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Research Article

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Potential of Therapeutic Apheresis for Prolongation of Pregnancy in Early-Onset Preeclampsia

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ABSTRACT Preeclampsia with onset between 20 and 34 weeks is conditioned by the development of endothelial dysfunction caused by increased secretion of antiangiogenic factors, activation of the immune system, and the synthesis of inflammatory mediators. This complication is responsible for the progression of multiple organ failure in the mother, and more than 60,000 maternal deaths annually worldwide. The only method of therapy at present is early delivery. Such tactics lead to high neonatal morbidity and mortality.

AIM OF STUDY To evaluate the possibilities of safely prolonging pregnancy using therapeutic apheresis methods in the development of early-onset preeclampsia.

MATERIAL AND METHODS A prospective randomized study was conducted involving 58 patients diagnosed with early-onset severe preeclampsia. The patients were divided into three groups. The patients of the first group underwent 2 sessions of cascade plasma filtration with a total processed plasma volume of 4810 (3250; 5680) ml. In the second group, hemoperfusion was performed with a perfusion volume of 18,460 (16.890; 21.350) ml in two sessions. At the stages of the study, the dynamics of clinical and laboratory parameters of the mother and newborn were assessed in comparison with the control group.

The use of cascade plasma filtration statistically significantly reduced the sFlt-1/PlGF ratio (p=0.017), pregnancy was prolonged by 32.5 (5.5; 42.5) days, the gestational age at delivery was 34.1 (29.6; 36.0) weeks. When using hemoperfusion, the level of neutrophil extracellular traps decreased statistically significantly. Pregnancy was prolonged by 26.5 (8; 52) days, the patients gave birth at a gestational age of 34.3 (33.5; 36.8) weeks. In the control group, the duration of pregnancy prolongation was 5.5 (2;7) days, p<0.017 compared with other groups. In this group, progression of laboratory signs of multiple organ failure and deterioration of fetal blood flow were noted. Newborns from the control group showed a statistically significantly greater need for surfactant: OR 7.3 95%CI [1.81; 29.6], p=0.005. Resuscitation bed-day and treatment in the department of premature infants for newborns from the control group were 12.5 (8.5; 16.8) and 15 (7; 22) days, respectively, p<0.017 compared with other groups.

CONCLUSION The use of therapeutic apheresis techniques in patients with early-onset preeclampsia may allow for safe prolongation of pregnancy in the interests of the fetus, which requires further study.

Keywords: early preeclampsia, cascade plasmafiltration, hemoperfusion

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BMI – body mass index
CF – cascade filtration
DBP – diastolic blood pressure
DSC – dextran sulfate cellulose
FGR – fetal growth restriction
HP – hemoperfusion
H.E.L.P. – heparin-mediated extracorporeal low-density lipoprotein precipitation
LDL – low-density lipoprotein
MOF – multiple organ failure
NETs – neutrophil extracellular traps
RDS – respiratory distress syndrome
PE – preeclampsia
PlGF – placental growth factor
SBP – systolic blood pressure
sFlt-1 – soluble fms-like tyrosine kinase-1

Preeclampsia (PE) complicates the course of 3–8% of all pregnancies and dramatically increases the risk of death from all causes, especially in women with early-onset PE development [1–3]. It is currently recognized that early-onset and late-onset PE have different pathogenesis. Early onset of this complication at 20 to 34 weeks is associated with impaired spiral artery remodeling which leads to placental malperfusion, and gross abnormalities of the placental villous tree at the molecular level. Oxidative stress developing against the background of placental villus ischemia promotes increased secretion of antiangiogenic factors, of which the most studied is soluble fms-like tyrosine kinase-1 (sFlt-1), a decrease in the blood level of proangiogenic placental growth factor (PlGF), activation of the immune system, including neutrophils with an increase in the formation of special DNA-containing structures - neutrophil extracellular traps (NETs) and activation of the synthesis of inflammatory mediators [4]. All these processes form the key factor in the pathogenesis of early-onset PE — the development and progression of endothelial dysfunction [5–12]. Late-onset PE, which manifests after 34 weeks of gestation, is not associated with impaired spiral artery remodeling. Placental perfusion in late-onset PE is maintained and even increases, and sFlt-1 concentration and PlGF secretion are close to the normal range. Currently, it is believed that cases of late-onset PE, which account for almost 80% of all cases of PE, are caused by the mother's genetic predisposition to cardiovascular diseases, which manifests itself during pregnancy due to a decrease in the adaptive capacity of the cardiovascular system [12–15].

