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HELLP SYNDROME: CLINICAL AND LABORATORY FEATURES AND IMBALANCE BETWEEN ANGIOGENIC PLACENTAL GROWTH FACTORS

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Aim *To investigate the clinical and laboratory characteristics of the HELLP syndrome, compare the clinical manifestations of nephropathy in women with moderate and severe preeclampsia (PE) and HELLP syndrome, and examine their association with blood concentrations of PlGF and sFlt-1.*

Material and methods *The study analyzed the clinical course and outcomes of pregnancies in 141 women who were divided into four groups: HELLP syndrome, severe PE, moderate PE, and control group. Diagnostic evaluation comprised clinical examination, laboratory tests, including biochemical and immunological studies, diagnostic tests, and evaluation of the imbalance between placental angiogenic factors (sFlt-1, PlGF).*

Results *In women with HELLP syndrome, the sFlt-1/PlGF ratio (Mo 254 ± 93.51 pg/ml) was significantly lower than in patients with severe (Mo 439.08 ± 112.29) and moderate PE (306, 62 ± 164.59). In addition to liver injury, almost all patients had evidence of other organ involvement in the pathological process. Renal failure was more severe in patients with PE: serum creatinine concentrations in the HELLP-syndrome, severe PE, and moderate PE were (Mo) 110.80 ± 20.62 μmol / l, 73.26 ± 4.55 μmol/l, and 71.73 ± 6.16 μmol/l, respectively. LDH levels had a moderate direct correlation with creatinine (r = 0.539) and total bilirubin (r=0.606) levels, and inverse correlation with platelet counts (r= -0.384). The role of the imbalance between placental angiogenic factors in the development of clinical manifestations of HELLP syndrome is discussed.*

Conclusion *Probably, HELLP syndrome is not a more severe form of PE. HELLP syndrome is a clinical form of thrombotic microangiopathy. Apparently, PE is just a trigger for the development of HELLP syndrome.*

Keywords*: HELLP syndrome, pre-eclampsia, thrombotic microangiopathy, placental growth factor (PlGF), soluble fms-like tyrosine kinase-1 (sFlt-1).*

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In recent years, there has been a disturbing annual increase in maternal mortality from preeclampsia (PE) and its complications, despite improvements in the early diagnosis and labor management. This trend has some explanations, but special attention in this area has largely focused on a variety of conditions that can mimic PE. In the time that has elapsed since L. Weinstein in 1982 coined the term HELLP syndrome that refers to an acronym used to describe the clinical condition developing during pregnancy and leading to hemolysis, elevated liver enzymes, and low platelets, the number of controversial issues of diagnosis and treatment of this disease has steadily increased. Initially, a condition called HELLP-syndrome was attributed to the complicated course of PE. However, with gaining research evidence, it turned out that the HELLP syndrome is accompanied by PE symptoms only in 80% of cases. Apart from affecting the liver, it has some atypical manifestations with the involvement of other organs (heart, kidneys, lungs, brain, etc.), and also may develop or progress in the postpartum period. HELLP-syndrome, especially occurring after childbirth, has an estimated maternal mortality of 1 to 25% and high perinatal mortality (7-30%) [1-3]. Clinical and laboratory manifestations, as well as a morphological picture of liver damage in HELLP syndrome have much in common with PE.

However, the question about the causes of differences in the phenotypic manifestations of PE remains open: why do some women develop a “pure” PE, whereas others experience HELLP syndrome without PE. There are a variety of theories attempting to explain these differences. A major role in the development of HELLP syndrome plays antiphospholipid syndrome (APS) and another type of thrombophilia associated with factor V Leiden (FVL) and factor II (FII) 20210A gene mutations. Also, there is a current debate about whether or not HELLP syndrome is thrombotic microangiopathy (TMA). Recent studies have been concerned with polymorphisms of genes encoding the regulatory proteins of the complement system, which links HELLP syndrome with a more threatening type of TMA- atypical hemolytic uremic syndrome (aHUS) [4].

HELLP syndrome is thought to complicate 0.8-1% of pregnancies and occurs in 10-20% of patients with severe PE and eclampsia. However, various types and presenting features of HELLP syndrome are little known to clinicians. Also, there is a reason to believe that HELLP syndrome is not PE as such.

