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CAN PLACENTAL HISTOPATHOLOGICAL LESIONS BE A GUIDE TO MATERNAL AND NEONATAL OUTCOMES IN PATIENTS WITH PREECLAMPSIA?

PREEKLAMPSİLİ HASTALARDA PLASENTAL HİSTOPATOLOJİK LEZYONLAR MATERNAL VE NEONATAL SONUÇLAR İÇİN BİR REHBER OLABİLİR Mİ?

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ABSTRACT

Objective: The aim of this study was to investigate the predictive role of massive perivillous fibrinoid deposition (MPFD), syncytial knots, and accompanying histopathological features of placentas of preeclampsia (PE) on maternal and neonatal outcomes.

Matherials and Methods: A retrospective clinicopathological study was conducted in a tertiary unit. In the study, 51 pregnant women admitted with PE and 55 normotensive healthy pregnant women matched for age and gestational age were compared. Information regarding clinical characteristics, neonatal findings, and placental properties such as syncytial knots, vascular structure density, placental area, volume, and weight) was retrieved.

Results: Massive perivillous fibrinoid deposition, syncytial knots and decreased vessels in terminal villi were significantly frequent in the PE group compared to the controls. However, these histopathological findings were not associated with clinical and neonatal outcomes.

Conclusions: Syncytial knot and perivillous fibrin deposition are significant microscopic findings of preeclampsia. However, the presence and amount of fibrin deposition were not correlated with perinatal outcome.

Keywords: Preeclampsia, massive perivillous fibrinoid deposition, syncytial knots, neonatal outcomes, obstetric complications

ÖZET

Amaç: Bu çalışma preeklampsi (PE) plasentalarında perivillöz fibrinoid birikimini (PFB), sinsityal düğümleri ve eşlik eden histopatolojik özelliklerin klinik etkisini araştırmayı amaçladı.

Gereç ve Yöntem: Retrospektif bir klinikopatolojik çalışma olarak üçüncü basamak hastanede yürütüldü. Çalışmaya obstetri kliniğinde PE tanısı konmuş olan 51 gebe ile yaş ve gestasyonel süre açısından eşleştirilmiş 55 normotansif sağlıklı gebe dahil edildi. Klinik özellikler ve gebeliğe ait veriler (maternal-gestasyonel yaş, gravida, parite, intrauterin büyüme geriliği, oligohidramniyoz & anhidramniyoz durumu, koryoamniyonit varlığı, umblikal arter doppler pulsatilite indeksinde artış, preterm doğum, yenidoğanın 1. ve 5. dakika apgar skorları, doğum ağırlığı, hemogram parametreleri, umblikal kord kan gazı (umblikal arter) pH, baz açığı ve kalsiyum düzeyleri) karşılaştırıldı. Ayrıca, sinsityal düğümler, vasküler yapılanma yoğunluğu, plasental alan, volüm ve ağırlık gibi plasental veriler de hesaplandı.

Bulgular: Perivillöz fibrinoid birikimi ve sinsityal düğümler, PE grubunda kontrollere kıyasla anlamlı derecede sık ve yoğundu. Terminal villuslarda azalmış damarlar, artmış sinsityal düğüm ve artmış perivillöz fibrin birikimi PE ile ilişkilidir. Parametrelerin klinik ve neonatal etkileri araştırıldığında, sadece umblikal kord kan gazı analizinde kalsiyum seviyelerinde gruplar arasında anlamlı fark elde edildi (p=0.008).

Sonuç: Sinsityal düğüm ve perivillöz fibrin birikimi preeklampsinin önemli mikroskobik bulgularıdır. Fibrin birikiminin varlığı ve miktarı, fetal ağırlık ve plasentanın makroskopik özellikleri (plasenta ağırlığı, alanı ve hacmi) ile ilişkili değildi. Bu bulguların klinik önemi henüz bulunamamıştır.

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Anahtar Kelimeler: Preeklampsi, masif perivillöz fibrinoid birikimi, sinsityal düğümler, neonatal sonuçlar, obstetrik komplikasyonlar

INTRODUCTION

Preeclampsia (PE) is characterized by hypertension and at least one end-organ dysfunction and is one of the leading causes of maternal mortality (1, 2). It is accepted as a multisystem disease and affects 2-8% of all pregnancies (3). It is suggested that abnormal placentation, deteriorated utero-placental perfusion, and damaged placental tissue along with systemic maternal endothelial dysfunction play a major role in the development of PE. However, the exact pathophysiology and the ultimate primary factors are still unknown (4). In early pregnancy physiology, spiral arteries transform from thick-walled muscular vessels into sac-like loose vessels due to the invasion of cytotrophoblasts (3, 5). The failure of this vascular remodeling is considered as the morphological basis of impaired placental perfusion in preeclampsia (6).