Early-onset PE has a negative impact on both maternal and neonatal outcomes. More than late-onset PE, early-onset PE is associated with renal injury, liver injury/failure, central nervous system injury, cerebrovascular accident, cardiomyopathy, pulmonary edema, adult respiratory distress syndrome (RDS), and death [16–20]. PE is the cause of more than 60,000 maternal deaths annually worldwide, and ranks third among the causes of maternal mortality after hemorrhage and embolism [2, 18]. Early-onset PE significantly worsens neonatal outcomes, causing intrauterine growth retardation, placental abruption, premature birth and associated complications, including neonatal RDS, cerebral palsy, necrotizing enterocolitis, retinopathy of prematurity and perinatal death [21–24]. The only method of etiopathogenetic therapy at present is removal of the placenta and, consequently, earlier termination of pregnancy to prevent unfavorable maternal outcomes. In turn, such tactics lead to premature births and high neonatal morbidity and mortality [24, 25].

In connection with the discovery and description of antiangiogenic factors and factors damaging the endothelium, as well as their role in the pathogenesis of early-onset PE, reports began to appear on new approaches to the treatment of this complication. In this regard, special attention is drawn to various methods of therapeutic apheresis of plasma antiangiogenic factors, low-density lipoproteins, and oxidative stress products, aimed at reducing the aggressiveness of endothelial dysfunction and maximally prolonging pregnancy in order to improve neonatal outcomes [13, 25–33].

Aim of the study was to evaluate the possibilities of safe pregnancy prolongation using therapeutic apheresis methods in the development of early-onset preeclampsia.

Objectives of the study:

1. To study the effect of therapeutic apheresis methods on the concentration of pathogenetically significant markers of severe PE.
2. To compare the dynamics of clinical and laboratory signs of multiple organ failure (MOF) during cascade filtration (CF) and hemoperfusion (HP) in patients with severe PE.
3. To assess the state of uteroplacental hemodynamics when using therapeutic apheresis and indications for emergency delivery in patients with severe PE.
4. To assess safe terms of pregnancy prolongation in patients with severe PE.
5. To analyze maternal and neonatal outcomes in prolongation of pregnancy complicated by early-onset PE.

MATERIALS AND METHODS

To assess the possibility of safely prolonging pregnancy in patients with early-onset PE using therapeutic apheresis methods, a prospective randomized study was conducted from 2019 to 2022 at the Vidnovsky Perinatal Center, Moscow Region. The sample size was calculated based on the results of a study on the efficacy of therapeutic apheresis using a dextran sulfate cellulose (DSC) column for selective removal of sFlt-1 in patients with early-onset PE [27]. The apheresis group in this study consisted of 11 patients, and the control group consisted of 22 patients. The control points of the study were: the duration of pregnancy prolongation from inclusion in the group to delivery, and the duration of respiratory support of the newborn. Additionally, the sample size was calculated based on an open pilot study of the efficacy of low-density lipoprotein (LDL) apheresis using heparin-mediated extracorporeal lipoprotein precipitation (H.E.L.P.) with a therapeutic apheresis group of 6 patients and a control group of 6 patients [28]. The control points in this study were the duration of pregnancy prolongation from inclusion in the group to delivery and the resuscitation assessment of the newborn according to the Apgar scale at the 5th minute after birth. The sample size calculation was performed in MedCalc® Statistical Software version 19.6.3 (MedCalc Software Ltd, Ostend, Belgium; https://www.medcalc.org; 2021) using the method of comparing two means with statistical significance α=0.05 and power (1-β)=0.8 (Table 1).

