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Pregnancy outcomes in correlation with placental histopathology in subsequent pregnancies complicated by preeclampsia

Michal Levy[a,*], Michal Kovo[a], Letizia Schreiber[b], Ilia Kleiner[a], Liron Koren[a], Giulia Barda[a], Eldar Volpert[a], Jacob Bar[a], Eran Weiner[a]

[a] Departments of Obstetrics & Gynecology, The Edith Wolfson Medical Center, Holon, Israel, Affiliated with Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel
[b] Department of Pathology, Affiliated with Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel

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ABSTRACT

Objective: In attempt to deepen our understanding of the etiopathogenesis of preeclampsia we aimed to study the placental component and pregnancy outcomes in two consecutive pregnancies complicated by preeclampsia in the same patient.

Study design: Pregnancy and placental reports of all pregnancies complicated by preeclampsia between 2008 and 2018 were reviewed. Included were only cases with recurrent preeclampsia in two consecutive pregnancies Neonatal outcomes and placental histopathology were compared between the first preeclampsia delivery (first preeclampsia group) and the subsequent preeclampsia delivery (subsequent preeclampsia group), thus each subject served as her own control in two consecutive pregnancies. Placental lesions were classified according to the current "Amsterdam" criteria. Adverse neonatal outcome was defined as ≥1 early neonatal complication.

Results: Included in the study a total of 83 cases with recurrent preeclampsia. The first preeclampsia group delivered at an earlier gestational age (35.7 ± 3.7 vs. 36.8 ± 3.1 weeks, p = 0.03) and had higher rates of severe features (44.6% vs. 25.3%, p = 0.03), placental weight < 10th percentile (44.5% vs. 26.5%, p = 0.02), maternal vascular malperfusion (MVM) lesions (84.3% vs. 62.6%, p = 0.002), SGA (44.5% vs. 33.7%, p = 0.03), and adverse neonatal outcome (55.4% vs. 34.9%,p = 0.01), compared to the subsequent preeclampsia group. Using multivariate logistic regression analysis, severe features (aOR = 1.36, 95%CI = 1.12–2.36), MVM lesions (aOR = 1.12, 95%CI = 1.04–1.87) and adverse neonatal outcome (aOR = 1.26 95%CI = 1.14–2.23) were found to be independently associated with the first preeclampsia group.

Conclusion: The first event of preeclampsia is characterized by an earlier, more severe presentation, as well as a higher rate of MVM lesions, SGA, and adverse neonatal outcome, compared to preeclampsia in a subsequent pregnancy.

1. Introduction

Preeclampsia is one of the leading causes of maternal and neonatal morbidity and mortality in the western world, complicating 5–10% of all pregnancies [1,2]. The main impact on the fetus is the result of uteroplacental vascular insufficiency, which may lead to fetal growth restriction (FGR) with its comorbidities, as well as morbidities associated with iatrogenic prematurity [3,4].

In recent years, significant advances have occurred in our understanding of the pathophysiology and mechanisms of hypertensive disorders of pregnancy, particularly preeclampsia [5,6].

Impaired early placentation and dysfunctional trophoblast development leading to defective placental angiogenesis has been one of the primary mechanisms suggested [7,8]. Defective placentation resulting in maternal vascular malperfusion (MVM) and fetal vascular malperfusion (FVM) lesions is more profound as the clinical course of the disease is more severe [9,10]. We recently published that MVM and FVM lesions are independently associated with increased risk for recurrence of preeclampsia [11].

Preeclampsia is more prevalent in the first pregnancy than in subsequent pregnancies. However, the protective effect of multiparity is lost with the change of partner [12] and also when the time interval between births is long [13]. Even though preeclampsia is more prevalent among nulliparous, it is also accepted that pregnant women with

* Corresponding author at: Division of Maternal Fetal Medicine, Department of Obstetrics and Gynecology, The Edith Wolfson Medical Center, P.O. Box 5, Holon 58100, Israel.
E-mail address: levmichal@gmail.com (M. Levy).

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a history of preeclampsia are at increased risk for recurrence, with a recurrence rate that varies between 6.8% and 65% [14–17].