This study aimed to investigate the clinical and laboratory characteristics of the HELLP syndrome, to compare the clinical manifestations of nephropathy in women with moderate and severe preeclampsia (PE)

and HELLP syndrome, and examine their association with blood concentrations of PlGF and sFlt-1.

Material and methods

We analyzed the course of pregnancy in 141 women at 19 to 41 weeks of gestational age. The study comprised women aged 18—41 years (mean age 31.35 ± 1.14 years) who were treated at the V.I. Kulakov National Medical Research Center for Obstetrics, Gynecology and Perinatology from 2011 to September 2016. Patients were divided into 4 groups: group 1 (n=36) patients with complete and partial HELLP syndrome (19-40 weeks' gestation); group 2 (n=35) patients with severe PE (25.6—39.5 weeks' gestation); group 3 (n=35) patients with moderate PE (29-40 weeks' gestation); group 4 (control group, n=35) healthy patients with uncomplicated obstetrics and gynecological history, and physiological course of current pregnancy (34—41 weeks' gestation). The control group patients were selected retrospectively after the childbirth: during the entire pregnancy, and after delivery, they had no symptoms of PE and HELLP syndrome. Diagnostic criteria for the complete HELLP syndrome included a combination of three symptoms that developed during pregnancy and stopped within 48 hours after delivery: 1) low platelets (platelet count < 150×10^9/L or a decrease in platelet count by 25% from baseline); 2) increased lactic dehydrogenase (LDH) (> 600 U/I); 3) elevated cytolysis markers (ALT and/or AST>70 U/L). In the absence of thrombocytopenia or cytolysis, the condition was diagnosed as a partial HELLP syndrome (ELLP and HEL syndromes). Twenty nine patients (80%) had the total HELLP syndrome. Of seven (20%) patients with partial HELLP, four (11%), and three (9%) patients had no thrombocytopenia and increased enzymes, respectively. Among the patients with HELLP-syndrome, 32 patients with thrombocytopenia (there were 32 patients with thrombocytopenia). Among the patients with HELLP syndrome, who had thrombocytopenia (n=32), 11 patients (30.6%), 12 (33.3%), and 9 (25%) patients had class-I (platelet count 4-50 $\times10^9$/l), class-II (platelet count 51- 98×10^9/l), and class-III (platelet count 104-152×10^9/ l) HELLP syndrome according to Mississippi classification, respectively.

Chronic arterial hypertension (CAH) was found in 11.1% of patients with complete and partial HELLP syndrome. Considering the difficulties in differentiating between moderate and severe PE in patients with CAH, we excluded the patients of groups 1 and 2, who had a history of CAH and developed PE. In the control group, 8.5% of patients had CAH, but none of them developed PE and experienced progression of hypertension during pregnancy. Apparently, CAH cannot be regarded as a risk factor for the development of HELLP syndrome. At the same time, 25.7%, 22.2%, and 14.2% of patients with moderate PE, HELLP syndrome, and severe PE, respectively, had stages 1-3b chronic kidney disease (CKD), whereas in the control group only 5.7% of patients had CKD. Of note, four (8.3%) patients who developed HELLP syndrome had a history of hepatitis A, and one patient had chronic hepatitis C with minimal activity.

Analysis of the patients' medical history in the HELLP syndrome group showed that four patients (11.1%) had an allogeneic renal transplant, four (11.1%) patients were diagnosed with systemic lupus erythematosus before pregnancy, and four patients had an APS, one of which was secondary APS. In one patient with primary APS, recurrent deep vein thrombosis, and a history of multiple episodes of pulmonary thromboembolism, the HELLP syndrome developed twice, and in her second pregnancy, she received therapeutic doses of low molecular weight heparin (anti-factor Xa level was 0.72-1.2). The level of sFlt-1 was regularly monitored during pregnancy and was within the normal range, but the withdrawal of low molecular weight heparin a day before the caesarean section resulted in a decrease in the platelet count to 86,000 in μL and an increase in LDH to 680 IU/L. These laboratory changes were accompanied by oliguria, pain in the upper right abdomen, and severe headache with a maximum blood pressure of 130/86 mmHg.