Table 1

Sample size calculation

Pilot study data			Sample size calculation	
sFlt-1 apheresis on DSC column [27]				
Control point	Study group, n=11	Control group, n=22	Study group	Comparison group
Prolongation of pregnancy from inclusion in the study to delivery (days), M±S	10.4±5.4	3.0±2.9	3	6
Need for respiratory support in newborns (days), M±S	9±11	6±5	5	9
LDL apheresis (H.E.L.P.) [28]			Sample size calculation	
Control point	Study group, n=6	Control group, n=6	Study group	Comparison group
Prolongation of pregnancy from inclusion in the study to delivery (days), M±S	15±5.2	6.3±6.4	2	2
Assessment of the newborn's condition according to the Apgar scale at the 5th minute, M±S	6.7±0.5	6.3±1.2	16	16

Note: : LDL — low-density lipoprotein; DSC — dextran sulfate cellulose; H.E.L.P. —heparin-mediated extracorporeal low-density lipoprotein precipitation; sFlt-1 — soluble fms-like tyrosine kinase-1

Thus, at a significance level of α=0.05 and a statistical power of 80%, the number of patients in each group should have been at least 16.

The inclusion criteria for the study were gestational age from 24±0 weeks to 34±0 weeks; PE with clinical symptoms: systolic blood pressure (SBP) of at least 160 mmHg at least 2 times with an interval of 4 hours, diastolic blood pressure (DBP) of at least 110 mmHg at least 2 times with an interval of 4 hours, first detected after the 20th week of pregnancy; daily proteinuria of more than 0.33 g/l; any of the two criteria: impaired uteroplacental blood flow (increased pulsatility index of the uterine artery) or fetal blood flow (increased pulsatility index of the umbilical artery). Exclusion criteria included active labor, HELLP syndrome, pulmonary edema, headache, fetal anomalies, intrauterine infection, placentation anomalies, multiple pregnancy, umbilical artery reversal, and abnormal fetal heart rate (bradycardia or decelerations) before study entry.

In accordance with the inclusion criteria, 58 patients were randomized into three groups using the sealed envelope method. Taking into account the possible dropout of patients from the study groups, 26 envelopes were prepared for each group;

recruitment to the groups was carried out until the calculated number of study group patients who underwent 2 therapeutic apheresis procedures according to the study design (Fig. 1) was reached. Allocation was not blinded. Subsequently, 8 patients were excluded from the study: 2 patients from the cascade filtration (CF) group due to premature rupture of membranes and the onset of premature labor; 1 patient due to diagnosis of congenital malformations of the fetus incompatible with life; 1 patient due to failure to comply with the therapy protocol because of the development of acute respiratory viral infection. One patient withdrew from the hemoperfusion (HP) group due to signs of premature detachment of a normally located placenta; 2 patients due to the appearance of signs of acute respiratory disease; and 1 patient refused to participate in the study. There were no dropouts from the comparison group. The primary endpoint of the study was clinical and laboratory parameters after completion of therapeutic apheresis procedures. The secondary endpoint was the duration of pregnancy prolongation and gestational age at birth. The third endpoint was early neonatal and maternal outcomes (Fig. 1).

