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Placental histopathological lesions in correlation with neonatal outcome in preeclampsia with and without severe features

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ABSTRACT

Objective: We aimed to compare pregnancy outcome and placental histopathology in women with preeclampsia (PE) with and without severe features.

Methods: The medical records and placental pathology reports of all pregnancies complicated by PE during 2008–2016, were reviewed. Results were compared between those with and without severe features (severe PE vs. mild PE groups), according to current ACOG guidelines. Placental lesions were classified to maternal/fetal vascular supply lesions, and maternal/fetal inflammatory responses. Small for gestational age (SGA) was defined as neonatal birth-weight ≤10th%. Composite adverse neonatal outcome was defined as one or more of the following: sepsis, transfusion, phototherapy, respiratory morbidity, cerebral morbidity, NEC, or death.

Results: The severe PE group (n = 284) was characterized by lower gestational age at delivery ($p < 0.001$), and higher rates of antenatal corticosteroid use ($p = 0.003$), and cesarean deliveries ($p < 0.001$) as compared to the mild PE group (n = 151). More placentas < 10th% and more composite maternal vascular malperfusion (MVM) lesions were observed in the severe PE group as compared to the mild PE group ($p < 0.001$ for both). In multivariate analysis, composite placental MVM lesions were independently associated with severe PE (aOR = 1.75, 95%CI 1.4–4.9).

Higher rates of SGA ($p = 0.016$), and composite adverse neonatal outcome ($p = 0.002$) characterized the severe PE group. In multivariate analysis, adverse neonatal outcome was independently associated with gestational age (aOR = 0.54, 95%CI 0.49–0.68), SGA (aOR = 1.75, 95%CI = 1.15–3.59), severe PE (aOR = 1.8, 95%CI = 1.13–3.54) and placental MVM lesions (aOR = 2.13, 95%CI = 1.05–4.39).

Conclusion: More pronounced placental pathology and higher rate of adverse neonatal outcome characterize preeclampsia with severe features as compared with the milder form of the disease.

1. Introduction

Preeclampsia (PE) is a multi-system disorder of pregnancy [1] that could lead to immediate and long-term detrimental maternal and neonatal consequences. Maternal complications include eclampsia, placental abruption, renal and hepatic failure during pregnancy, as well as increased risk of chronic hypertension, cardiovascular disease, stroke, and metabolic syndrome later in life [2–4]. Neonatal complications include prematurity related consequences, compromised motor development [5], intra uterine fetal growth restriction (FGR) with increased risk of diabetes and cardiovascular morbidity in adulthood [6].

PE has two main clinical presentations, PE with and without severe features [1]. The severe form of the disease includes severe hypertension and symptoms of end-organ injury. In comparison to PE without severe features, severe PE was shown to be associated with adverse neonatal outcomes, including higher rates of preterm birth and small for gestational age (SGA) [7,8].

The etiology and pathophysiology of PE have not been fully elucidated yet [9]. Studies suggest that endothelial dysfunction, systemic inflammation or infection, genetic and immunologic aberrations are involved in the development of PE [10,11]. It is generally accepted that abnormal placentation plays a central role in the pathophysiology of PE [12,13]. This abnormality leads to the release of circulating anti-angiogenic factors that in turn cause systemic endothelial dysfunction, resulting in hypertension, proteinuria, and numerous systemic manifestations [14].

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The association between ischemic placental diseases, such as PE and FGR, and placental histopathology lesions, mostly of maternal vascular malperfusion (MVM) lesions, has been studied in different clinical presentations [15]. These presentations include early and late onset of PE [16], severe PE with and without HELLP syndrome [17,18] as well as early vs. late FGR [19,20]. Only few studies investigated the association between the severity of PE and placental histopathology findings [21–23], and none of these studies looked for a correlation with neonatal outcomes.

Therefore, we aimed to fill this gap and to examine the association between neonatal outcome and placental histopathologic lesions, in pregnancies complicated by PE, with and without severe features.

2. Materials and methods

The medical records and pathological reports of all patients who were diagnosed with PE and delivered at a single university hospital from 2008 to 2017 were reviewed. Cases eligible for the study were identified from our computerized data system. The study group included singleton pregnancies complicated by preeclampsia, delivered between 24 and 42 gestational weeks, and who had placental histopathological evaluation, according to our departmental protocol. Excluded from the study multiple pregnancies, pregnancies complicated by neonatal chromosomal, structural anomalies, and intrauterine infection, as well as cases that underwent termination of pregnancy.