Histopathological examination of the placenta, which forms the direct connection between the fetus and mother, is considered as a valuable tool to define the extent of impaired placentation. This evaluation can also provide differential diagnosis of acute and chronic events. The definitive treatment of preeclampsia is the removal of placenta, therefore it is hypothesized that this syndrome is driven by soluble factors secreted from placenta. Without defining these mediators, delivery will continue to be the only treatment of PE (3). Distal villous hypoplasia, placental infarctions, small placenta by weight, fibrinoid necrosis, and maternal vascular malperfusion (MVM) are the main histopathological findings of the placenta that can be observed in pre-eclampsia (7, 8).

Maternal floor infarction (MFI), the rough orange peel-like appearance of the fibrinoid layer along the maternal surface of the placenta, was first described by Benirschke and Driscoll in 1967 (9). In massive perivillous fibrinoid deposition (MPFD), fibrin deposition is more prominent and intense (10). However, the differences between MFI and MPFD is considered as negligible and usually these two terms are used synonymously. The terminology, especially for MFI which does not contain true infarct lesions, is misleading (10). MPFD leads to the obliteration of the intervillous space and the secondary villous atrophy through the accumulation of fibrinoid deposits at chorionic villi. MPFD can be associated with anticipated complications of preeclampsia like preterm birth, intrauterine growth restriction (IUGR), and neurological sequelae, (11). Additionally in these patients, several changes in the terminal villus capillaries, increased amounts of syncytial bridges and knots, and thicker trophoblast basement membranes are observed in histopathological examination of the placentas (12). In PE, Tenney and Parker first documented and defined increased syncytial knots and villus clusters as "Tenney Parker Changes" (13).

The clinic importance of histopathological abnormalities in PE is debated (7). The literature on which combinations and in what extent these alterations are more important in the means of maternal and neonatal outcomes is scarce. In this study, we aimed to investigate the combination and extent of MPFD and other accompanying histopathological placental findings of PE with respect to obstetric outcomes and to compare these results with uncomplicated controls.

MATERIAL AND METHODS

This is a retrospective clinicopathological study conducted at a tertiary referral hospital over the period January 2018–July 2019. Before initiating the study, approval was obtained from the Faculty Ethical Committee (Date: 5.11.2019, No:19). In the study 51 pregnant women admitted with PD and 55 normotensive uncomplicated pregnant women matched in age and gestational age were compared. Multifetal gestations, pregnancies with major fetal congenital abnormalities, and patients with preexisting chronic diseases such as cardiovascular disease, chronic hypertension, and diabetes were excluded from the study.

Diagnosis of preeclampsia was based on the recommendations of the American College of Obstetricians and Gynecologist Task Force on Hypertension in Pregnancy as being new onset hypertension after twenty weeks of gestation with involvement of at least one end-organ (3). Consequently, patients with systolic blood pressure (SBP) of at least 140 mmHg or diastolic blood pressure (DBP) of at least 100 mmHg measured on more than one occasion at least 4 hours apart while the patient is on bed rest and having at least one end organ sign of damage were labeled PE (3).

Patient information was obtained from the hospital registration system. Sociodemographic, clinical, laboratory and histopathological data of all the patients were collected. Clinical features, maternal and gestational age, gravida, parity, presence of intrauterine growth restriction, presence of oligohydramnios, presence of chorioamnionitis, umbilical artery Doppler pulsatility index, 1st and 5th. minute Apgar scores, birth weight, hemogram parameters, umbilical cord blood pH, base deficit and

calcium levels were retrieved. In addition, placental properties such as syncytial knots, vascular structuring density, placental area, volume, and weight were also noted.

