Original Article

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Comparison of Placental Histopathology in Early-Onset and Late-Onset Preeclampsia: A Prospective Cohort Study

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ABSTRACT

Purpose: To compare histopathological findings associated with reduced uteroplacental perfusion between [early-onset preeclampsia (EOPE), <34 weeks] and [late-onset preeclampsia (LOPE), ≥34 weeks] placentas, and to evaluate whether placental morphology may contribute to understanding differences between these subtypes.

Methods: This prospective observational cohort study was performed with the participation of women diagnosed with preeclampsia according to 2013 American College of Obstetricians and Gynecologists criteria who were divided into EOPE and LOPE subgroups. Placenta samples were collected after delivery, fixed in formalin, and evaluated after hematoxylin-eosin staining. Histopathological findings were assessed according to Amsterdam Placental Workshop Group Consensus criteria and reviewed by a blinded perinatal histopathologist. Comparisons between groups were performed using Student's t-test, Mann-Whitney U test, chi-square test, Fisher's exact test, and binary logistic regression where appropriate. A p value <0.05 was considered statistically significant.

Results: A total of 75 women were recruited, 33 (44%) with EOPE and 42 (56%) with LOPE. Villous infarction and cytotrophoblast cell proliferation were significantly more prevalent in the EOPE group ($p=0.026$ vs. $p=0.043$). Fibrinoid necrosis showed a non-significant tendency toward higher prevalence in EOPE. Syncytiotrophoblastic knotting was present in over 93% of cases in both groups ($p=0.852$). Perivillous fibrin deposits were present in all cases. Hemolysis, elevated liver enzymes, low platelets syndrome was observed only in the EOPE group (24.24% vs. 0%; $p=0.001$). Intrauterine growth restriction was significantly more common in EOPE (odds ratio 4.70) (48.48% vs. 16.67%; $p=0.003$). Mean birth weight, placental weight and Apgar scores at 1 minute and 5 minutes were all significantly lower in the EOPE group.

Conclusion: Placental defects revealing reduced uteroplacental perfusion included villous infarction and cytotrophoblastic proliferation which were significantly more prevalent in EOPE. Syncytiotrophoblastic knotting and perivillous fibrin deposition were highly prevalent in both groups, suggesting shared ischemic mechanisms. These findings support the hypothesis that EOPE and LOPE may differ in the degree and pattern of placental involvement while sharing several underlying pathophysiological mechanisms. Further studies are needed before routine implementation can be recommended in all preeclamptic pregnancies.

Keywords: Histopathology, preeclampsia, placenta, trophoblasts, placenta diseases

INTRODUCTION

Preeclampsia is a pregnancy-specific disorder characterized by new-onset hypertension after 20 weeks of gestation, with or without proteinuria, and it may lead to multi-organ dysfunction and adverse maternal and fetal outcomes. It affects approximately 2-8% of pregnancies worldwide and continues to be a major cause of maternal and perinatal mortality.[1,2] Despite extensive research, its underlying mechanisms are still not fully understood, and in daily practice management remains largely symptomatic. In most cases, delivery is still the only definitive treatment.[3]

Rather than a single disease entity, preeclampsia is increasingly considered a heterogeneous syndrome. It is commonly divided into [early-onset preeclampsia (EOPE), <34 weeks] and [late-onset preeclampsia (LOPE), ≥34 weeks] forms, which differ in

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several important aspects.[4] EOPE is generally linked to impaired trophoblast invasion and defective spiral artery remodeling. This results in reduced uteroplacental perfusion, angiogenic imbalance, indicated typically by increased soluble fms-like tyrosine kinase-1 (sFlt-1) and decreased placental growth factor (PlGF) concentrations, and oxidative stress. LOPE, on the other hand, seems to be more closely associated with the maternal cardiovascular and metabolic background, although placental lesions and maternal vascular malperfusion (MVM) findings may also be observed in this phenotype.[4]

These differences are also reflected at the biomarker level. For example, increased sFlt-1/PlGF ratios are more closely related to placental insufficiency, even in cases that are clinically classified as late-onset.[5] This supports the suggestion that gestational age alone may not fully capture the biological diversity of the condition.

The placenta has a central role in the development of preeclampsia. Many of the characteristic lesions are now grouped under the concept of MVM, as defined by the Amsterdam Consensus Criteria.[6] This includes findings such as placental hypoplasia, infarction, retroplacental hemorrhage, and distal villous hypoplasia. Studies using this framework have shown that these lesions tend to be more frequent and more severe in early-onset disease.[7,8] Still, interpretation is not always straightforward. Interobserver variability remains an issue, and not all features are equally reproducible. Interestingly, infarction appears to be one of the more consistent findings across observers.[9] Even with these benefits, direct comparisons of placental histopathology between EOPE and LOPE are still relatively limited. In particular, it is not entirely clear how useful routine placental examination is in distinguishing between these subtypes in clinical practice.