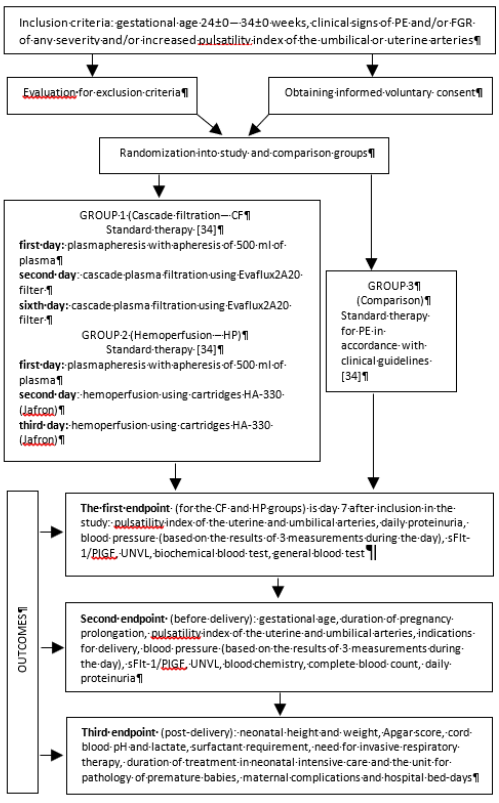

Fig. 1. Study design

The source information was stored and systematized in Microsoft Office Excel 2010 spreadsheets. Statistical analysis of the data obtained during the study was performed using MedCalc® Statistical Software version 19.6.3 (MedCalc Software Ltd, Ostend, Belgium; https://www.medcalc.org; 2021). For all statistical tests, a two-sided alpha level of $p<0.05$ was used. Due to the small number of the study groups, the distribution was not tested for normality; the distribution in the groups was considered to be different from normal. Nonparametric tests were used in statistical analysis. Descriptive statistics are presented as median (M) and 25th–75th quartiles (Q_{25} and Q_{75}). Comparison of independent groups by numerical indicators was performed using the Kruskal–Wallis test (in the case of three groups) and the Mann–Whitney U-test (in the case of two groups). For comparison of related samples of numerical indicators (comparison between different stages of the study in the same group), the Friedman test (in the case of several samples) and the Wilcoxon signed-rank test (for two samples) were used. For the analysis of qualitative features, the Pearson's chi-squared test and the McNemar test were used. The Holm–Bonferroni method was used to control the group probability of error in multiple comparisons.

After allocation to the study groups, all patients underwent therapy and examination in accordance with clinical guidelines, which included a three-step administration of antihypertensive drugs, prevention of fetal RDS, and administration of magnesium sulfate to prevent maternal convulsions and provide fetal neuroprotection [34]. On the first day, patients from the CF and HP groups underwent low-volume plasmapheresis; the volume of non-selective plasma apheresis was no more than 10% of the circulating plasma volume. Plasmapheresis was performed to assess the viability of venous access and improve the rheological properties of blood. In accordance with the study design, on the 2nd and 6th days after inclusion in the study, cascade filtration was performed in the CF group using a PFM-500 membrane plasma filter (Plazmo-filter JSC) and an Evaflux 2A20 fractionator (SB-Kawasumi Laboratories, INC., Japan). The volume of processed autoplasma in two sessions was 4810 (3250; 5680) ml. In the HP group on the same days as in the previous group, HP was performed using a hemoperfusion cartridge based on cross-linked styrene-divinylbenzene copolymers Jafron 330 (Jafron Bi-omedical Co., Ltd., China). The perfusion volume was 18460 (16890; 21350) ml in two sessions. Therapeutic apheresis procedures were performed using a GEMMA device (Plazmo-filter JSC). In the Comparison group, PE therapy, and clinical and

laboratory monitoring were performed in accordance with clinical recommendations [34]. Obstetric tactics and timing of delivery were determined based on the dynamics of clinical and laboratory manifestations of PE and the antenatal state of the fetus.

All pregnant women were examined upon inclusion in the study (stage 1). At this stage, the examination included the assessment of blood pressure (based on the results of 3 measurements during the day); sFlt-1/PIGF (the level of PIGF and sFLT-1 (VEGFR1) in the serum of patients was detected using commercial enzyme immunoassay kits SEA114Hu "PLGF" and SEB818Hu "VEGFR1" Cloud-Clone Corp (Houston, TX, USA) in accordance with the manufacturer's protocol); neutrophil extracellular trap (NET) level [35]; biochemical blood test; daily proteinuria level; complete blood count; pulsatility index of the uterine and umbilical arteries. The second stage corresponded to the first endpoint of the study, at this stage patients from groups 1 and 2 (CF and HP) were examined. The third and fourth stages of the study corresponded to the second and third endpoints and included patients from all groups (see Fig. 1).

The study was approved by the Ethics Committee of the Federal Research and Clinical Center of Resuscitation and Rehabilitation (Protocol No. 1/25/18 dated 02/07/2025).

STUDY RESULTS

All the patients were diagnosed with severe PE (ICD code: O14.1) upon inclusion in the study based on clinical and laboratory data. Analysis of concomitant diseases did not reveal statistically significant intergroup differences in nosological forms of concomitant diseases (Table 2).

As can be seen from Table 2, the most frequent concomitant diseases aggravating the course of PE were lipid metabolism disorder and chronic arterial hypertension, which were diagnosed in more than 30% of cases in all groups. According to modern concepts, these diseases play an important role in the pathogenesis of PE, since they can contribute to the progression of endothelial dysfunction. For example, acute atherosis of the placental vasculature during pregnancy complicated by PE is similar to atherosclerosis [36]. Endothelial dysfunction plays an important role in the pathophysiology of coronary heart disease, as well as in PE. Thus, PE may be the result of cardiovascular dysfunction, which is manifested by insufficient adaptation of the cardiovascular system aimed at satisfying the increased metabolic needs of pregnancy [37, 38].