Hematoxylin-eosin (H-E) slides of placentas were re-examined under a Nikon eclipse e200 microscope by two pathologists who were blinded to the clinical status of the patients. During this evaluation, perivillous fibrinoid deposition, density of the vessels and syncytial knot of the placenta were noted. Pathological and clinical findings were then correlated. According to Katzman (16), perivillous fibrin storage can be divided into three categories: MPFD I; 0-25% of villi are surrounded by fibrin deposits, MPFD II; 25-50% of villi containing fibrin and MPFD III; more than 50% villi are encased by fibrin deposits on at least one slide. The initial macroscopic evaluation results were retrieved (Figure 1). Subsequently, microscopic re-examination was conducted for defining and grading perivillous fibrin deposition (Figure 2), increase in syncytial knot amount (Figure 3) and vascular structures (Figure 4).

Figure 1: The macroscopic examination of the placental vasculature

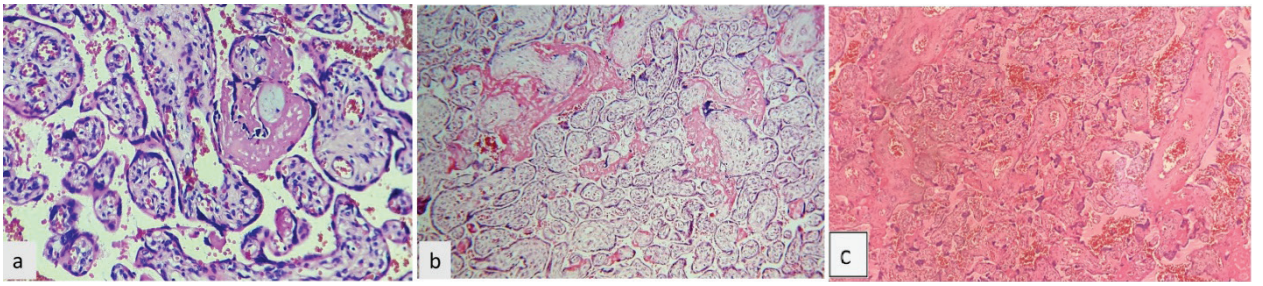

Figure 2: Perivillous fibrin deposition: a. slight increase around villi (H-E, x200), b. moderate increase (H-E, x100), c. severe increase (H-E, x100)

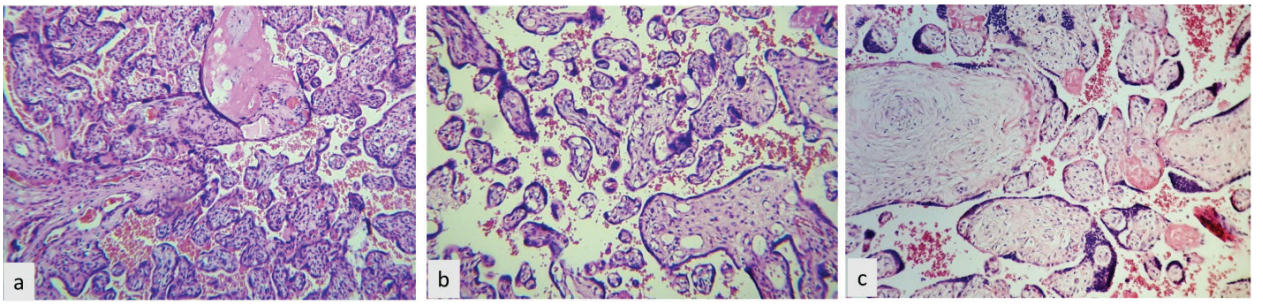

Figure 3: Syncytial knot increase: a. slight increase (H-E, x100), b. moderate increase (H-E, x100), c. severe increase (H-E, x200)

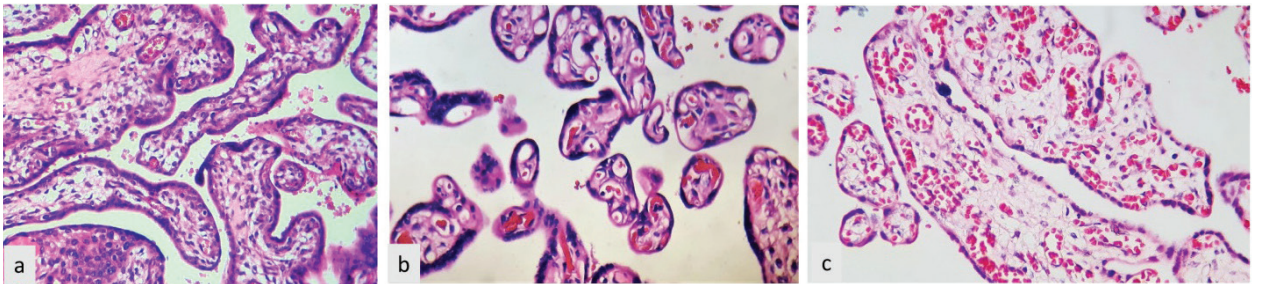

Figure 4: Vascular structures of the placental villi complex a. slight increase (H-E, x200) b. moderate increase (H-E, x400) c. severe increase (H-E, x400)

