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# The placental component and obstetric outcome in severe preeclampsia with and without HELLP syndrome

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ABSTRACT

*Objective:* We aimed to compare obstetric outcome and placental-histopathology in pregnancies complicated by preeclampsia with severe features with and without HELLP syndrome.
*Methods:* Labor, maternal characteristics, neonatal outcome and placental histopathology of pregnancies complicated with severe preeclampsia during 2008–2015 were reviewed. Results were compared between those without signs of HELLP syndrome (severe preeclampsia group) and those with concomitant HELLP syndrome (HELLP group). Placental lesions were classified to maternal vascular lesions consistent with malperfusion, fetal vascular lesions consistent with fetal thrombo-occlusive disease, and inflammatory lesions. Small-for-gestational-age (SGA) was defined as birth-weight ≤10th% and ≤5th%. Composite adverse neonatal outcome was defined as one or more early neonatal complications.
*Results:* Compared to the severe preeclampsia group (n = 223), the HELLP group (n = 64) was characterized by earlier gestational-age, 34.1 ± 2.7 vs. 35.3 ± 3.4 weeks, p = 0.010, higher rates of multiple pregnancies (p = 0.024), and thrombophilia (p = 0.028). Placentas in the HELLP group had higher rates of vascular and villous lesions consistent with maternal malperfusion (p = 0.023, p = 0.037 respectively). By multivariate logistic regression analysis models, vascular and villous lesions of maternal malperfusion were independently associated with HELLP syndrome (aOR 1.9, aOR 1.8, respectively). SGA was also more common in the HELLP group, both below the 10th percentile (p = 0.044) and the 5th percentile (p = 0.016). Composite adverse neonatal outcome did not differ between the groups.
*Conclusion:* Severe preeclampsia and HELLP syndrome have similar placental histopathologic findings. However, HELLP syndrome is associated with higher rates of placental maternal vascular supply lesions and SGA suggesting that the two clinical presentations share a common etiopathogenesis, with higher placental dysfunction in HELLP syndrome.



## 1. Introduction

Preeclampsia is one of the major entities in obstetrics that can have serious consequences for both the infant and the mother due to medically indicated preterm birth, fetal growth restriction (FGR), placental abruption, and maternal end-organ damage [1]. Microangiopathic Hemolysis, Elevated Liver enzymes and Low Platelet (HELLP) syndrome is considered as one of the severe forms of preeclampsia, but the relationship between the two entities is controversial [2,3].

Abnormal placentation is known to be significantly associated with preeclampsia [4] and it is expressed through abnormal placental vascular lesions. The placental component in preeclampsia has been studied thoroughly in different clinical manifestations as in term and preterm preeclampsia [5], preeclampsia with and without FGR [6], or with and without severe features [7]. Studies have shown that abnormal placental morphology is more dominant in early-onset disease [8] and in preeclampsia with severe features, while lesions of fetal vascular supply are more

*Abbreviations:* HELLP, hemolysis elevated liver enzymes and low platelet; SGA, small for gestational age; NICU, neonatal intensive care unit; MIR, maternal inflammatory response; FIR, fetal inflammatory response.

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common in preeclampsia with than those without FGR [9]. Only three studies investigated the differences in placental histopathology and neonatal outcome in pregnancies complicated with severe preeclampsia, with and without HELLP syndrome [10–12], using different placental pathological criteria, relatively small samples, and with contradictory results and conclusions.

We aimed, therefore, to study the obstetric outcome, placental histopathologic lesions and umbilical cord abnormalities, in pregnancies complicated with preeclampsia with severe features, with and without HELLP syndrome, using the validated placental pathological criteria.

## 2. Materials and methods

The medical records and pathological reports of all patients who were diagnosed with preeclampsia and delivered at a single university hospital from 2008 to 2015 were reviewed. Cases eligible for the study were identified from our computerized data system.

The study group included patients who delivered between 24 and 42 gestational weeks, complicated with preeclampsia with severe features, and their placentas were sent to histopathological evaluation, according to our departmental protocol.

Excluded from the study pregnancies complicated by preeclampsia without severe features, neonatal chromosomal or structural anomalies, or pregnancies complicated by intrauterine infection.

Preeclampsia was diagnosed according to the current American College of Obstetricians and Gynecologists criteria [13]. Preeclampsia with severe features (severe preeclampsia) was defined when systolic blood pressure was ≥160 mm Hg and/or diastolic blood pressure was ≥110 mm Hg on 2 occasions ≥ 6 h apart. Blood pressure was measured by well-trained nurses, the cuff was wrapped around the left arm, the position of the arm was at heart level, and the patient was in a sitting position. Severe preeclampsia was defined also when there was an evidence of new development of renal insufficiency (elevated serum creatinine greater than 1.1 mg/dL, or doubling of serum creatinine in the absence of other renal disease), pulmonary edema, new-onset of cerebral or visual disturbance, or severe persistent right-upper-quadrant/epigastric pain unresponsive to medication.