In this study, we aimed to compare a broad range of histopathological features between EOPE and LOPE cases and to explore whether these differences may contribute to understanding the phenotypic variation between EOPE and LOPE. We hypothesize that EOPE is associated with a higher burden of MVM-related lesions compared with late-onset disease, reflecting more severe primary placental dysfunction.

METHODS

Study Design and Participants

We conducted a prospective observational cohort study in line with the STROBE guidelines at İstanbul Kanuni Sultan Süleyman Training and Research Hospital between April 2014 and January 2015. Ethical approval for this study was obtained from the University of Health Sciences Turkey, Kanuni Sultan Süleyman Training and Research Hospital Clinical Research Ethics Committee (approval no: 3, date: 26.09.2014). Written informed consent was obtained from all participants prior to enrollment. The study was conducted in accordance with the Declaration of Helsinki and applicable national regulations governing human research.

Women diagnosed with preeclampsia between 24 and 42 weeks of gestation were eligible for inclusion. Preeclampsia was defined according to the 2013 American College of Obstetricians and Gynecologists criteria,[10] based on new-onset hypertension (≥140/90 mmHg on two occasions at least four hours apart after 20 weeks of pregnancy) accompanied by proteinuria (≥300 mg/24 h). In the absence of proteinuria, diagnosis required evidence of end-organ involvement, including thrombocytopenia, renal insufficiency, impaired liver function, pulmonary edema, or new-onset neurological symptoms.

For the purpose of analysis, patients were grouped into early-onset (<34 weeks) or late-onset (≥34 weeks) preeclampsia. Gestational age was estimated based on the last menstrual period and confirmed by first-trimester crown-rump length measurements.

Women were excluded if they had chronic hypertension, pre-existing diabetes mellitus, autoimmune disease, chronic renal disease, were active smokers, or if fetal chromosomal or structural abnormalities, or intrauterine infection was present. Cases with insufficient placental material were also not included in the final analysis.

Clinical Data Collection

Maternal demographic and obstetric characteristics, including age, gravidity, parity, history of abortion, number of living children, gestational age at delivery, mode of delivery, birth weight, fetal sex, and Apgar scores were prospectively recorded. Laboratory findings at the time of diagnosis were also collected.

Intrauterine growth restriction (IUGR) was defined as an estimated fetal weight below the 10th percentile for gestational age on ultrasound. Hemolysis, elevated liver enzymes, low platelets (HELLP) syndrome was diagnosed using standard clinical and laboratory criteria, including hemolysis, elevated liver enzymes, and low platelet count.

Placental Histopathological Evaluation

Placental specimens were obtained immediately after delivery. After removal of membranes and umbilical cord, each placenta was weighed and fixed in 10% neutral buffered formalin for 48 hours. Tissue sampling included both central and peripheral regions, along with any visible lesions. Sections were embedded in paraffin, cut at a thiclness of 3-4 μm, and stained with hematoxylin and eosin. All slides were evaluated by an experienced histopathologist who was unaware of the clinical grouping. Histopathological evaluation was performed according to the Amsterdam Placental Workshop Group Consensus Statement criteria, with specific reference to MVM-related lesions. Villous infarction was defined as areas of ischemic villous necrosis characterized by loss of villous architecture and ghost-like villi with karyorrhectic debris. Fibrinoid necrosis was defined as deposition of eosinophilic fibrin-like material replacing villous stroma. Syncytiotrophoblastic knotting was assessed semi-quantitatively based on the proportion of terminal villi showing knot formation and categorized as absent (<10%), mild (10-30%), moderate (30-70%), or severe (>70%). Perivillous fibrin deposition was graded according to estimated percentage

of intervillous space involvement (<20%, 20-30%, >30%). Cytotrophoblastic proliferation was defined as persistence or increased prominence of cytotrophoblast cells along villous surfaces beyond expected gestational age-related regression. This was also assessed semi-quantitatively and categorized as absent, mild (focal increase in ≤10% of villi), moderate (10-30%), or severe (>30% of villi showing prominent proliferation).