Statistical analysis

The IBM SPSS Statistics (Version 21.0, SPSS Inc.) program was used for the statistical analyses. When the study data were evaluated, the relationships between descriptive statistical methods mean±standard deviation (SD) were used. The Kolmogorov-Smirnov test was performed for whole data for distribution of compliance before the assessment. When comparing the groups, the Student T test was used for parameters showing normal distribution. The Kruskal-Wallis test and Mann Whitney U test were used for data that did not have normal distribution. A *p*-value <0.05 was considered statistically significant.

RESULTS

A total of 106 patients (51 placentas of patients with PE and 55 placentas as control) were analyzed. The clinicopathological features and neonatal outcomes are compared for the PE and control groups in Table 1. Microscopic examination of the placenta revealed that fibrin deposit (p=0.006) and syncytial knots (p=0.000) accumulation were higher in the PE group, while the number of vessels (p=0.026) was lower. While placental volume was found to be similar between the groups, placental area, placental weight, and fetal weight were significantly higher in the control group (p values: 0.602, 0.027, 0.002, and 0.039, respectively). First and 5th minutes Apgar scores were similar. However, umbilical-cord blood gas pH, base deficit and calcium levels, which are more objective parameters of fetal well-being, were statistically significantly lower in the preeclampsia group.

Patients with PE (n=51) and controls (n=55) were divided into 3 groups (MPFD I; 33, MPFD II; 44, and MPFD III; 29)

Table 1: Comparison of clinicopathological features and neonatal outcomes of the patients with preeclampsia and control group

	Preeclampsia (n=51) Mean±SD (Median)	Control (n=55) Mean±SD (Median)	p value
Age (years)	31.00±7.36	30.22±6.42	0.523
Gravida	2.37±1.29 (2)	2.79±1.54 (3)	0.138
Parity	1.00±1.03 (1)	1.73±1.03 (2)	**0.002***
IUGR (n) [%]	7 [13.7%]	11 [20.0%]	0.395
Oligo/anhydramnios (n) [%]	8 [15.6%]	22 [40.0%]	**0.005***
MPFD (n) [%]			
I	10 [19.6%]	23 [41.8%]	**0.006*Ψ**
II	22 [43.1%]	22 [40.0%]	
III	19 [37.2%]	10 [18.1%]	
Syncytial knots	18.90±9.37	12.09±6.78	**0.000***
The number of vascular structures	33.57±8.10	36.89±7.03	**0.026***
Placental volume (cm^3)	421.43±300.95	448.48±214.64	0.602
Placental area (cm^2)	203.31±101.87	221.24±65.21	**0.027***
Placental weight (gr)	349.04±157.86	461.20±192.58	**0.002***
Fetal weight (gr)	2001.20±978.32	2367.80±1001.70	**0.039***
Fetal weight/ placental weight ratio	5.90±2.93	5.58±3.12	0.614
Apgar 1	6.36±1.73	6.83±2.05	0.232
Apgar 5	8.02±1.46	8.13±1.80	0.742
Umbilical-cord blood gas pH	7.27±0.92	7.32±0.12	**<0.001***
Umbilical-cord blood gas base deficit	-6.25±4.15	-4.44±4.69	**0.003***
Umbilical-cord blood gas calcium level (mmol/L)	1.21±0.19	1.28±0.12	**0.031***
Maternal calcium level (mg/dL)	8.58±0.64	8.86±0.64	**0.033***
Maternal PLR	131.98±67.52	136.17±50.28	0.717

*: p<0.05 statistically significant, MPFD: Massive perivillous fibrinoid deposition, IUGR: Intrauterine growth restriction, PLR: Platelet lymphocyte ratio, ΨKruskal-Wallis test was used for comparison

according to the severity of perivillous fibrin deposition. Maternal sociodemographic and pregnancy characteristics with respect to MPFD are presented in Table 2. The three groups were comparable in terms of the means of these characteristics. It was found that the density of MPFD were positively correlated with preeclampsia (p=0.021).