A significant place in the structure of concomitant pathology is occupied by diabetes mellitus, diseases of the genitourinary and digestive systems, as well as the thyroid gland. At the same time, anemia, autoimmune diseases, and myopia were rare in the studied group of patients. Most patients included in the study had at least two concomitant diseases that could contribute to the progression of severe PE and decompensation of multiple organ failure (MOF). However, the absence of statistically significant intergroup differences in concomitant pathology allows us to consider the groups representative in this regard.

The groups were also comparable in terms of age, body mass index (BMI) and gestational age at inclusion in the study (Table 3).

At inclusion in the study, patients in the Comparison group had statistically significantly higher DBP compared to patients in the CF group (see

Table 2

Intragroup distribution by nosological forms of concomitant diseases

Diagnosis, *n* (%)	Pearson's χ^2 (p)	CF (n=16)	HP (*n*=16)	Comparison (*n*=26)	Total (*n*=58)
Lipid metabolism disorder I, II, III degree	0.739 (0.612)	7 (44)	6 (37.5)	8 (30.8)	21 (36.2)
Chronic arterial hypertension	1,993 (0.369)	8 (50)	4 (25)	8 (30.8)	20 (34.5)
Diseases of the genitourinary system	0.518 (0.771)	6 (37.5)	5 (31.3)	7 (26.9)	18 (31.3)
Diabetes mellitus (including gestational one)	4.165 (0.125)	7 (43.8)	4 (25)	4 (15.4)	15 (25.9)
Thyroid diseases	1.475 (0.478)	3 (18.8)	3 (18.8)	1 (3.8)	7 (12.1)
Diseases of the digestive system	5.178 (0.075)	4 (25)	1(6.3)	1 (3.8)	6 (10.3)
Mild anemia	0.046 (0.997)	1 (6.3)	1 (6.3)	2 (7.7)	4 (6.9)
Myopia	1.247 (0.536)	1 (6.3)	–	2 (7.7)	3 (5.2)
Autoimmune diseases	1.683 (0.431)	1 (6.3)	1 (6.3)	–	2 (3.4)
Varicose veins, complicated	2.671 (0.263)	1 (6.3)	–	–	1 (1.7)
Arrhythmia	2.671 (0.263)	–	1 (6.3)	–	1 (1.7)
Total	2754 (0252)	39 (243)	26 (162.5)	33 (127)	98 (169)

Table 3

Intergroup comparison of main baseline parameters

Parameter	Groups			Kruskal-Wallis test
	CF, n=16	HP, n=16	Comparison, n=26	
Age, years	34 (29; 38)	33.5 (29; 35)	33.5 (27; 37)	0.650
BMI, kg/m2	33.3 (27.9; 37.5)	29.9 (25.4; 33.5)	30.9 (27.2; 33.1)	0.407
Gestational age at inclusion in the study, weeks	28.6 (26.5; 31.1)	31 (27.7; 32.1)	30.2 (28.3; 39)	0.165
SBP, mmHg	150 (140; 162.5)	160 (140;166.5)	160 (150; 178)	0.169
DBP, mmHg	90 (82.5; 95)*	90 (87.5; 100)	100 (95; 100)*	0.006
Proteinuria, g/l	1.3 (0.4; 3.0)	0.3 (0.1; 1)	2 (0.5; 3)	0.052
Platelets, 10^9/l	204 (166.5; 270.5)	215.5 (196.5; 243)	230.5 (153; 281)	0.920
Erythrocytes, 10^{12}/l	4.07(3.84; 4.28)	4.08 (3.7; 4.36)	4.0 (3.7; 4.3)	0.595
Hemoglobin, g/l	120 (106.5; 128)	114.5 (109; 123.5)	120.5 (109; 126)	0.858
Leukocytes, 10^9/l	9.4 (7.6; 12.4)	9.9 (7.2; 11.3)	9.4 (7.9; 10.9)	0.928
Proteinemia, g/l	59.3 (54.9; 65.8)	62.2 (54.2; 67.1)	55.9 (53.5; 62)	0.194
Albuminemia, g/l	31.2 (29.1; 34.9)	32.3 (30.6; 34.3)	31.3 (29; 32.8)	0.566
Bilirubin, mmol/l	5.8 (4.5; 8.4)	6.4 (4.3; 8.2)	4.3 (3.4; 6)**	0.019
ALT, IU/l	17.5 (12.4; 31.6)	14.7 (11.1; 24.9)	20.3 (15; 24.5)	0.319
AST, IU/l	24.9 (19.6; 34.3)	21.5 (17.8; 27.5)	21.3 (19; 24.9)	0.423
LDH, IU/l	394 (345; 422.3)	305 (265.5; 361.5)**	413.5 (337; 480)	0.006
Alkaline phosphatase, IU/l	216 (167.3; 280)	213 (187.5; 242)	292.5 (223; 326)**	0.005
Creatinine, μmol/l	76 (58.3; 89)	65 (59.5; 71.5)	72.5 (62; 80)	0.178
Urea, mmol/l	4.8 (3.5; 5.4)	2.9 (2.3; 4.8)	4.3 (3.7; 5.5)	0.202