Only ten women in group 1 were tested for antiphospholipid antibodies (APA), four (12%) had signs of APS, another three had non-criteria manifestations of APS (antibodies to annexin, phosphatidylethanolamine, prothrombin). The diagnosis of APS was made in accordance with criteria adopted in Sapporo in 1998 (updated in 2004—2006), based on a combination of arterial, venous and/or microcirculatory thrombosis and/or pregnancy morbidity (three or more unexplained consecutive spontaneous abortions before the 10th week of gestation, one or more unexplained deaths of a morphologically normal fetus at or beyond the 10th week of gestation, one or more premature births of a morphologically normal neonate before the 34th week of gestation because of eclampsia or severe preeclampsia or placental insufficiency) with serological markers (anticardiolipin antibody of IgG and/or IgM isotype, present in medium or high titer and/or anti-β_2-glycoprotein-I antibody of IgG and/or IgM isotype, and/or lupus anticoagulant). Three patients (8.8%) with HELLP syndrome had systemic lupus erythematosus, diagnosed before pregnancy, according to the 1997 ACR diagnostic criteria; at the time of pregnancy, the disease was in the stage of persistent clinical and laboratory remission (SLEDAI 2-6).

Four patients with HELLP syndrome had had a history of an allogeneic renal transplant. All of them had cadaveric renal transplantation 4-7 years before the onset of pregnancy. During the pregravid stage and pregnancy, they received combination immunosuppressant therapy with cyclosporine and prednisone. Before pregnancy, they had neither clinical nor morphological signs of drug-induced TMA, and during pregnancy, cyclosporine concentration was regularly monitored with dose correction if needed.

The diagnosis of PE was made by the 2008 WHO criteria, which included the presence of hypertension and proteinuria (>0.3 g/day) after the 20th week of gestation, with possible development of organ dysfunction. Severe PE was classified as the presence of two episodes of hypertension of more than 160/110 mmHg. resistant to antihypertensive therapy and/or proteinuria >5 g/day.

Before the onset of PE, none of the women had proteinuria and signs of renal dysfunction. Renal

dysfunction was defined as a glomerular filtration rate below 100 ml/min by the Reberg-Tareev and/or serum creatinine level above 90 μmol/l. Proteinuria was defined as the daily protein excretion of more than 0.3 g. These clinical and laboratory indicators were recorded either at hospital admission for PE or planned delivery. All women were regularly monitored for these parameters, starting from the second trimester of pregnancy. Plasma levels of sFlt-1 and PlGF with the calculation of the sFlt-1/PlGF ratio in 14 patients of the study group were examined at hospital admission, in all patients in the PE group, and in the women in the control group before delivery.

Serum concentrations of PlGF and sFlt-1 in the pregnant women were measured by electrochemiluminescence diagnostic assays Elecsys PlGF and Elecsys sFlt-1 (F. Hoffmann-La Roche, Switzerland) on the automatic analyzer Cobas-e411 (KONE, Finland). Normal ranges of PlGF, sFlt1, and sFlt-1/ PlGF ratio were considered 170-50 pg/ml, 950-2800 pg/m, and 4-20, respectively. These tests were performed in 17, 12, and 16 patients with HELLP syndrome (group 1), 12 patients with severe PE (group 2), and 16 patients with moderate PE (group 3), respectively.

Exclusion criteria of the study were as follows: chronic viral hepatitis with a high activity; hereditary hemolytic anemia; type 1diabetes mellitus; a history of idiopathic thrombocytopenic purpura; paroxysmal nocturnal hemoglobinuria. Also, women with TMA progression after childbirth were excluded from the study.

All results were entered into MS Excel spreadsheets. For the sample, the results were expressed as the mean, median, standard deviation, variance, and confidence intervals. The normality of the distribution was tested by the Kolmogorov-Smirnov test. Spearman's rank correlation was used for non-normally distributed quantitative variables. A value of $p < 0.05$ was considered statistically significant. In determining the correlation for the normal distribution, the Pearson coefficient was calculated. Correlation coefficient (r) was graded as no correlation - 0–0.25, weak - 0.25–0.50, moderate - 0.5–0.75, and strong - 0.75–1. To compare quantitative parameters of two independent samples, the Student's t-test was used. Differences were considered statistically significant at $P < 0.05$; p less than 0.05, but more than 0.001 was considered as a tendency to significance. For comparison of several (more than 2) samples, the ANOVA was used.