Statistical Analysis

Statistical analyses were performed using NCSS 2007 software (NCSS, LLC, USA). Continuous variables are presented as mean ± standard deviation. Depending on distribution, comparisons were made using either Student's t-test or the Mann-Whitney U test. Standard binary logistic regression using maximum likelihood estimation was performed to explore factors associated with disease phenotype (EOPE versus LOPE). Disease phenotype was entered as the dependent variable, while IUGR, villous infarction, and cytotrophoblastic proliferation were included as independent variables based on their clinical relevance and univariate associations. HELLP syndrome was excluded from multivariable modeling due to zero-event distribution in the LOPE group, which precluded stable estimation of effect size. Given the limited sample size and sparse event distribution for some variables, the multivariable analysis should be considered exploratory and hypothesis-generating.[11] A p value <0.05 was considered statistically significant. No formal sample size calculation was performed. All eligible patients meeting the inclusion criteria during the study period were consecutively recruited. Therefore, the study should be considered exploratory. Given the close relationship between gestational age and preeclampsia phenotype (EOPE versus LOPE), gestational age was not included in the multivariable model. Therefore, the observed associations should be interpreted with caution, as residual confounding by gestational age cannot be excluded. The outcome coding used in the logistic regression analysis was clarified in the revised manuscript. In the logistic regression model, LOPE was coded as the outcome category (LOPE=1, EOPE=0). Therefore, odds ratios (ORs) below 1 indicate variables more strongly associated with EOPE. For ordinal histopathological variables, overall group comparisons were performed using chi-square tests for trend or Pearson's chi-square tests based on categorical distribution. Binary variables were analyzed using Pearson's chi-square test or Fisher's exact test where appropriate. All p values represent overall comparisons across categories rather than pairwise subgroup comparisons. Liver amniotransferase levels were compared using the Mann-Whitney U test because of non-normal distribution and extreme values.

RESULTS

Demographic, Clinical, and Laboratory Characteristics

Seventy-five women with preeclampsia were included, 33 (44%) with EOPE and 42 (56%) with LOPE. No significant differences were observed between groups in maternal age, gravidity, parity, number of abortions, or number of living children. Mean gestational age at delivery was markedly lower in the EOPE group (30.42±2.93 vs. 37.45±2.10 weeks; p<0.0001), as was mean birth weight (1480.61±504.63 g vs. 2760.36±685.24 g; p<0.0001). Systolic blood pressure at diagnosis was significantly higher in EOPE cases (165.00±13.91 vs. 153.81±14.18 mmHg; p=0.001). Diastolic blood pressure did not differ significantly between groups (102.94±10.79 vs. 100.19±9.91 mmHg; p=0.255). Apgar scores at 1 minute (5.93±2.36 vs. 7.51±1.86; p=0.002) and 5 minutes (8.03±1.30 vs. 9.10±1.16; p=0.001) were significantly lower in the EOPE group. Mode of delivery did not differ significantly between groups (cesarean: 78.79% vs. 59.52%; p=0.076). Female fetal sex was more prevalent in LOPE (66.67% vs. 42.42%; p=0.036).

HELLP syndrome occurred exclusively in the EOPE group (24.2% vs 0%, p=0.001). IUGR was identified in 48.48% of EOPE versus 16.67% of LOPE cases (p=0.003; OR 4.70, 95% CI 1.63-13.59). Eclampsia rates did not differ significantly (6.06% vs. 2.38%; p=0.420). Platelet counts were significantly lower in EOPE (198.28±87.51 vs. 236.28±73.43 $\times 10^3/\mu L$; p=0.045) and lactate dehydrogenase was significantly elevated (382.33±303.02 vs. 255.90±63.54 U/L; p=0.008). Placental weight was significantly lower in EOPE (319.24±120.86 vs. 393.57±129.42 g; p=0.013). Hemoglobin, hematocrit, urea, creatinine, aspartate aminotransferase, alanine aminotransferase, and spot urinary protein did not differ significantly between groups (p>0.05 for all; Table 1).

Histopathological Findings

All placental histopathological parameters are detailed in Table 2A and B. Villous infarction was significantly more prevalent in the EOPE group (48.48% vs. 23.81%; p=0.026; OR 3.01, 95% CI 1.12-8.07) (Figure 1). Infarcts were focal in 33.33% and multifocal in 15.15% of EOPE cases, versus 16.67% and 7.14% in LOPE, respectively.

Cytotrophoblastic cell proliferation was also significantly elevated in EOPE (15.15% vs. 2.38%; p=0.043). Fibrinoid necrosis was present in 69.70% of EOPE versus 47.62% of LOPE cases (p=0.065). Diffuse fibrinoid necrosis was observed in 6.06% of EOPE and 7.14% of LOPE cases.