According to some investigators, the rates of severe preeclampsia and early preeclampsia were significantly higher in repeated preeclampsia as compared to nulliparous women with preeclampsia [18,19]. The obviate explanations for this are chronic factors, genetic or environmental, that tend to worsen with time. In contrast, other authors demonstrated that the recurrence of preeclampsia tends to present with a milder course [17,20,21] which can be explained with the "immunological theory," arguing that immunologic intolerance between the mother and the fetus play a significant role in the pathogenesis of preeclampsia. The intolerance tend to ameliorate with the next encounter [12,22,23].

In attempt to shed new light on this issue and deepen our understanding of preeclampsia, we studied the differences in the severity of preeclampsia, placental histopathology, and pregnancy outcomes in subsequent pregnancies complicated by preeclampsia in the same patient. We hypothesized that the first pregnancy will be associated with a more severe course, a higher rate of placental lesion associated with malperfusion, and worse neonatal outcomes.

2. Materials and methods

The medical records of all women who were diagnosed with preeclampsia and delivered at a single university hospital from January 2008 to August 2018 were reviewed. Included in the study: patients with at least two pregnancies diagnosed with preeclampsia, who delivered between 24 and 42 weeks of gestation, and their placentas were sent for histopathological evaluation, according to our departmental protocol. We compared two study groups: One included all the pregnancies when preeclampsia occurs in the first time (first preeclampsia group), and the second one included the recurrent preeclampsia (subsequent preeclampsia group). In this manner each patient served as her own control in two subsequent pregnancies.

Preeclampsia was diagnosed according to American College of Obstetricians and Gynecologists criteria [24] and was defined based on elevated blood pressure and proteinuria. The hypertensive component was based on a systolic blood pressure $\geq$140 mm Hg and/or diastolic blood pressure $\geq$90 mm Hg on two occasions $\geq$6 h apart. Proteinuria was defined as the excretion of $\geq$300 mg of protein in a 24-h urine collection or alternatively a urine dipstick of $\geq +1$. Preeclampsia was defined as having severe features with systolic blood pressure $\geq$160 mm Hg and/or a diastolic blood pressure $\geq$110 mm Hg on two occasions $\geq$6 h apart. In addition, preeclampsia was defined as having severe features if there was either evidence of new development of renal insufficiency, evidence of pulmonary edema, new-onset cerebral or visual disturbance, severe persistent right-upper-quadrant/epigastric pain, thrombocytopenia (< 100,000/microliter), or impaired liver function. Data regarding pregnancy outcome was obtained from our computerized files as well. Approval was obtained from the Local Ethics Committee (# 0102-15-WOMC, 8.6.2015).

2.1. Data collection

The following data were collected from the women's medical and surgical files of each pregnancy: age, gravidity, parity, gestational age at delivery (GA), prepregnancy BMI, pre-gestational DM (PGDM), gestational DM (GDM), Doppler studies, smoking status, thrombophilia (defined as any thrombophilia, inherited or acquired, which necessitated thromboprophylaxis according to the practice bulletins of the American College of Obstetricians and Gynecologists) [25,26], the use of Acetylsalicylic acid (Aspirin) during pregnancy as prevention therapy [27], Low molecular weight Heparin (LMWH) treatment during pregnancy, anti-hypertension therapy during pregnancy, severity of preeclampsia (with or without severe features), magnesium-sulfate therapy during labor, induction of labor and Cesarean delivery rates. Gestational age was confirmed by first-trimester ultrasonography.

Immediately after birth, all neonates were examined by pediatricians. Birth-weight percentile for gestational age was assigned using the updated local growth charts [28]. Small for gestational age (SGA) was defined as actual birthweight $\leq$10th percentile for gestational age. Besides, Apgar scores, cord blood pH, neonatal intensive care unit (NICU) admission, seizures, hypoglycemia, intraventricular hemorrhage (IVH), mechanical ventilation, respiratory distress syndrome (RDS), necrotizing enterocolitis (NEC), phototherapy, sepsis, and blood transfusion were also collected from the neonatal records.

2.2. Placental pathology

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 [29,30] as previously reported by us [11,31]. Briefly, placental weight was determined 24 h after delivery (untrimmed and fixed), and the percentile was determined according to placental weight charts [32]. From each placenta, six tissue samples were embedded in paraffin blocks for microscopic assessment: one role of the free membranes, (chorion and amnion with attached decidua capsularis), one at the cord insertion, one from central tissue that appeared abnormal on gross examination, two from normally appearing central tissue, and one at the margin visible abnormal areas on gross examination.