Notes: * - p <0.017 between groups; Mann–Whitney U test with Bonferroni correction; ** - p <0.017 compared with other groups; Mann–Whitney U test with Bonferroni correction; ALT — alanine aminotransferase; AST — aspartate aminotransferase; DBP — diastolic blood pressure; BMI — body mass index; LDH — lactate dehydrogenase; SBP — systolic blood pressure

Table 3). In patients from the HP group, the LDH level was statistically significantly lower at baseline than in the other two groups. On the other hand, the bilirubin concentration in the Comparison group was statistically significantly lower than in the other two groups. At the same time, the values of the listed parameters did not exceed the reference values. All the patients had proteinuria at inclusion in the study, which did not differ statistically significantly between the groups. There were no statistically significant intergroup differences in the initial levels of total plasma protein and albuminemia, but in all three groups the mean group values of these parameters were below the reference values for this gestational age. Thus, the laboratory data of the patients at inclusion in the study confirmed the diagnosis of PE, and the identified intergroup differences had no clinical significance, and could not affect the results of the study.

The use of therapeutic apheresis methods in pregnant women in both the CF and HP groups allowed prolonging pregnancy to 34.1 (29.6; 36.0) and 34.3 (33.5; 36.8) weeks, respectively; which is statistically significantly longer than in the Comparison group, in which the average term of delivery was 31.4 (29.4; 33.5) weeks. The duration of pregnancy prolongation was statistically significantly longer in the study groups, and amounted to 32.5 (5.5; 42.5) days in the CF group and 26.5 (8; 52) days in the HP group, while in the Comparison group it was 5.5 (2; 7) days (Fig. 2).

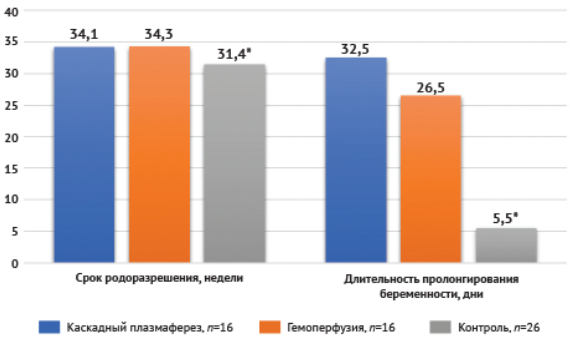

Fig. 2. Intergroup comparison of the timing of delivery and duration of pregnancy prolongation (* — p<0.017 compared with other groups, Mann–Whitney U test with Bonferroni correction)

Table 4

Intergroup comparison by timing of delivery

Timing of delivery	Groups, *n* (%)			Pearson's χ^2
	CF, n (%)	HP, n (%)	Comparison, n (%)	
Full-term pregnancy (more than 37 weeks)	3 (18.75)	4 (25)	2 (7.7)	χ^2=12.511 p=0.014
Late preterm pregnancy (34.0–36.6 weeks)	7 (43.75)	5 (31.25)	2 (7.7)	
Early preterm pregnancy (<34 weeks)	6 (37.5)	7 (43.75)	22 (84.6)*	