Syncytiotrophoblastic knotting was detected in 93.94% of EOPE and 92.86% of LOPE placentas, with no significant difference between groups (p=0.852 for presence; p=0.617 for severity grade) (Figure 2). Perivillous fibrin deposits were universal (100% in both groups), with no significant difference in severity grading (p=0.374). Severe perivillous fibrin deposition (>30%, p=0.374) was noted in 15.15% of EOPE versus 7.14% of LOPE cases.

Villous hypovascularity was present in 78.79% of EOPE versus 69.05% of LOPE cases (p=0.293). Moderate-to-severe hypovascularity was more frequent in EOPE (54.54% vs. 33.33%). Villous fibrosis was present in 54.55% of EOPE and 47.62% of LOPE cases (p=0.551). Subcorionic hematoma was observed in 54.55% of EOPE and 71.43% of LOPE cases (p=0.131). No statistically significant differences were found for acute chorioamnionitis (Figure 3), fetal vessel acute inflammation, extravillous trophoblast proliferation, villous capillary congestion, thickening of villous vessel walls, fetal

Table 1. Demographic, clinical, and laboratory characteristics by group

Variable	LOPE (n=42)	EOPE (n=33)	*p* value
Maternal age (years), mean ± SD	29.40±6.78	29.12±5.99	0.851
Gravidity, mean ± SD	2.60±2.15	2.97±2.26	0.275
Parity, mean ± SD	1.10±1.50	1.39±1.44	0.173
Abortus, mean ± SD	0.43±1.25	0.45±0.83	0.301
Living children, mean ± SD	0.07±0.46	0.12±0.42	0.217
Gestational age at delivery (wk), mean ± SD	37.45±2.10	30.42±2.93	<0.0001*
Birth weight (g), mean ± SD	2760.36±685.24	1480.61±504.63	<0.0001*
Placental weight (g), mean ± SD	393.57±129.42	319.24±120.86	0.013*
Systolic BP at diagnosis (mmHg)	153.81±14.18	165.00±13.91	0.001*
Diastolic BP at diagnosis (mmHg)	100.19±9.91	102.94±10.79	0.255
Apgar score-1st minute, mean ± SD	7.51±1.86	5.93±2.36	0.002*
Apgar score-5th minute, mean ± SD	9.10±1.16	8.03±1.30	0.001*
SVD, n (%)	17 (40.48%)	7 (21.21%)	0.076
Cesarean delivery, n (%)	25 (59.52%)	26 (78.79%)	
Fetal sex-female, n (%)	28 (66.67%)	14 (42.42%)	0.036*
Fetal sex-male, n (%)	14 (33.33%)	19 (57.58%)	
IUGR, n (%)	7 (16.67%)	16 (48.48%)	0.003*
HELLP syndrome, n (%)	0 (0.00%)	8 (24.24%)	0.001*
Eclampsia, n (%)	1 (2.38%)	2 (6.06%)	0.420
Hemoglobin (g/dL), mean ± SD	11.99±1.91	11.95±1.76	0.929
Hematocrit (%), mean ± SD	36.07±4.75	34.61±4.47	0.180
Platelet Count ($\times 10^3/\mu$L), mean ± SD	236.28±73.43	198.28±87.51	0.045*
Urea (mg/dL), mean ± SD	20.81±6.89	23.85±8.92	0.101
Creatinine (mg/dL), mean ± SD	0.61±0.16	0.61±0.13	0.950
AST (U/L), mean ± SD	20.50±8.13	41.67±69.15	0.979
ALT (U/L), mean ± SD	12.55±7.58	21.88±33.64	0.607
LDH (U/L), mean ± SD	255.90±63.54	382.33±303.02	0.008*
Spot urinary protein (dipstick), mean ± SD	1.93±0.81	2.27±0.87	0.124
+1, n (%)	15 (36.59%)	7 (26.92%)	
+2, n (%)	14 (34.15%)	5 (19.23%)	
+3, n (%)	12 (29.27%)	14 (53.85%)	

*$p<0.05$. Data presented as mean ± SD or n (%). For delivery mode and fetal sex, *p* value is shown on the first category row. Spot protein subgroup denominators exclude 8 patients with 24-hour urine collection
LOPE: Late-onset preeclampsia, EOPE: Early-onset preeclampsia, SD: Standard deviation, BP: Blood pressure, wk: Weeks, SVD: Spontaneous vaginal delivery, IUGR: Intrauterine growth restriction, HELLP: Hemolysis, elevated liver enzymes, low platelets, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, LDH: Lactate dehydrogenase

vascular thrombosis, chronic villitis, intervillous hemorrhage, or placental calcification ($p>0.05$ for all).