Results

In patients of PE group, arterial hypertension developed at 26.92 ± 2.52 weeks' gestation; for HELLP syndrome this period was not evaluated due to the presence of patients with CAH. Mean systolic and diastolic blood pressure were 145.92 ± 10.30 and 91.29 ± 5.07 mmHg., respectively, whereas in patients with severe and moderate PE these values were 169.31 ± 5.07 and 104.41 ± 2.59 mmHg., and 149.56 ± 5.96 and 96.08 ± 2.36 mmHg, respectively.

The average terms of delivery in group 1, 2, 3, and the control group were 32.07 ± 1.7, 32.65 ± 1.22, 35.81 ± 0.98, and 38.97 ± 0.39 weeks, respectively. Two (6%) patients with HELLP-syndrome underwent emergency delivery in the 2nd trimester at of 19 and 21 weeks' gestation. One patient with a primary APS and multiple-gestation pregnancy developed HELLP syndrome at 19 weeks' gestation.

It is noteworthy that patients with HELLP syndrome had the highest rate of antenatal fetal death (22.2%) with only 77.8% of live-born babies, while in groups 1, 2, and 3 all babies were born alive (Table 1). Patients with HELLP syndrome had a higher incidence of complications: four of them (11.1%) had placental abruption, and six of 36 (16.7%) had bleeding of various severity (up to 2000 ml).

Compared with patients with HELLP syndrome, women with severe and moderate PE had higher sFlt-1/PlGF ratios. There was also a moderate strength correlation between the sFlt-1/PlGF ratio and term of delivery: the higher was the sFlt-1/PlGF ratio, the earlier the patient required delivery (r = -0.38). Patients with HELLP syndrome had the highest values of sFlt-1 and PlGF (874.1 and 669.7 pg/ml), and term of delivery of 25 weeks' gestation, which was the earliest in patients, who were tested for PE markers. In patients with severe PE, the maximum values of sFlt-1 and PlGF were 1183 pg/ml and 860.6 pg/ml, and the term of delivery was 26 and 31 weeks' gestation.

Significant proteinuria and decreased renal function were observed in 23 (63.9%) patients with HELLP syndrome (Table 2). The 24-hour proteinuria was significantly higher in patients with severe PE, while decreased renal function was registered only in the HELLP syndrome group. Among patients with HELLP syndrome, the lowest glomerular filtration rate was 16 ml/min/1.73 m2 (mean 69.83 ± 9.88 ml/min/1.73 m2). No proteinuria was observed in the control group patients.

In patients of group 1, renal damage was more pronounced, and the severity of nephropathy was manifested not only in greater proteinuria but also in more significant renal dysfunction. In patients with HELLP syndrome, the levels of hemoglobin and platelet

Table 1. Clinical characteristics of newborns

	group 1 (HELLP syndrome), n=36	group 2, severe PE, n=35	group 3, moderate PE, n=35	group 4,	*p*
Live births	p	35 (100%)	35 (100%)	35 (100%)	
Newborn birth weight, g	2038,89±354,61	1631,81±205,6	2458,5±297,89	3376,6±158,35	$p_{1,2;1,3}<0,05$; $p_{1,4;2,3;2,4;3,4}<0,001$
Newborn height, cm	42,61±2,88	41,05±1,98	46,05±1,88	51,17±0,72	$p_{1,3}<0,05$; $p_{1,4;2,3;2,4;3,4}<0,001$
Apgar 1	6,77±0,61	6,69±0,51	7,44±0,27	7,94±0,07	$p_{1,3;1,4;2,3}<0,05$; $p_{2,4,34}<0,001$
Apgar 5	7,66±0,49	7,69±0,41	8,33±0,26	8,85±0,11	$p_{1,3;2,3}<0,05$; $p_{1,4,2,4,3,4}<0,001$

count were significantly lower than among those with moderate and severe PE. There was a moderate direct correlation between hemoglobin level and platelet count (r = 0.332). The level of LDH was tested only in patients with HELLP syndrome, averaging 1103.69±209.01 U/l. This test, unfortunately, is not included in the panel of standard tests for pregnant women. LDH levels had a moderate direct correlation with creatinine (r = 0.539) and total bilirubin (r=0.606) levels, and inverse correlation with platelet counts (r= -0.384). Schistocytes count was performed only in 18 patients with HELLP syndrome, averaging 0.11±0.07%. In patients with HELLP syndrome, cytolysis showed a seven - fold increase from normal without significant differences between ALT and AST levels; there was a strong direct correlation between ALT and AST (r= 0.829). Also, patients of this group had significantly higher levels of bilirubin compared with healthy controls and patients with PE, although bilirubin levels did not go beyond the reference range.