The placental morphological and microscopic data are compared with MPFD in Table 3. There is an inverse relation between the number of syncytial knots and the vessels evaluated by microscopy. The density of syncytial knots was positively correlated with the grade of fibrin deposits (MPFD I; 9.70±6.02, MPFD II; 15.30±6.77, MPFD III; 21.93±9.75, p=0.000). In contrast, the number of veins decreased significantly (MPFD I; 40.61±5.87, MPFD II; 34.82±6.74, MPFD III; 29.97±7.13, p=0.000). Morphometric measurements of the placenta, such as area, volume, and weight, and also the ratio of fetal weight to placental weight, were comparable within MPFD graded groups.

The relation between MPFD and maternal serum and umbilical-cord blood gas analysis is shown in Table 4. There was no significant difference between the groups

Table 2: Maternal sociodemographic and clinicopathological characteristics according to MPFD grade

	MPFD I (n=33) Mean±SD (Median)	MPFD II (n=44) Mean±SD (Median)	MPFD III (n=29) Mean±SD (Median)	p value
Maternal age (years)	29.61±6.49	31.30±7.30	30.66±6.71	0.599
Gestational week at delivery	32.42±4.81	33.36±4.90	34.45±4.02	0.336
Gravida	2.91±1.55 (3)	2.43±1.40 (2)	2.46±1.34 (2)	0.343
Parity	1.68±1.21 (1)	1.40±1.00 (1)	0.92±0.97 (1)	0.053
IUGR (n)	3	9	6	0.350
Preeclampsia/control (n) [%]	10/23 [30.3%]	22/22 [50.0%]	19/10 [65.5%]	**0.021***
Oligo & anhydramnios (n)	10 [30.3%]	11 [25.0%]	9 [31.0%]	0.817
Chorioamnionitis (n)	3 [9.0%]	0 [0.0%]	1 [3.4%]	0.119
Placenta previa (n)	3 [9.0%]	5 [11.3%]	1 [3.4%]	0.492
Abruptio (n)	2 [6.0%]	0 [0.0%]	0 [0.0%]	0.107
Increased UAD PI (n)	1 [3.0%]	3 [6.8%]	1 [3.4%]	0.691
Preterm delivery (n)	24 [72.7%]	27 [61.3%]	20 [68.9%]	0.560
Apgar 1	5.96±2.35	6.63±1.88	7.07±1.28	0.164
Apgar 5	7.50±1.86	8.15±1.57	8.48±1.37	0.064

*: p<0.05 statistically significant, MPFD: massive perivillous fibrinoid deposition, UAD: The fetal umbilical artery Doppler, PI: pulsatility index

Table 3: Comparison of MPFD grade with other placental pathological findings

	MPFD I (n=33) Mean±SD	MPFD II (n=44) Mean±SD	MPFD III (n=29) Mean±SD	p value
Syncytial knots	9.70±6.02	15.30±6.77	21.93±9.75	**<0.001***
The number of vascular structures	40.61±5.87	34.82±6.74	29.97±7.13	**<0.001***
Placental volume (cm^3)	398.97±219.83	451.69±258.29	449.10±306.78	0.682
Placental area (cm^2)	203.75±74.03	209.89±71.46	225.38±114.41	0.916
Placental weight (gr)	404.59±186.58	400.03±195.59	398.52±165.15	0.955
Fetal weight (gr)	2137.07±1098.64	2143.10±1015.58	2291.90±903.77	0.818
Fetal weight/ placental weight ratio	6.04±4.16	5.24±1.22	6.20±3.40	0.617

*: p<0.05 statistically significant, MPFD: massive perivillous fibrinoid deposition

Table 4: Relation of MPFD grade with maternal and fetal blood parameters

	MPFD I (n=33) Mean±SD	MPFD II (n=44) Mean±SD	MPFD III (n=29) Mean±SD	p value
Umbilical-cord blood gas pH	7.29±0.16	7.31±0.74	7.28±0.07	0.117
Umbilical-cord blood gas base deficit	-5.97±6.53	-4.67±3.23	-5.57±3.38	0.411
Umbilical-cord blood gas calcium level (mmol/L)	1.31±0.14	1.20±0.19	1.25±0.11	**0.008***
Maternal calcium level (mg/dL)	8.85±0.50	8.68±0.76	8.66±0.62	0.375
RBC (M/uL)	3.93±0.45	4.17±0.54	4.39±0.60	**0.004***
MCV (fL)	85.63±7.33	86.67±6.16	86.52±10.09	0.580
MCH (pg)	28.49±3.00	28.95±2.43	28.72±4.00	0.622
RDW_SD (fL)	44.18±4.57	42.30±5.98	44.67±4.66	0.072
MPV (fL)	12.97±17.81	10.65±1.26	10.03±1.42	**0.037***
PDW (%)	16.10±0.61	16.41±0.37	16.20±0.52	**0.031***
Platelet (K/uL)	235.75±55.66	212.09±65.48	223.44±72.03	0.244
Lymphocyte (K/uL)	1.68±0.76	1.83±0.50	2.07±0.71	0.057
PLR	164.03±71.24	123.64±48.11	116.12±46.03	**0.004***