In multivariable logistic regression analysis, IUGR ($p=0.041$) and cytotrophoblastic proliferation ($p=0.042$) remained significantly associated with disease phenotype, whereas villous infarction did not retain statistical significance ($p=0.395$) (Table 3). Since LOPE was coded as the outcome category (LOPE=1, EOPE=0), ORs below 1 in the multivariable model indicate stronger associations with EOPE.

DISCUSSION

In this study, we compared placental histopathological findings between early- and LOPE and observed both differences and substantial overlap between the two groups. Some features appeared to cluster with early-onset disease, whereas others were common across the spectrum. Overall, our findings support the concept that preeclampsia represents a heterogeneous disorder with overlapping but not identical placental phenotypes.

Table 2A. Histopathological findings in EOPE and LOPE ordinal histopathological findings

	LOPE n=42 (%)	EOPE n=33 (%)
Villous infarction		
Absent	32 (76.19%)	17 (51.52%)
Focal	7 (16.67%)	11 (33.33%)
Multifocal	3 (7.14%)	5 (15.15%)
Overall *p* value		0.026*
Cytotrophoblastic proliferation		
Absent	41 (97.62%)	28 (84.85%)
Mild	1 (2.38%)	4 (12.12%)
Severe	0 (0.00%)	1 (3.03%)
Overall *p* value		0.043*
Fibrinoid necrosis		
Absent	22 (52.38%)	10 (30.30%)
Focal	17 (40.48%)	21 (63.64%)
Diffuse	3 (7.14%)	2 (6.06%)
Overall *p* value		0.065
Syncytiotrophoblastic knotting		
Absent (<10%)	3 (7.14%)	2 (6.06%)
Mild (10-30%)	20 (47.62%)	11 (33.33%)
Moderate (30-70%)	16 (38.10%)	17 (51.52%)
Severe (>70%)	3 (7.14%)	3 (9.09%)
Overall *p* value		0.617
Perivillous fibrin deposition		
Mild (<20%)	18 (42.86%)	10 (30.30%)
Moderate (20-30%)	21 (50.00%)	18 (54.55%)
Severe (>30%)	3 (7.14%)	5 (15.15%)
Overall *p* value		0.374
Villous hypovascularity		
Absent	13 (30.95%)	7 (21.21%)
Mild	15 (35.71%)	8 (24.24%)
Moderate	12 (28.57%)	14 (42.42%)
Severe	2 (4.76%)	4 (12.12%)
Overall *p* value		0.293
Villous fibrosis		
Absent	22 (52.38%)	15 (45.45%)
Mild	16 (38.10%)	10 (30.30%)
Moderate	4 (9.52%)	7 (21.21%)
Severe	0 (0.00%)	1 (3.03%)
Overall *p* value		0.321
Intervillous hemorrhage		
Absent	11 (26.19%)	9 (27.27%)
Mild	20 (47.62%)	12 (36.36%)
Moderate	9 (21.43%)	11 (33.33%)
Severe	2 (4.76%)	1 (3.03%)
Overall *p* value		0.642

*$p<0.05$. Overall *p* values for ordinal variables were calculated using chi-square test for trend or Pearson's chi-square test based on distribution across all categories of each lesion, rather than pairwise comparisons
LOPE: Late-onset preeclampsia; EOPE: Early-onset preeclampsia

Table 2B. Binary histopathological findings

Feature	LOPE n=42	EOPE n=33	*p* value
Subcorionic hematoma, n (%)	30 (71.43%)	18 (54.55%)	0.131
Acute chorioamnionitis, n (%)	11 (26.19%)	8 (24.24%)	0.847
Fetal vessel acute ınflammation, n (%)	3 (7.14%)	1 (3.03%)	0.431
Extravillous trophoblast prolif., n (%)	28 (66.67%)	21 (63.64%)	0.784
Villous capillary congestion, n (%)	12 (28.57%)	9 (27.27%)	0.901
Villous vessel wall thickening, n (%)	5 (11.90%)	8 (24.24%)	0.161
Fetal vascular thrombosis, n (%)	0 (0.00%)	2 (6.06%)	0.106
Chronic villitis, n (%)	2 (4.76%)	1 (3.03%)	0.704
Placental calcification, n (%)	17 (40.48%)	12 (36.36%)	0.717