Analysis of organ damage in HELLP syndrome patients showed that not only the liver and kidneys were involved in the pathological process. Skin lesions were noted in five (13.9%) patients and were represented by livedo reticularis (2 patients had a generalized livedo reticularis); three patients with minimal platelet counts had multiple petechiae and confluent hematomas on the limbs. Seven (19.4%) patients had various neurological symptoms, represented mainly by general cerebral symptoms: impaired perception, mental disorientation in space and time, drowsiness, fog before the eyes. In the PE group, patients complained only of a headache. Due to complaints of visual impairment and fog before the eyes, 12 (33.3%) patients with HELLP syndrome were examined by an ophthalmologist, who found retinal edema and neuroepithelial detachment in four and two patients, respectively. The neuroepithelial detachment was accompanied by multiple retinal microscotomas revealed by perimetry. In addition to arterial hypertension, 11 (30.5%) patients with HELLP syndrome had signs of minimal to severe pulmonary hypertension; one of them developed clinically significant pulmonary edema, three showed signs of slightly dilated heart chambers, two had pericardial effusion up to 1 cm, and one had a 40% reduction of the ejection fraction (Table 3).

Discussion

The findings of our study cast doubt on the concept that PE develops by a sequential progression from moderate to severe, and to HELLP syndrome. Apparently, HELLP syndrome is not a more severe form of PE, as was previously thought. Probably, the imbalance of PlGF and

Table 2. Comparative clinical and laboratory characteristics in groups with HELLP syndrome and PE

Показатели	group 1 (HELLP syndrome), n=36	group 2, severe PE, n=35	group 3, moderate PE, n=35	group 4,	*p*
SAD, mmHg	p	169,31±5,07	149,56±5,96	-	$p_{1,2;2,3}$<0,001
DBP mmHg	91,29±5,07	104,41±2,59	96,08±2,36	-	$p_{1,2;2,3}$<0,001
Hemoglobin, g/l	88,08±7,25	119,05±4,64	117,91±4,63	119,62±3,66	$p_{1,2;1,3;1,4}$<0,001
Platelets, $\times 10^9$ / l	92,97±20,93	185,27±18,96	205,75±26,79	224,02±18,66	$p_{1,2;1,3;1,4}$<0,001; p_{34}<0,05
LDH, U/l	1103,69±209,01	-	-	214,11±78,66	$p_{1,4}$<0,001
ALT, U/l	285,55±148,71	27,63±5,46	26,01±6,12	16,48±2,43	$p_{1,3;1,4}$<0,001; $p_{12,24,34}$<0,05
AST, U/l	205,51±72,55	29,55±5,17	33,04±11,95	21,53±2,47	$p_{1,2;1,3;1,4}$<0,001
Bilirubin total, μmol/l	13,98±4,00	8,79±1,25	9,80±1,33	10,26±1,09	$p_{1,2;2,4}$<0,05
Creatinine, μmol/L	110,80±20,62	73,26±4,55	71,73±6,16	65,86±4,07	$p_{1,2;1,3;1,4;2,4}$<0,05
GFR, ml/min/1.73m2	69,83±9,88	82,66±10,21	77,80±13,48	107,33±5,52	$p_{1,4}$<0,001, $p_{3,4}$<0,05
Proteinuria, g/l	1,74±0,77	2,09±0,42	1,07±0,29	-	
24-hour proteinuria, g	2,51±0,91	2,87±0,49	1,91±1,72	-	
Fibrinogen, g/l	4,55±0,62	4,71±0,43	5,53±0,53	5,63±0,37	$p_{1,2;1,4}$<0,05
APTT, sec	33,31±2,77	31,54±6,35	31,69±7,71	27,90±-0,79	$p_{1,4}$<0,001
Prothromin by Quik,%	111,31±6,15	119,30±3,89	117,43±5,89	111,11±4,02	$p_{2,4;1,4}$<0,05
D-dimer, μg/l	5947,58±2982,76	1271,96±180,07	1474,16±292,31	1899,92±362,62	$p_{1,4}$<0,001; $p_{1,2;1,3;2,4;3,4}$<0,05
	n=17	*n*=12	*n*=16		
PlGF (pg/ml)	135,15±56,30	52,28±8,66	110,79±19,37	-	$P_{1,2,2,3}$<0,05
SFLT-1 (pg/ml)	12135±3184,02	15869±1856,72	28895,41±20616,36	-	
SFLT-1 /PlGF (pg/ml)	254±93,51	439,08±112,29	306,62±164,59	-	$P_{1,2,2,3}$<0,05