HELLP syndrome was defined on the basis of the following criteria: a. hemolysis (based on low serum haptoglobin levels, and/or serum bilirubin ≥1.2 mg/dL, and/or a suggestive peripheral blood smear), b. elevated liver enzymes (alanine amino transferase or aspartate amino transferase ≥ twice upper level), c. low platelets (platelet count ≤ 100 000/μl). In the current study, we included patients complicated by complete or partial HELLP syndrome. Partial HELLP was defined as cases meeting two out of three criteria [3,14].

All patients were treated with magnesium sulfate for eclampsia prophylaxis, according to current guidelines [13] and with antihypertensive medications as appropriate.

For the purpose of the study pregnancy outcome and placental pathology reports were compared between pregnancies with severe preeclampsia without HELLP syndrome (severe preeclampsia group) and pregnancies with severe preeclampsia complicated by HELLP syndrome (HELLP group).

Approval for the study was obtained from the local ethics committee (decision number 0102-15-WOMC dated 6.8.2015).

### 2.1. Data collection

The following data were collected from the patient's medical and surgical files: age, gravidity, parity, body mass index (BMI kg/m$^2$), pre-gestational diabetes mellitus, gestational diabetes mellitus, chronic hypertension, history of previous preeclampsia, pre-pregnancy diagnosis of thrombophilia (defined as any thrombophilia, inherited or acquired, that necessitated thromboprophylaxis [15,16]) smoking, pregnancies achieved by assisted reproductive techniques (either ovulation induction or in-vitro fertilization), gestational age at delivery, mode of labor (Cesarean delivery vs. vaginal delivery). Gestational age was confirmed by first-trimester ultrasonography. Ultrasound studies before labor were collected. Fetal growth restriction (FGR) was defined as a prenatal ultrasound fetal weight estimation (FWE) < 10th percentile.

Laboratory blood studies were collected as well including prelabor: hemoglobin (Hb) g/dl levels, white blood cells (WBC) $10^3$/μl, platelets (PLT) $10^3$/μl, creatinine mg/dl, bilirubin (total) mg/dl, uric acid mg/dl, lactate dehydrogenase (LDH) U/l, aspartate amino transferase (AST) U/l, and alanine aminotransferase (ALT) U/l.

Immediately after birth, all neonates were examined by pediatricians. Birth weight percentiles for gestational age were assigned using the updated local growth charts [17]. Small for gestational age (SGA) was defined as actual birth-weight ≤10th percentile or ≤5th percentile for gestational age. The following data were collected from the neonatal records: Apgar scores, cord blood pH, neonatal intensive care unit (NICU) admissions, sepsis (positive blood or cerebrospinal fluid culture), need for blood transfusion, need for phototherapy, respiratory distress syndrome, need for mechanical ventilation or support, necrotizing enterocolitis, intraventricular hemorrhage (all grades), hypoxic ischemic encephalopathy, seizures, and death.

### 2.2. Placental examination

As part of our departmental protocol, in every case of preeclampsia placentas are sent for histopathological evaluation. Placental pathology examinations were performed using our standard protocol, by a single pathologist (author L.S). Placental lesions were classified according to the criteria adopted by the Society for Pediatric Pathology [18,19] and as was previously reported by us [20].

Briefly, placental weight was determined 24 h after delivery, and the percentile was determined according to placental weight charts [21]. From each placenta 6 tissue samples were embedded in paraffin blocks for microscopic assessment: one roll of the free membranes, (chorion and amnion with attached deciduas capsularis), and section of umbilical cord. Five full thickness disc samples: one at the cord insertion, one in central tissue that appeared abnormal on gross examination, two from central tissue, and one at the margin, of visible abnormal areas on gross examination. Placentas derived from twin pregnancies were examined and reported separately.

Lesions of maternal vascular supply included: placental hemorrhages (marginal, and retro-placental hematoma), vascular changes associated with maternal malperfusion (acute atherosis and mural hypertrophy), and villous changes associated with maternal malperfusion (increased syncytial knots, villous agglutination, increased intervillous fibrin deposition, distal villous hypoplasia, and parenchymal infarcts).

Lesions of fetal vascular supply were defined as findings consistent with fetal thrombo-occlusive disease: vascular lesions (thrombosis of the chorionic plate and stem villous vessels) and villous changes (villous stromal-vascular karyorrhexis and avascular villi).

Findings consistent with chorioamnionitis were defined according to the structure proposed by the Society for Pediatric Pathology [22]. Maternal inflammatory response (MIR), was divided into three stages and two grades: stage 1 – acute subchorionitis or