Lesions of maternal vascular supply as part of MVM lesions included: placental hemorrhages (marginal and *retro*-placental), vascular changes related to maternal malperfusion [acute atherosis and mural hypertrophy (decidual arteriopathy)], and villous changes related to maternal malperfusion (increased syncytial knots, villous agglutination, increased intervillous fibrin deposition, distal villous hypoplasia, and villous infarcts).

Lesions of fetal vascular supply as part of FVM lesions included: findings consistent with fetal thrombo-occlusive disease (FTOD): 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 high power field (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 three 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.

2.3. Statistical analysis

Data were analyzed with Epi Info, version 7.0 (Centers for Disease Control and Prevention, Atlanta, GA). Continuous variables were calculated as mean ± standard deviation (SD) and compared using the Student's *t*-test or the non-parametric Mann-Whitney test as appropriate. Categorical variables were calculated as rate (percentage) and compared with Chi square or Fisher's exact test as appropriate. All tests were two tailed, and the threshold for statistical significance was defined as p-value < 0.05.

Composite MVM lesions was defined as one or more of lesions resulting from loss of integrity of the maternal circulation as placental

marginal, and retroplacental hemorrhages, vascular changes related to MVM as acute atherosis and mural hypertrophy, and villous changes related to MVM as increased syncytial knots, villous agglutination, increased intervillous fibrin deposition, and villous infarcts.

Composite FVM lesions were defined as one or more lesions consistent with FTOD: thrombosis of the chorionic plate and stem villous vessels, hypovascular, fibrotic, and avascular villi.

Composite adverse neonatal outcome was defined as one or more of the following early neonatal complications: cord blood Ph < 7.1, seizures, hypoglycemia, IVH, mechanical ventilation, RDS, NEC, phototherapy, sepsis or blood transfusion.

Multivariate regression analyses were performed to identify independent associations with severe preeclampsia, composite MVM lesions and composite adverse neonatal outcome. Those served (separately) as the dependent variables while the study groups (first vs. subsequent preeclampsia), maternal age, gestational age at delivery, mode of delivery, Aspirin use, and LMWH use served as independent variables.

3. Results

During the study period, 34,825 deliveries occurred, of which preeclampsia was diagnosed in 2437 deliveries (7%). We identified eighty-three cases of repeated preeclampsia which established the study cohort (Fig. 1). The first preeclampsia event constituted the "first preeclampsia group" (n = 83), and the subsequent preeclampsia pregnancy constituted the "subsequent preeclampsia group" (n = 83).

Maternal and pregnancy characteristics of the first and the subsequent preeclampsia groups are presented in Table 1. Preeclampsia with severe features was more prevalent in the first preeclampsia group compared with the subsequent preeclampsia group (44.6% versus 25.3%, p = 0.01, respectively). In addition, the first preeclampsia group was characterized by a lower GA at delivery compared to the subsequent preeclampsia group (35.7 ± 3.7 vs. 36.8 ± 3.1 weeks, p = 0.03). Aspirin treatment during pregnancy, as expected, was significantly more prevalent among the subsequent preeclampsia group (24.0% versus 1.2%, p < 0.001).

Placental characteristics are presented in Table 2. Placental weight < 10th percentile and composite MVM lesions were more common in the first preeclampsia group (44.5% vs. 26.5%, p = 0.02 and 84.3% vs. 62.6%, respectively; p = 0.002). Other placental lesions did not differ between the groups.

Table 3 presents neonatal outcomes of the study groups. The rate of SGA was significantly more prevalent among the first preeclampsia group (44.5% versus 33.7%, p = 0.03). Composite adverse neonatal outcome was found in 55.4% of the neonates in the first preeclampsia group compared to 34.9% of the subsequent preeclampsia group, (p = 0.01).

Using multivariate logistic regression analysis, after adjustment was performed for maternal age, gestational age at delivery, mode of delivery, Aspirin use, and LMWH use, preeclampsia with severe features (aOR = 1.36, 95% CI = 1.12–2.36), composite MVM lesions (aOR = 1.12, 95% CI = 1.04–1.87) and composite adverse neonatal outcome (aOR = 1.26 95% CI = 1.14–2.23) were found to be independently associated with the first preeclampsia group (Table 4).