sFlt-1 leading to PE is only a trigger for the development of the HELLP syndrome. We came to this conclusion based on our findings showing that the sFlt1/PlGF ratio in patients with HELLP syndrome was almost twice lower than in patients with severe PE, and one and a half times lower than in patients with moderate PE. In an attempt to find an explanation for such a significant difference, we analyzed data from the literature. It is known that PE develops as a result of disruption of placenta formation due to a failure in superficial cytotrophoblast invasion at the earliest gestational age. As a consequence, the ischemic placenta produces anti-angiogenic substances, the main one being sFlt-1, which, when linked to vascular endothelial and placental growth factors (PlGF), lead to proteinuria and hypertension [5—8].

A search of the literature revealed significant differences in the changes of PlGF and sFlt-1 the concentrations and their ratio during physiological pregnancy and pregnancy complicated by PE. It is the sFlt-1/PlGF ratio that changes most markedly, and not sFlt-1 and PlGF separately. It is generally accepted that the imbalance between sFlt-1 and PlGF is the most informative in the diagnosis of PE, and the degree of the imbalance correlates with the severity of PE [9—15]. These indicators have proved to be valuable as prognostic markers of PE, while at the same time, sFlt-1 remains at low levels up to the 33-36th weeks' gestation during normal pregnancy, followed by a rise of about 145 pg/ml per week until delivery. That is why an elevated sFlt-1/PlGF ratio is useful in predicting adverse outcomes before 34 weeks of gestation. Also, according to recent studies, only a cutoff value of 86.2 for the sFlt-1/PlGF ratio predicted adverse outcomes, with a sensitivity and specificity of 77.8% and 80.0%, respectively [13]. In our study, two patients with HELLP syndrome with the onset of the disease before 34 weeks' gestation had a normal sFlt-1/PlGF ratio, and four patients had the ratios of less than 86.2. Thus, the notion that HELLP syndrome is a complication of severe PE is not supported by the results of our study. At the same time, no previous study has investigated the sFlt-1/PlGF ratio only in patients with HELLP syndrome.

Another characteristic feature of the HELLP syndrome in our study was the high incidence of renal dysfunction, which was registered in 63.9% of patients, who had not only an isolated decrease in the glomerular filtration rate but normal creatinine levels, as in the groups with a moderate and severe PE. The mean creatinine concentration was 110.80 ± 20.62, which was significantly higher than that in patients with PE. It should be noted that an isolated reduction in glomerular filtration rate is the first manifestation of renal failure in patients with TMA and was first described in patients with APS-associated nephropathy. At the same time, there may be a time lag between the onset of the disease and azotemia, when creatinine level increases after clinical presentation of TMA [16, 17]. In PE, an isolated decrease in glomerular filtration rate develops as a result of a decrease in the fenestration of glomerular endothelium, which is critically dependent