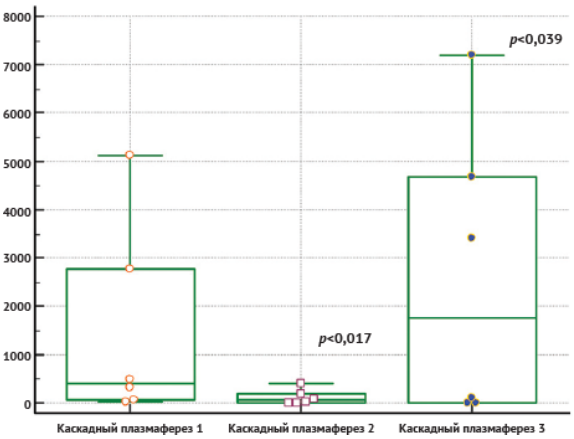

Fig. 3. Dynamics of the sFlt-1/PlGF ratio at the stages of the study in the cascade plasma filtration group (Friedman test, Wilcoxon signed-rank test with Bonferroni correction)

At inclusion in the study, patients in the Comparison group had statistically significantly higher DBP compared to patients in the CF group (see Table 3). In patients from the HP group, the LDH level was statistically significantly lower at baseline than in the other two groups. On the other hand, the bilirubin concentration in the Comparison group was statistically significantly lower than in the other two groups. At the same time, the values of the listed parameters did not exceed the reference values. All the patients had proteinuria at inclusion in the study, which did not differ statistically significantly between the groups. There were no statistically significant intergroup differences in the initial levels of total plasma protein and albuminemia, but in all three groups the mean group values of these parameters were below the reference values for this gestational age. Thus, the laboratory data of the patients at inclusion in the study confirmed the diagnosis of PE, and the identified intergroup differences had no clinical significance, and could not affect the results of the study.

The use of therapeutic apheresis methods in pregnant women in both the CF and HP groups allowed prolonging pregnancy to 34.1 (29.6; 36.0) and 34.3 (33.5; 36.8) weeks, respectively; which is statistically significantly longer than in the Comparison group, in which the average term of delivery was 31.4 (29.4; 33.5) weeks. The duration of pregnancy prolongation was statistically significantly longer in the study groups, and amounted to 32.5 (5.5; 42.5) days in the CF group and 26.5 (8; 52) days in the HP group, while in the Comparison group it was 5.5 (2; 7) days (Fig. 2).

However, by the time of delivery, the sFlt-1/PlGF index increased again, not differing from the initial value during this period. In contrast to the CF group, in the group of patients who received HP sessions, no statistically significant decrease in the sFlt-1/PlGF ratio was observed (Fig. 4).

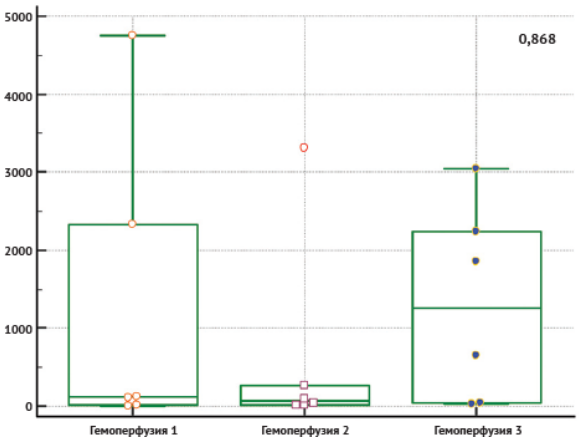

Fig. 4. Dynamics of the sFlt-1/PlGF ratio at the stages of the study in the hemoperfusion group (Friedman test)

Opposite data were obtained when assessing NET level after the use of therapeutic apheresis methods. In the group of patients who received CF sessions, there was no statistically significant reduction in NETs (Fig. 5).

By the time of delivery, in the CF group, the NET level increased even more, and was statistically significantly higher compared to the initial value. In contrast to the CF group, in the HP group, after sessions of therapeutic apheresis, there was a statistically significant stable decrease in this indicator. By the time of delivery, the NET level in this group did not differ from the initial value (Fig. 6).