4. Discussion

This study aims to compare pregnancy outcomes and placental histopathology in cases of first versus subsequent preeclampsia occurrence in the same woman.

Our main findings were: 1) Preeclampsia in the first occurrence tend to present earlier and with a higher rate of severe features compared to the subsequent occurrence. 2) MVM lesions and placental weight < 10th percentile were found to be more prevalent in the first occurrence of preeclampsia as compared to the subsequent occurrence. 3)

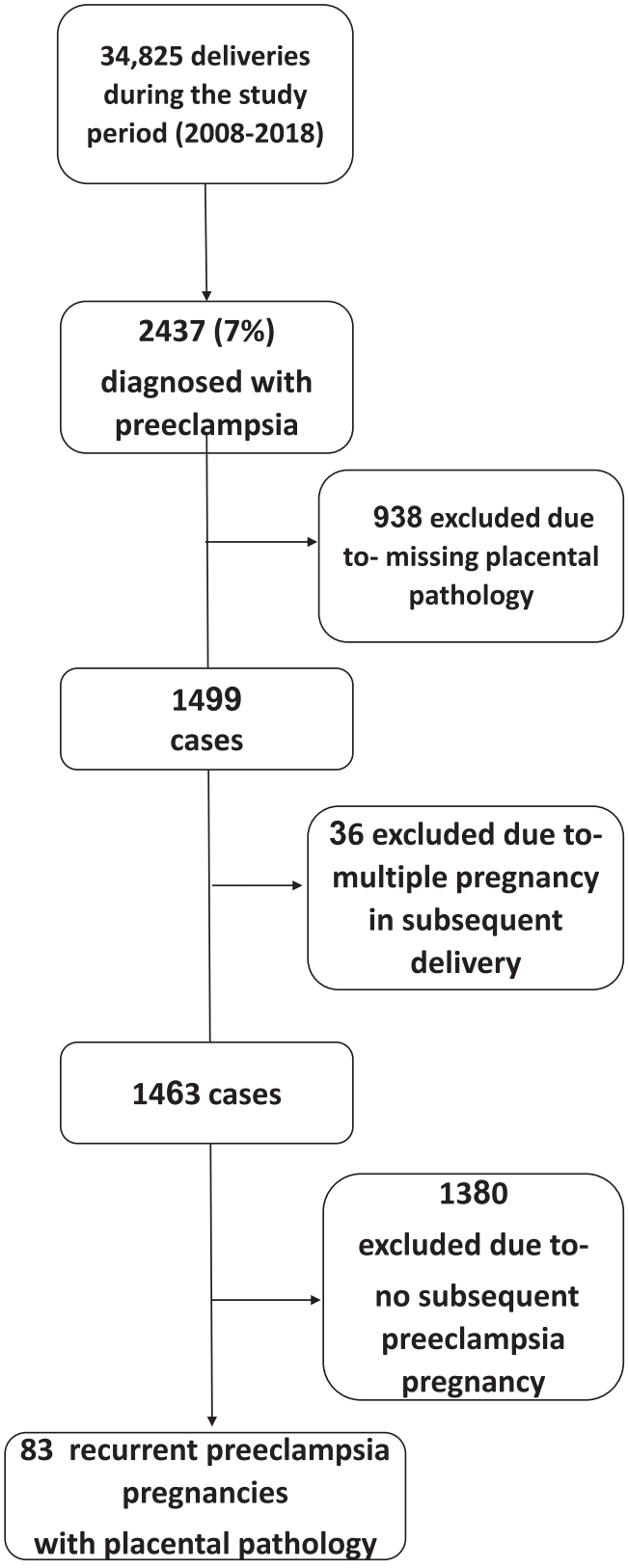

Fig. 1. Study design.

Regarding adverse neonatal outcome – SGA and composite adverse neonatal outcome were found to be significantly more common in the first preeclampsia occurrence. 4) In multivariate analysis, after adjustment for confounders, preeclampsia with severe features, composite MVM lesions and composite adverse neonatal outcome were found

Table 1
Maternal demographics and pregnancy characteristics of the study groups.