LOPE: Late-onset preeclampsia; EOPE: Early-onset preeclampsia

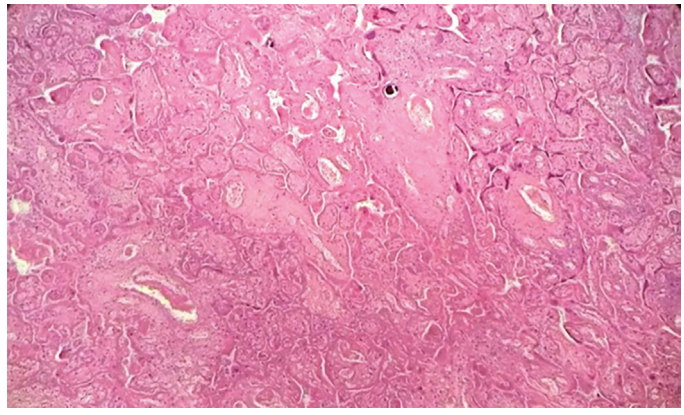

Figure 1. Villous infarction in early-onset preeclampsia placenta. Histopathological section of a placenta from a patient with early-onset preeclampsia showing villous infarction characterized by extensive areas of coagulative necrosis involving terminal villi. Loss of villous architecture, increased fibrinoid deposition, and collapse of intervillous spaces are evident. The lesion is consistent with maternal vascular malperfusion [Hematoxylin and eosin (H&E) stain, original magnification ×100]

Villous infarction was more frequent in EOPE,[12,13] which is consistent with impaired uteroplacental perfusion. This finding is biologically plausible and consistent with the current understanding of placental insufficiency in EOPE. In our cohort, this finding paralleled clinical severity, as indicated by lower birth weight, lower Apgar scores, and a higher rate of IUGR which were all seen in the EOPE group.[14] Rather than being a purely descriptive histological feature, infarction seems to reflect functionally relevant placental damage.

A similar pattern was observed for cytotrophoblastic proliferation. Normally, these cells become less prominent as gestation progresses. Their persistence, therefore, likely

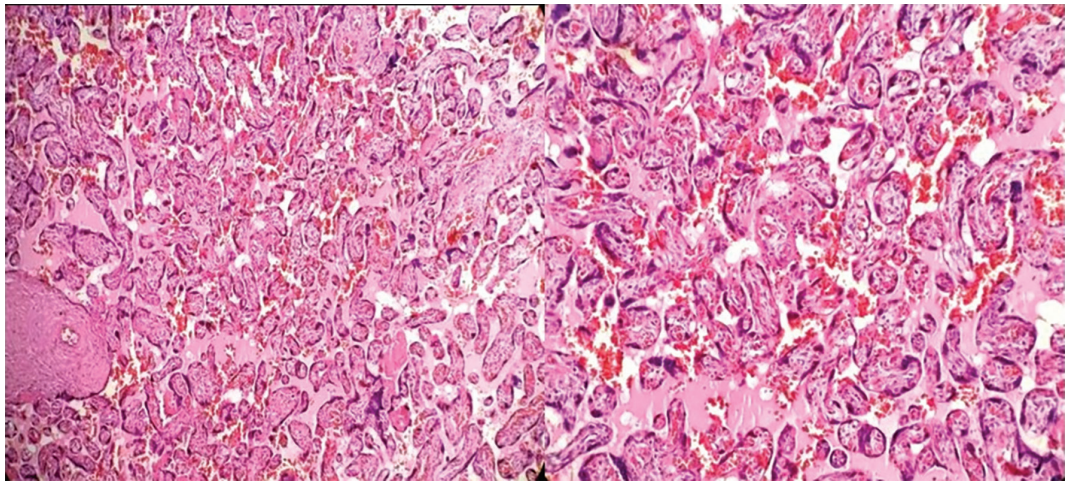

Figure 2. Syncytiotrophoblastic knotting in preeclamptic placenta. Placental tissue demonstrating increased syncytiotrophoblastic knot formation characterized by aggregation of syncytial nuclei at the villous surface. This finding is observed in both early-onset and late-onset preeclampsia cases and reflects villous maturation disturbance and placental stress (H&E stain, original magnification ×200)