*: p<0.05 statistically significant, MPFD: Massive perivillous fibrinoid deposition, RBC: Red blood cell, MCV: Mean cell volume, MCH: Mean cell hemoglobin, RDW_SD: Red blood cell distribution width, MPV: Mean platelet volume, PDW: Platelet distribution width, PLR: Platelet lymphocyte ratio

for umbilical-cord blood gas pH and base deficit values. When the hemogram parameters were examined, red blood cell (RBC) (p=0.004), mean platelet volume (MPV) (p=0.037), platelet distribution width (PDW) (p=0.031) and platelet lymphocyte ratio (PLR) (p=0.004) was found to differ between MPFD groups (Table 4).

DISCUSSION

In this study, we found that MPFD and syncytial knots were more frequent and denser in the PE group compared to the controls. However, the MPFD groups were not associated with umbilical-cord blood gas pH or base deficit. Apgar scores were also similar in the three MPFD groups. Only umbilical-cord blood gas calcium levels were found to be associated with MPFD grades.

In preeclampsia, abnormal placentation and impaired uteroplacental blood flow play a major role in both pathophysiology and maternal-neonatal outcomes. Since definitive treatment cannot be established unless the placenta is removed, delivery still holds as the cure of PE (3).

Observation of gross alterations within the placenta can guide the physician during the diagnosis of obstetric complications. The placenta is a unique organ which can reflect a lot of important information about the fetal well-being. Detailed examination of the placenta may provide many feto-maternal clues such as the traces of a diary held close to birth. Therefore, defining macroscopic and microscopic placental abnormalities of specific disorders would eventually aid clinicians not only to uncover the pathogenesis, but also to develop prognostic markers for perinatal and obstetric outcomes (7). Placental histopathological examination should be considered especially in the presence of abnormal conditions related to the fetal birth weight, gestational week, and delivery. During the evaluation, placental maturity and weight, umbilical cord evaluation (insertional anomalies, inflammation, single umbilical artery, congenital remnants), meconium staining, cystic abnormalities, thrombosis, chorioamnionitis, villitis, chorangiosis, excessive fibrin deposition, syncytial knotting, calcification, langhans cells and hofbauer cells, vascular abnormalities, and choriocarcinoma should be noted when identified.

The placenta has an average weight of 508 g and is 185 mm in length, 497 ml in volume and 23 mm in thickness at term in normal conditions (13). Our placental data was composed of patients with earlier gestational ages as a result of the high preterm birth rates related to PE. Placental volume parameters (weight, area, volume) were lower in the PE group compared to the gestational age matched normotensive control group. The ratio between placenta weight and newborn weight has been reported as 1:6 in previous studies in accordance with our study (14). We found that fetal weight, an indicator of poor placental nutrition, was statistically significantly lower in the PE group. In addition, the placenta/fetal weight ratio was lower, but no statistical difference was found between groups.