Таблица 3. Органная дисфункция у пациенток с различными видами ПЭ

Проявления	1-я группа (HELLP-синдром), *n*=36	2-я группа тяжелая ПЭ, *n*=35	3-я группа умеренная ПЭ, *n*=35	4-я группа контроль, *n*=35
Почечные проявления				
Протеинурия>0,3г/л	29 (80,5%)	35 (100%)	35 (100%)	
Нарушение функции	23 (63,9%)	11 (31,4%)	3 (8,6%)	0
Изолированное снижение СКФ	14 (38,9%)	10 (28,6%)	3 (8,6%)	0
Олигурия	29 (80,5%)	12 (34,2%)	6 (17,1%)	
Поражение печени				
Цитолиз	33 (91,6%)	0	0	0
Поражение сердца и легких				
Легочная гипертензия (давление легочной артерии > 35 мм рт ст)	11 (30,5%)	-	-	0
Отек легких	1 (2,8%)	-	-	0
Диастолическая дисфункция (E/A	3 (8,3%)	-	-	0
Дилятация левых отделов сердца (КДР >5,2 см)	3 (8,3%)	-	-	0
Выпот в перикарде более 80 мл	2 (5,5%)	-	-	0
Снижение фракции выброса менее 55%	1 (2,8%)	-	-	0
Выпот в плевральных полостях	4 (11,1%)	-	-	0
Поражение головного мозга и органа зрения				
Дезориентация, нарушение восприятия	7 (19,4%)	0	0	0
Сонливость	7 (19,4%)	13 (37,1%0		0
Головная боль	7 (19,4%)	26 (74,3%)	13 (37,1%)	0
«Туман перед глазами»	12 (33,3%)	-	-	0
Отек сетчатки	4 (11,1%)	2 (5,7%)	-	0
Отслойка нейроэпителия сетчатки	2 (5,5%)	0	-	
Поражение кожи				
Сетчатое ливедо	5 (13,9%)	0	0	0

on the podocyte-derived vascular endothelial growth factor [18]. The results of our study can be considered as indirect evidence that the HELLP syndrome may be a clinically manifested variant of TMA. This suggestion is confirmed by a strong direct correlation between levels of LDH and creatinine. Interestingly, the most severe renal dysfunction was observed in patients with the post-delivery progression of TMA.

Two patients had a severe renal failure, which required several sessions of renal replacement therapy. They had very low glomerular filtration rate (13—26 ml/min), in one of them developed nephrotic-range proteinuria. At the same time, these two patients had clinical signs of "pure" PE before delivery, when they experienced oliguria with a decrease in glomerular filtration rate while having normal levels of creatinine. These data suggest that PE can become the main trigger for the development of HELLP syndrome. Also interesting are higher levels of total bilirubin compared with patients with PE and healthy pregnant women. Our Turkish colleagues drew attention to this phenomenon, having studied the course of HELLP syndrome in 171 pregnant women. They reported that bilirubin >2.0 mg/dL, LDH >1290 U/L, and low platelets (<50,000/mm3) were independent prognostic risk factors for predicting adverse maternal outcomes [19]. Apparently, microangiopathic hemolysis increases bilirubin level, but taking into account moderate degrees of hyperbilirubinemia, it cannot be the main diagnostic marker of microangiopathic hemolysis.

Analysis of organ dysfunction revealed a variety of neurological and ophthalmologic symptoms without evidence of cerebrovascular disease. The main clinical presentation is general cerebral symptoms. These presenting signs are considered highly specific for TMA. For instance, primary Sneddon syndrome, a form of slowly progressing TMA with predominant brain involvement, is characterized by ischemic cerebral manifestations including symptoms of encephalopathy and cognitive impairment in the absence of clear clinical signs of cerebrovascular disorders. And only neuroimaging studies identify ischemic lesions, indicating a clinically asymptomatic or minimally symptomatic development of brain damage [20]. Focal symptoms in TMA patients with cerebral involvement are unstable, and 80% of them experience a complete restoration of motor functions, which is obviously associated with the development of cerebral circulation disorders in small-sized arteries located outside the motor brain structures [20]. The most common neurologic manifestation of HELLP syndrome was a headache; the same symptoms are typical for all types of TMA: a migraine-like headache, epileptic seizures, less often chorea and peripheral neuropathy. In TMA, thrombosis often affects not only kidneys, brain, heart, and liver, but also ocular vessels.

Ocular manifestations of the HELLP syndrome can also be caused by ischemic lesions in the occipital cortex, that is, visual problems can occur as a result of damage to cortical visual centers in the absence of direct signs of damage to the organs of the visual system. For example, as has been reported in the literature, that color vision abnormality may develop in HELLP syndrome patients as a result of posterior reversible encephalopathy. This ophthalmic sign was the first manifestation of the disease, preceding the clinical presentation of the HELLP syndrome [21—24]. By analogy with the more studied ocular manifestations of APS, the damage to the microvasculature of the organs of the visual system can result in isolated ischemic retinal edema, in some cases leading to neuropathy [25-28]. Then multiple retinal detachments and corresponding microscotomas may be observed, as it was revealed in our study. The damage to the visual organ can be one of the first clinical manifestations of HELLP syndrome, while up to a third of patients may not have visual problems.