	First preeclampsia (n = 83)	Subsequent preeclampsia (n = 83)	*p* value
Maternal age (years)	34.0 ± 5.6	35.5 ± 4.9	0.06
Nulliparity (%)	57 (68.7)	0	< **0.001**
GA at delivery (weeks)	35.7 ± 3.7	36.8 ± 3.1	**0.03**
BMI (kg/m^2)	25.9 ± 10.6	27.6 ± 9.2	0.27
PGDM (%)	1 (1.2)	4 (4.8)	0.36
GDM (%)	19 (22.8)	25 (30.1)	0.37
Any DM (%)	20 (24.0)	29 (34.9)	0.17
Pathological Doppler studies (%)	9 (10.8)	4 (4.8)	0.24
Smoking (%)	9 (10.8)	7 (8.4)	0.79
Thrombophilia (%)	2 (2.4)	5 (6.0)	0.44
Acetylsalicylic acid (Aspirin) (%)	1 (1.2)	20 (24.0)	< **0.001**
Low molecular weight Heparin (%)	3 (3.6)	6 (7.2)	0.49
Anti-hypertensive therapy during pregnancy (%)	5 (6.0)	9 (10.8)	0.40
Preeclampsia mild (%)	46 (55.4)	62 (74.7)	**0.01**
Preeclampsia with severe features (%)	37 (44.6)	21 (25.3)	**0.01**
Magnesium Sulfate during labor (%)	38 (45.7)	24 (28.9)	**0.03**
Induction of labor (%)	63 (75.9)	62 (74.6)	1.00
Cesarean delivery (%)	59 (71.0)	65 (78.3)	0.37

Continuous variables are presented as mean ± SD and categorical variables as n (%). p-values in bold are statistically significant. GA – gestational age, BMI – body mass index, PGDM – pregestational diabetes mellitus GDM – gestational diabetes mellitus, DM – diabetes mellitus.

independently associate with the first preeclampsia occurrence.

According to our findings, the first occurrence of preeclampsia results in characterized by a more severe clinical course and respectively more abnormal placental histopathology and more adverse neonatal outcome compare to the subsequent occurrence. Our findings are in agreement with other studies: Van Rijn et al. published the outcome of subsequent pregnancies in 120 women and found that outcomes of the subsequent pregnancy after first pregnancy with early-onset preeclampsia is generally favourable [21]. Van Oostwaard et al. also concluded that among women that experienced hypertension in pregnancy, the recurrence rate in the next pregnancy is relatively low, and the course of disease is milder for most women with recurrent disease [17]. Seeho et al. studied women with early-onset preeclampsia and found maternal and perinatal outcomes in the subsequent pregnancy are generally better than in the first pregnancy [20]. Importantly, none of the previous studies have correlated these findings with detailed placental histopathology reports and detailed neonatal outcomes.

The more indolent course of recurrent preeclampsia when compared to the first occurrence of the disease can be explained with the "immunological theory". According to that hypothesis, which constitutes one of the pathoetiology proposed for preeclampsia, an analogy might exist between chronic graft rejection and preeclampsia [22,33]. Suggesting that immunologic intolerance between the mother and the fetus may play an important role in the pathogenesis of preeclampsia [23]. When focusing on this theory, naturally the next occurrence of preeclampsia should be less clinically severe attributing this improvement to maternal immune tolerance [34,35].

There are several limitations to note in this study. First, due to its retrospective design, we included only pregnancies whose placentas were initially sent for histopathological examination. Unfortunately, some placentas, mainly during the first years of the study period, were not sent to histopathological examination. This might represent selection bias to the study population. Second, the pathologist was not blinded to clinical information, so an observer bias cannot be excluded. Third, during the subsequent pregnancy 20 patients were treated with low-dose aspirin as preventive therapy that could interfere with placental histopathology [36,37]. Importantly, however, all our main findings were controlled for Aspirin use (among other confounders) in the regression analyses performed.

Several strengths should be denoted in the current study. First, according to our knowledge, this is the first study that compared two consecutive pregnancies complicated with preeclampsia, with correlation to placental histopathology. Second, we had relatively large cohort from a single center over a 10-year period what allowed us to reach

Table 2
Placental histopathological lesions in the study groups.

