency of accelerated villous maturation (PE: 55.8%; HELLP: 69.5%) and decidual arteriopathy (PE: 29.5%; HELLP: 24.7%). However, regarding those parameters, there were no significant differences between the groups. The frequency of arteriopathy was also slightly higher in placentas from pregnancies with SGA infants as compared with placentas belonging to appropriate for gestational age (AGA) infants (SGA group: 28.8%; AGA group: 26.1%), but this difference was not significant (*P* < 0.46). There also was not any difference in the frequency of chorioamnionitis in PE and HELLP (PE: 5.3%; HELLP: 3.7%; *P* = 0.61). Results are illustrated in Figure 1.

**Placental Weight**

Mean placental weight, adjusted for gestational age, was significantly higher in the Swedish HELLP group than in the PE group (PE: 310.5 g; HELLP: 391.6 g; *P* < 0.001). There was also a significantly higher frequency of placentas with high weight in relation to gestational age in the Swedish HELLP group in comparison with the PE group (PE: 3.2%; HELLP: 23.8%; *P* = 0.016). There was no statistically significant difference in the frequency of placenta with normal or low weight in relation to gestational age (see Figure 2). Only one of the patients in the HELLP group had hydrops fetalis. This patient was excluded when comparing mean placental weight but was included when comparing placental weight in relation to gestational age. The placental weight is also presented together with the normal growth curve in Figure 3.

**Birth Weight**

There were significantly more SGA infants (*P* < 0.001) in the PE group (71.9%) compared with the HELLP group (23.5%; see Figure 4).

**Discussion**

Our study showed significantly higher frequencies of infarction, intervillous thrombosis, and abruption in placentas from the severe PE patients without HELLP compared with the severe PE patients with HELLP. In the Swedish severe PE patients with HELLP, there was also a significantly higher mean placental weight adjusted for gestational age and significantly more heavy placentas than in the severe PE group without HELLP. Furthermore, we found more SGA infants in the PE group. These results indicate that HELLP and PE may have different underlying pathophysiologic mechanisms and courses, influencing the fetus differently, resulting in more SGA children in the severe PE population without HELLP syndrome.

A previous study by Smulian et al. examining placental lesions and birth weight in severe PE and HELLP patients, showed no differences in weight and histopathology, except from a significantly higher frequency of abruption in the PE population. Another study, by Raval et al., investigating the maternal and neonatal outcome in severe PE and HELLP, did not found a difference in birth weight either. Furthermore, Gul et al. reported no difference in the percentage of intrauterine growth restriction between PE and HELLP but a higher incidence of fetal mortality in HELLP patients.

The studies by Smulian et al. and Raval et al. include considerably smaller materials than this study, which could explain their different results compared with ours. Moreover, in their definition of HELLP, Raval et al. did not include hemolysis, and Smulian et al. separated HELLP from severe PE. Gul et al. carried out a study larger than the present one but used less strict criteria for HELLP, because they included patients with platelet counts ≤150 000 per microliter, as well...
as patients with only moderately elevated liver enzymes (alanine aminotransferase and/or aspartate aminotransferase >40 IU/L). Thus, different composition of clinical material, as well as other definitions of the diseases, might explain the discrepancy between these studies and the present study.

Although we have found a higher frequency of infarctions in the PE as compared with the HELLP group, we did not find a significant difference in the rate of decidual arteriopathy, as expected. We found no difference between the SGA and AGA groups either. This might be related to random sampling error, because the true frequency of decidual arteriopathy is optimally demonstrated in placental bed biopsies. Zhang et al. showed recently that there is poor correlation between the histological diagnosis of maternal vasculopathy and the clinical manifestations of PE.

Our finding of higher frequency of intervillous thrombosis in placentas from PE in comparison with HELLP is intriguing but correlates with a recent study by de Luca Brunori et al. Intervillous thromboses are not associated with parenchyma loss in the placenta, but they probably reflect fetomaternal hemorrhage at the trophoblastic interface. Evidence of placenta barrier breakage, at the villous structural level, in PE has been presented recently. We could not find any difference in the frequency of accelerated villous maturation. However, it is of importance to mention that accelerated villous maturation cannot be adequately evaluated when the placenta is >37 weeks.

Within the Swedish material, we found a significantly higher percentage of large for gestational age placentas and higher mean placental weight in the HELLP as compared with the PE group. The reasons for this difference are not obvious. It was not because of placental edema, as only one of the included patients showed hydropic signs. It may be related to the limited size of the Swedish HELLP group. Because the Dutch and Swedish placentas were weighed differently, they were not comparable in this aspect; thus, it was not feasible to analyze the combined, larger material.

A possible reason for the differences in placental lesions between PE and HELLP patients could be that the HELLP syndrome is associated with a more rapid and aggressive clinical course. As seen in the Table, there is a longer time period between diagnosis and delivery in the PE than in the HELLP patients. PE might develop over a longer time and have a greater impact on the pathology of the placenta. HELLP, on the other hand, seems more acute, and an extensive pathological placenta has less time to develop.

Furthermore, we suggest that PE is a more vascular disease than HELLP, resulting in different placental histopathology. Although the pathogenesis of PE is unknown, it seems to be a consequence of a defect remodeling of the placental arteries, resulting in a defect placentation, a subsequent relative hypoxic environment, and manifested in the placenta as infarction, abortion, and decidual arteriopathy. The association between PE and growth restriction is well established, and the poor placenta, seen in many pre-eclamptic patients, has been correlated with SGA infants. This correlates well with our finding that children from PE mothers are more growth restricted than children from HELLP mothers.

Moreover, studies have shown that growth-restricted infants have a higher risk of developing premature atherosclerosis and that intrauterine exposure to PE influences adult blood pressure, but also that PE mothers have a higher risk of developing hypertension, as well as other cardiovascular diseases. We could not find studies assessing the long-term risk for developing cardiovascular diseases on HELLP patients.

Fischer et al. investigated vascular reactivity in both PE and HELLP patients and showed that vascular resistance during reactive hyperemia was increased in women with PE in comparison with both a control group and the HELLP group. They concluded that the vasodilatory reactivity is reduced in PE but not in the HELLP syndrome, suggesting different pathogenetic mechanisms in the 2 populations and probably a more pathological vascular development in PE than in HELLP.

The present study demonstrates the importance of a well-defined material and well-defined clinical criteria. The lack of
homogenous criteria and definitions might explain various results in different studies on PE. It is of great importance that further studies use strict definitions and criteria.

This study shows that PE and HELLP have different histopathology and that there is a higher frequency of SGA in PE than in HELLP. This might indicate various underlying pathogenetic mechanisms and different clinical courses. However, whether the discrepancy between these clinical entities with regard to placental pathology and birth weight is a primary or a secondary phenomenon is an open question and needs to be addressed in further studies. The present study is retrospective and, therefore, has its limitations. Prospective studies and studies on basic mechanisms on both PE and HELLP are needed to evaluate whether PE is a different clinical entity than HELLP.

**Perspectives**
The histopathologic profile and the range of placental lesions differ between HELLP and PE placentas, suggesting dissimilar underlying pathogenetic mechanisms. The finding that there are fewer SGA children in the HELLP syndrome might propose different future risk profiles concerning the newborn infant.

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**Disclosures**
None.

**References**
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