H&E: Hematoxylin and eosin

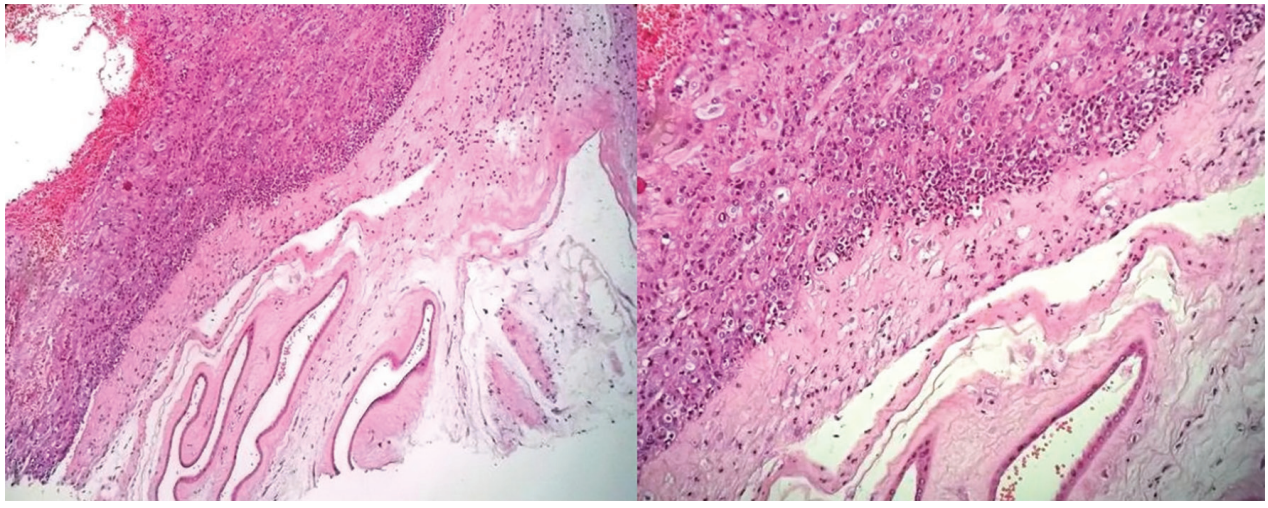

Figure 3. Acute chorioamnionitis. Histological section showing acute chorioamnionitis characterized by neutrophilic infiltration within the chorionic plate and fetal membranes. The inflammatory cells are predominantly located in the subchorionic space, consistent with an acute inflammatory response (H&E stain, original magnification ×100)

H&E: Hematoxylin and eosin

Table 3. Binary logistic regression analysis of key parameters

Parameter	B	SE	OR	95% CI	*p* value
IUGR	-1.24	0.61	0.29	0.09-0.95	0.041*
Villous infarction	-0.51	0.60	0.60	0.19-1.93	0.395
Cytotrophoblastic proliferation	-2.29	1.18	0.10	0.01-1.02	0.042*

*$p < 0.05$
B: Regression coefficient, SE: Standard error, OR: Odds ratio, CI: Confidence interval, IUGR: Intrauterine growth restriction

indicates an ongoing response to stress, possibly hypoxia-related.[15] We found that this feature remained significant even after multivariate analysis, which suggests that it may be associated with phenotypic differences between EOPE and LOPE, at least in the context of early-onset disease.

Not all findings behaved in the same way. Syncytiotrophoblastic knotting and perivillous fibrin deposition were present in almost all cases, regardless of subtype.[16] At first glance, this might suggest that they are important markers. However, their near-universal presence makes them less useful for distinguishing between EOPE and LOPE.

This point becomes clearer when our results are considered alongside previous work. A retrospective study by Atigan et al.[17] reported that syncytial knots and perivillous fibrin deposition were significantly increased in preeclamptic placentas compared to controls, but these findings were not associated with maternal or neonatal outcomes. In other words, the lesions were present, but they did not seem to carry prognostic information. Our data aligns with that observation but also extends it. While we observed high rates of these features, we found that other lesions, particularly villous infarction and cytotrophoblastic proliferation, were more closely linked to clinically relevant differences. This suggests that not all histopathological changes should be interpreted in the same way.

From a mechanistic perspective, many of the lesions that were more prevalent in EOPE, particularly villous infarction and cytotrophoblastic proliferation, are consistent with the spectrum of MVM.[18] These findings support the concept of inadequate spiral artery remodeling.[19] and reduced uteroplacental perfusion as central components of early-onset disease.[20] Such placental abnormalities may be consistent with angiogenic imbalance described in previous studies of preeclampsia; unfortunately, angiogenic biomarkers were not assessed in the present study.[21] In contrast, the relative absence of marked placental pathology in many LOPE cases supports the hypothesis that late-onset disease may be influenced to a greater extent by maternal cardiovascular, metabolic, and inflammatory factors rather than severe primary placental dysfunction. Under normal physiological conditions, cytotrophoblastic activity decreases with advancing gestation and so its persistence or reappearance in late gestation suggests ongoing placental stress. The independent association observed in adjusted models further suggests that this feature may represent a more specific marker of placental dysfunction in early-onset disease. In contrast, syncytiotrophoblastic knotting and perivillous fibrin deposition were present in nearly all cases, regardless of disease subtype. While these findings are consistent with placental stress, their lack of discriminatory value between EOPE and LOPE suggests that they reflect a common terminal pathway of placental injury rather than disease-specific mechanisms. This interpretation is supported by previous studies reporting similar lesions in preeclamptic placentas without clear correlation with clinical severity or outcomes. These observations support a model in which different histopathological lesions reflect different levels of biological specificity. Lesions such as infarction and cytotrophoblastic proliferation appear more closely linked to uteroplacental malperfusion and disease severity, whereas syncytial knots and fibrin deposition may represent nonspecific responses to chronic placental stress. Several studies have demonstrated that MVM-related lesions are not exclusive to EOPE and may also be frequently observed in late-onset disease, although often with a lower overall burden. This overlap suggests that placental malperfusion represents a shared pathological mechanism across the preeclampsia spectrum rather than a feature restricted to a single clinical phenotype. Previous reports using the Amsterdam Placental Workshop Group criteria have similarly shown that LOPE placentas may exhibit infarction, distal villous hypoplasia, and other MVM features, particularly in cases with more severe clinical presentation or fetal growth restriction.[22] These findings support a continuum model of placental involvement, in which EOPE and LOPE differ primarily in severity and extent of MVM rather than in completely distinct pathological mechanisms.