	First preeclampsia n = 83	Subsequent preeclampsia n = 83	p-value
Placental weight, grams	401.1 ± 146.5	456.3 ± 145.0	**0.01**
Placental weight < 10th percentile (%)	37 (44.5)	22 (26.5)	**0.02**
Maternal vascular malperfusion lesions (MVM)			
Placental hemorrhage	6 (7.2)	3 (3.6)	0.40
Vascular lesions of maternal malperfusion	39 (46.9)	16 (19.2)	< **0.001**
Villous lesions of maternal malperfusion	45 (54.2)	38 (45.7)	0.35
Composite maternal malperfusion lesions	70 (84.3)	52 (62.6)	**0.002**
Fetal vascular malperfusion lesions (FVM)			
Vascular lesions consistent with FTOD	11 (13.2)	7 (8.4)	0.45
Villous lesions consistent with FTOD	3 (3.6)	3 (3.6)	1.00
Composite fetal malperfusion lesions	10 (12.0)	10 (12.0%)	1.00
Inflammatory lesions			
MIR (stage 1–3)	10 (12.0)	8 (9.6)	0.80
FIR (stage 1–3)	2 (2.4)	3 (3.6)	1.00
Chronic villitis of unknown etiology	8 (9.6)	7 (8.4)	1.00

Continuous variables are presented as mean ± SD and categorical variables as n (%). p-values in bold are statistically significant. PE, preeclampsia FTOD; fetal thrombo-occlusive disease; MIR, maternal inflammatory response; FIR, fetal inflammatory response.

Table 3
Neonatal outcomes in the study groups.

	First preeclampsia (n = 83)	Subsequent preeclampsia (n = 83)	*p* value
Birth weight (grams)	2289.7 ± 958.6	2609.1 ± 820.9	0.8
Birth weight percentile	28.4 ± 31.2	36.8 ± 32.4	0.8
Birth weight < 10th percentile (%)	37 (44.5)	28 (33.7)	**0.03**
Birth weight < 5th percentile (%)	23 (27.7)	12 (14.4)	0.06
Umbilical Ph ≤ 7.1 (%)	11 (13.2)	5 (6.0)	0.62
Apgar 5 < 7 (%)	10 (12.0)	5 (6.0)	0.27
NICU (%)	36 (43.3)	32 (38.5)	0.63
Seizures (%)	0	0	1.00
Hypoglycemia (%)	14 (16.8)	7 (8.4)	0.16
Intraventricular hemorrhage	0	0	1.00
Mechanical ventilation (%)	8 (9.6)	4 (4.8)	0.36
Respiratory distress syndrome (%)	9 (10.8)	2 (2.4)	**0.05**
Necrotizing enterocolitis (%)	0	0	1.00
Phototherapy (%)	17 (20.4)	14 (16.8)	0.69
Sepsis (%)	1 (1.2)	3 (3.6)	0.62
Transfusion (%)	4 (4.8)	1 (1.2)	0.36
Composite adverse neonatal outcome (%)	46 (55.4)	29 (34.9)	**0.01**

Continuous variables are presented as mean ± SD and categorical variables as n (%). p-values in bold are statistically significant, IUGR – intrauterine growth restriction, NICU – Neonatal intensive care unit.

Table 4
Independent associations with First PE pregnancy – multivariate analysis.*

	aOR	95% CI
Preeclampsia with severe features	1.36	1.12–2.36
Composite of maternal malperfusion lesions	1.12	1.04–1.87
Composite adverse neonatal outcome	1.26	1.14–2.23

* Adjusted for: Maternal age, gestational age at delivery, mode of delivery, Aspirin use, and LMWH use.

statistical significance regarding placental histopathology and neonatal outcome. Third, the exclusion of twin pregnancies and the adjustment for potential confounders allows for a better estimation of placental lesions, adverse neonatal outcome and their correlation to the first preeclampsia group. Fourth, all our main findings were adjusted using multivariable analysis to all background confounders including Aspirin use in the recurrent pregnancy. Lastly, our study may contribute to better understanding of the clinical course and pathophysiology of preeclampsia.

In conclusion, our study shows that the first event of preeclampsia is associated with a higher rate of severe features, placental MVM lesions, and a higher rate of adverse neonatal outcome, compared to pre-eclampsia in the subsequent pregnancy. These findings reinforce the "immunological theory" that constitutes one of the primary theories for the development of preeclampsia. Further research is needed to evaluate this hypothesis on larger scale populations.

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None

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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