PE was diagnosed according to the current American College of Obstetricians and Gynecologists criteria [1], which were fully adapted by our institution for preeclampsia diagnosis and management. PE with severe features (severe PE) was defined by the presence of any of the following findings: systolic blood pressure was ≥160 mm Hg, or diastolic blood pressure was ≥110 mm Hg on 2 occasions ≥6 h apart, thrombocytopenia (platelet count ≤100,000/μL), severe persistent right-upper-quadrant/epigastric pain unresponsive to medication, elevated liver enzymes (alanine amino transferase or aspartate amino transferase ≥ twice upper level), hemolysis (based on low serum haptoglobin levels, and/or serum bilirubin ≥ 1.2 mg/dL, and/or a suggestive peripheral blood smear), 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, or new-onset of cerebral/visual disturbance. All patients with severe features were treated with magnesium sulfate for eclampsia prophylaxis, according to the current guidelines and with antihypertensive medications as appropriate [1].

For the purpose of the study, pregnancy outcome and placental pathology reports were compared between pregnancies complicated by PE with (severe PE group) and without severe features (mild PE 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), pregestational diabetes mellitus, gestational diabetes mellitus, chronic hypertension, history of previous PE, thrombophilia (defined as any thrombophilia, inherited or acquired, that necessitated thromboprophylaxis [24,25], maternal smoking, gestational age at delivery, antenatal corticosteroid administration, Magnesium Sulfate administration, and mode of labor (cesarean delivery vs. vaginal delivery). Gestational age was confirmed by first-trimester ultrasonography. Women were considered to receive antenatal corticosteroids if they received two dose of intramuscular Betamethasone 12 mg, 24 h apart, prior to delivery [26].

Immediately after birth, all neonates were examined by pediatricians. Birth weight percentiles for gestational age were assigned using the updated local growth charts [27]. SGA was defined as actual birthweight ≤ 10th 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 pregnancy complications 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 [28,29] and as was previously reported by us [18,30].

Briefly, placental weight was determined 24 h after delivery, and the percentile was determined according to placental weight charts [31]. Each placenta was fixed in formalin, and at least 5 samples were embedded in paraffin blocks for microscopic assessment.

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 villous 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 (hypovascular, fibrotic and avascular villi).

Findings consistent with chorioamnionitis were defined by the presence of an inflammatory neutrophil infiltrate at two or more sites on the chorionic plate and extra-placental membrane. Maternal inflammatory response (MIR), was divided into three stages; stage 1 – characterized by the presence of a few scattered neutrophils in the subchorionic space; stage 2 – characterized by many neutrophils (11–30 per HPF) in the lower half of the chorionic plate; and stage 3 – characterized by dense infiltrates of neutrophils (> 30 per HPF) throughout the chorionic plate. Fetal inflammatory response (FIR) was also divided into 3 stages: stage 1 – early, umbilical phlebitis; stage 2 – intermediate, umbilical arteritis; and stage 3 – concentric umbilical perivasculitis (necrotizing funisitis). Villitis of unknown etiology or chronic villitis, defined as lymphohistiocytic inflammation localized to the stroma of terminal villi but often extending to the small vessels of upstream villi, was recorded separately.

The umbilical cord was examined for the detection of hypercoiling and abnormal cord insertion. Umbilical coiling index was calculated by dividing the total number of coils by the length of the cord in centimeters. Hypercoiling was diagnosed in cases of umbilical coiling index > 0.3 coils/cm [32]. Abnormal cord insertion was defined as either velamentous, or marginal insertion.

2.3. Statistical analysis

Data were analyzed with SPSS software, version 21.0 (SPSS Inc; Chicago, Illinois). Continuous variables are presented as median [IQR]. Categorical variables are presented as rate (%). Continuous parameters were compared by Mann–Whitney's *U* test and categorical variables by chi-square test or by Fisher exact test, as appropriate. P-value of < 0.05 was considered statistically significant.

Composite placental maternal vascular malperfusion lesions was defined as the presence of one or more of maternal vascular supply abnormalities, and composite placental fetal vascular malperfusion lesions was defined as the presence of one or more fetal vascular supply abnormalities.