Study Limitations

There are several limitations to consider. First, the sample size was relatively modest, which may have limited statistical power to detect differences in less common placental lesions and increased the possibility of type II error. Second, the substantial difference in gestational age between EOPE and LOPE represents an important potential confounder, as some placental histopathological features vary physiologically throughout gestation. Therefore, part of the observed differences may reflect gestational age-related rather than disease-specific effects. In addition, the relatively low number of events for some variables, particularly cytotrophoblastic proliferation, may have affected the stability of the multivariable logistic regression model.

The wide confidence intervals observed for several regression estimates indicate limited statistical precision and support cautious interpretation of the multivariable findings. Therefore, the multivariable findings should be interpreted as exploratory and hypothesis-generating rather than confirmatory. Larger studies are needed to validate these associations. Third, all histopathological evaluations were performed by a single histopathologist, preventing assessment of interobserver reproducibility but strengthening observer consistency. Finally, molecular markers of placental dysfunction and angiogenic imbalance were not available for correlation with histopathological findings. Doppler velocimetry data were not available in this cohort, which represents a limitation of the study. The absence of Doppler velocimetry data limits the ability to distinguish placental insufficiency-related growth restriction from constitutionally small fetuses. In addition, multiple statistical comparisons were performed across clinical and histopathological variables. However, because no formal adjustment for multiple testing was applied, the statistically significant findings should be interpreted cautiously and considered exploratory and hypothesis-generating.

Although the study cohort was collected between 2014 and 2015, the principal outcomes relate to placental histopathology, which is unlikely to be materially affected by subsequent changes in clinical management. Moreover, the diagnostic criteria used for preeclampsia remain largely comparable to those currently applied. Nevertheless, evolving obstetric practices may influence the contemporary clinical profile of affected patients and should be considered when interpreting the results.

Despite these limitations, our findings contribute to the understanding of the heterogeneity of preeclampsia by demonstrating that not all placental lesions carry equal biological or clinical significance. While some changes reflect generalized placental stress, others appear more closely linked to disease severity and phenotype. In the present study,

villous infarction was more common in EOPE in univariate analyses, whereas cytotrophoblastic proliferation remained independently associated with disease phenotype in the exploratory multivariable model. These findings suggest that different placental lesions may vary in their ability to distinguish between preeclampsia subtypes.[23]

CONCLUSION

Our findings indicated that certain histopathological features, especially villous infarction and cytotrophoblastic proliferation, were more prominent in EOPE and may contribute to understanding phenotypic differences between EOPE and LOPE. Other features, although common, appear to reflect general placental stress rather than subtype-specific differences.

These findings suggest that EOPE and LOPE may differ in the degree and pattern of placental involvement while sharing several underlying pathophysiological mechanisms. A more systematic evaluation of placental findings may contribute to a better understanding of disease heterogeneity and placental involvement in preeclampsia. Further studies are needed to determine the potential clinical utility of histological examination of delivered placentas in preeclapmtic women.

Ethics

Ethics Committee Approval: This study was approved by the University of Health Sciences Turkey, Kanuni Sultan Süleyman Training and Research Hospital Clinical Research Ethics Committee (approval no: 3, date: 26.09.2014).

Informed Consent: All participants provided written informed consent prior to enrollment.

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Footnotes

Authorship Contributions

Surgical and Medical Practices: Z.G.Ö., B.Ö., Concept: Z.G.Ö., A.A.A., Design: Z.G.Ö., B.Ö., A.A.A., N.G., Data Collection or Processing: Z.G.Ö., B.Ö., Analysis or Interpretation: Z.G.Ö., B.Ö., Literature Search: Z.G.Ö., B.Ö., Writing: Z.G.Ö.

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