The cardiac manifestation was observed in 30.5% of patients. Acute left ventricular failure, first described in 1925 by E. Moskowitz in delineating the symptoms of fatal thrombotic thrombocytopenic purpura, is currently considered a predictor of poor outcome in the course of any TMA [29]. In such cases, lesions of large coronary vessels are registered quite rarely, and the substrate of acute heart failure is the thrombi in the myocardial microcirculatory bed. In patients with HELLP syndrome, cardiac involvement is often asymptomatic and may remain undiagnosed. Interestingly, according to a study of 49 patients with HELLP syndrome, an isolated decrease in the ejection fraction was observed in 21.7% of them [30]. There have been reports in the literature of cardiac arrhythmias occurring prior to onset of HELLP syndrome [31].

Therefore, organ dysfunction in patients with HELLP syndrome, on the one hand, indicates the severity of the disease compared even with severe PE; on the other hand, it can be considered as another indirect sign that the HELLP syndrome is TMA. Besides, the HELLP-syndrome in our study was accompanied by higher concentrations of D-dimer, which is difficult to interpret, given the low sensitivity and specificity of this test in pregnant women [32]. However, the severity of thrombinemia, regardless of the time of its development, was associated with inferior outcomes regarding blood pressure, proteinuria, and renal function. Correlation between thrombinemia and renal function suggests that thrombinemia is an additional factor in the progression of endothelial damage.

The identified risk factors for the development of the HELLP syndrome, such as systemic lupus erythematosus and kidney allogenic transplantation, are confirmed in the literature. Thus, Jakobsen et al. (2015), who studied the impact of systemic lupus erythematosus on pregnancy outcome in a cohort of pregnant lupus patients, HELLP syndrome was detected in 4.8% of patients. Therefore, if the frequency of HELLP syndrome does not exceed 0.8—1% in the population, patients with systemic lupus erythematosus have 4-6 times higher risk of developing HELLP syndrome [33].

The incidence of HELLP syndrome in patients after organ transplantation has not been studied. Only isolated cases have been reported on the development of the HELLP syndrome in these patients, with the subsequent transition to a generalized TMA - obstetric AGU [34, 35]. Recent research suggests that patients with HELLP syndrome should not become organ donors because of the high rate of TMA progression in the recipient after transplantation [36]. Immunosuppressive therapy is known to be to a possible

cause of drug-induced TMA. However, in our study, the concentrations of cyclosporin and tacrolimus were closely monitored, and the patients, who developed HELLP syndrome experienced rapid recovery after delivery without correction of immunosuppressive therapy, which is not typical for drug-induced TMA [37—39].

The presence of APS is a formidable risk factor for the development of HELLP syndrome, even with adequate anticoagulation throughout the pregnancy. According to the literature, the frequency of HELLP syndrome in patients with diagnostic criteria of APS reaches 3%, which is 3-4 times higher than in the population, while the frequency of PE reaches 16.4% [40]. APS can lead to earlier manifestations of the disease; there has been a case report of the onset of HELLP syndrome at 17 weeks' gestation. In our study, the patient with primary APS developed HELLP syndrome at 19 weeks' gestation. The manifestation of TMA in patients with APS is considered as a risk factor for the development of catastrophic APS, therefore approaches to the management of such patients should differ [41, 42]. Thus, the presence of systemic lupus erythematosus, APS (primary or secondary), and post-transplant TMA are independent risk factors for the development of the HELLP syndrome, rather than "pure" PE.

Conclusion

Our study results suggest that the HELLP syndrome is not a more severe form of PE. HELLP syndrome is a serious systemic disease, clinically manifested TMA, involving several organs and systems due to generalized endothelial injury. Apparently, PE is just a trigger for the development of the HELLP syndrome, which is activated by an imbalance between pro- and anti-angiogenic placental factors. HELLP syndrome should be rather considered as a separate form of PE with clinical manifestations, although similar to the symptoms of PE, but more severe. The validity of this assumption is confirmed by recent evidence that the obstetric ASUS most commonly occurs after the HELLP syndrome, which allows the treatment these two conditions as different stages of the same disease - complement-mediated TMA [4]. For the development of the HELLP syndrome, a combination of sFlt-1/PlGF imbalance with additional risk factors for endothelial injury (bleeding, placental abruption, etc.) is necessary, which again proves the universality of the "double-strike" theory of any forms of TMA.

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