The mean age of the PE group and the patients with increased fibrin deposits was higher, although not statistically significant. Advanced maternal age is a known risk factor for PE, as confirmed with previous published articles (15). The histological changes in preeclamptic/ eclamptic placentas include infarcts, increased syncytial knots, hypovascularity of the villi, cytotrophoblastic proliferation, thickening of the trophoblastic membrane, obliterative enlarged endothelial cells in the fetal capillaries, and atherosis of the spiral arteries in the placental bed (7). In our study group, we observed that with the increase of the amount of fibrin deposits, PE frequency increased in the groups. However, fibrin deposition did not change, even according to preterm labor, IUGR, oligo/anhidramnios and placental pathologies such as chorioamnionitis, placenta previa and abruptio. Perivillous fibrin deposition is associated with high perinatal morbidity/ mortality and may recur in subsequent pregnancies. Its etiopathogenesis and clinical important has not been elucidated yet (7). According to our results, syncytial knot and perivillous fibrin deposition are notable microscopic findings of preeclampsia. The presence and amount of fibrin deposition did not correlate with fetal weight and the macroscopic features (placental weight, area, and volume) of the placenta. However, they were downwardly affected in preeclampsia patients. We did not observe a significant difference in apgar scores in both PE group and the patients with increased MPFD as Sirenden et al. reported (16). We also found that umbilical-cord blood gas pH values were lower, and the base deficit was higher in the preeclampsia group as Sheikh et al. found (17). There was no remarkable difference in umbilical-cord blood gas pH and base deficit according to the degree of MPFD. The lower mean blood gas pH values in the preeclampsia group compared to the control group may be a result of the cumulative effect of the triad of decrease in the number of villi, increase in syncytial knots and MPFD.

Syncytial knot formation has been found to increase in complicated pregnancies (18). Tenney Parker Changes are used in the evaluation of placental well-being and the increase in syncytial knot formation is considered as a step in the pathophysiology of PE (18, 19). It has been shown that branching of the villous tree increases due to hypoxia in complicated pregnancies such as PE (20). Due to an effect which induces hypoxia and uteroplacental malperfusion like PE, syncytiotrophoblast functions are impaired, Tenney-Parker changes are formed and finally syncytial nucleis accumulate (12, 18, 19). Previous studies indicate that this pathological formation, with its microscopic appearance as syncytial knots or bridging, is one of the strongest findings of PE (18, 19). Consistent with this, our study revealed a significant increase in syncytial knot formation.

Villus formation continues throughout pregnancy and thinner villis occur in the formations in the last trimester (21, 22). Zigic et al. reported that there were adverse effects of advanced maternal age on the uteroplacental vascular bed by inducing the decrease in the number of vessels in the terminal villi (21). We showed that the number of vessels in terminal villi was lower in the preeclampsia group, which was consistent with the findings of Sankar et al. (22). In addition we found that as the degree of MPFD increases, the capillary vessels in the terminal villi decrease. To our knowledge, there is no investigation on this topic in the literature.

In the current study, lower calcium level in umbilical-cord blood gas analysis as well as lower maternal serum calcium levels were found in the PE group compared with the control group. It is a known fact that calcium plays a crucial role in the fetal-placental-preeclampsia axis (23, 24). Based on previous studies, patients with PE have low calcium levels and the benefits of prophylactic calcium replacement has been suggested (23, 24). Sende et al. similarly found that plasma calcium levels in PE group were significantly lower than in normotensive group (24). Haller et al. showed that the basal intracellular free Ca^{+2} level in platelets was higher in the PE group compared to the control group (25). As an important finding, they also clarified that this was a temporary state which lasts for 6 weeks after birth. In addition, this increase was observed not only in platelets but also in lymphocytes and erythrocytes (25, 26).

Falco et al. conducted a systematic review and meta-analysis investigating the prevalence of placental histopathological lesions in pregnancies complicated by PE. A total of eight studies were included in the analysis. In unblinded studies, the pooled prevalence of villous lesions was 11.6% and 48.2% in normal and PE pregnancies respectively, and the pooled prevalence of vascular lesions was 8.1% and 37.3% in normal and pre-eclamptic pregnancies respectively. In blinded studies, the pooled prevalence of villous lesions was 18.5% and 42.0% in normal and PE pregnancies respectively, and the pooled prevalence of vascular lesions was 9.8% and 38.9%, in normal and pre-eclamptic pregnancies respectively. The authors reported that the incidence of both placental villous and vascular histopathological lesions is four- to seven-fold higher in PE however they also emphasized that placental lesions are not specific to the diagnosis of PE (7).

The major limitation of the current study is the relatively small number of patients and its retrospective design. However, to the best of our knowledge, this is the first study that compared perivillous fibrin deposition rates with hemogram parameters showing that both are related with PE. We need further investigations.

In conclusion, there is still a lack of data regarding the importance of microscopic examination of the placenta in PE patients. Even macroscopic examination of the

placenta in the delivery room would provide important information. Decreased vessels in terminal villi, increased syncytial knot and increased perivillous fibrin deposit is associated with PE. However, these findings are not associated with adverse perinatal outcomes. More studies are needed to define if any of these alterations are related with different etiologies of PE and if they are associated with any other long-term outcome results.

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