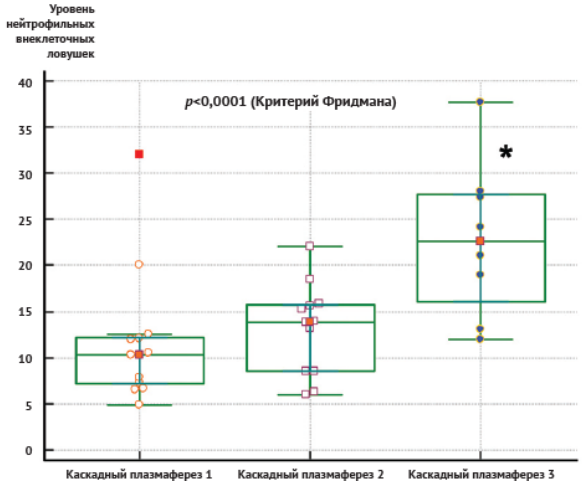

Fig. 5. Dynamics of the neutrophil extracellular traps (NETs) level in the cascade plasma filtration group at the stages of the study (Friedman test, *— p <0.017 — Wilcoxon signed-rank test with Bonferroni correction)

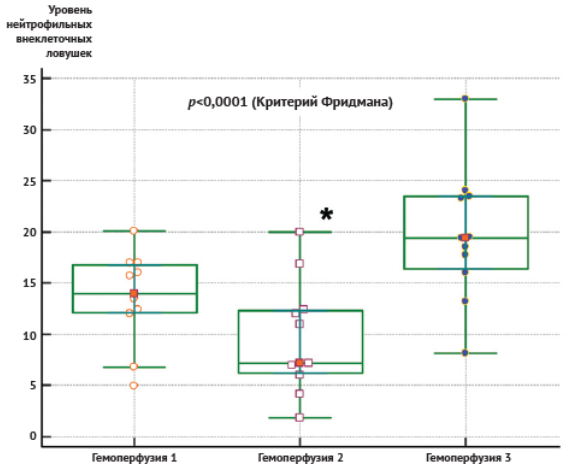

Fig. 6. Dynamics of the NETs level in the hemoperfusion group at the stages of the study (Friedman test, * — p <0.017 — Wilcoxon signed-rank test with Bonferroni correction)

By delivery, a statistically significant increase in the sFlt-1/PlGF ratio was noted in all groups, which was more pronounced in the Comparison group (Table 5). The NET level increased statistically significantly in the Comparison group and in the group of patients who received CF sessions. It should be noted that in the Comparison group the term of delivery was statistically significantly lower than in the other two groups. According to modern concepts, the NET level should increase with increasing gestational age, since neutrophil activation is a component of the mechanism that initiates labor [39]. Thus, we can speak about more pronounced neutrophil activity in the Comparison group. In the group of patients who received HP sessions, the NET level before delivery was statistically significantly lower compared to other groups.

In contrast to specific PE markers, no statistically significant intergroup differences were found for most of the studied clinical and laboratory parameters before delivery (Table 6).

As in the first stage of the study, significant intergroup differences in LDH levels (statistically significantly lower in the HP group) and alkaline phosphatase levels (statistically significantly higher in the Comparison group) remained. The higher DBP in the Comparison group noted at inclusion in the study decreased statistically significantly (p=0.008; Wilcoxon test). Before delivery, higher values of DBP were noted in the HP group compared to the CF group (p=0.003), although this indicator did not change statistically significantly in the dynamics of the HP group. However, the clinical significance of such intergroup differences is valueless, since they are isolated and multidirectional.

Table 5

Dynamics of severe preeclampsia markers

Parameter		Group			Kruskal-Wallis test
		CF, n=16	HP, n=16	Comparison, n=26	
sFlt-1/PlGF	Before treatment (Stage I)	401.9(66; 2775)	113.8(106; 2325)	536(144.5;4937.5)	0.863
	Before delivery (stage III)	1756.8 (4.4; 4687.5)**	1250.7 (41; 2238)**	4128 (8.6; 9389.4)*, **	0.038
NET level	Before treatment (Stage I)	10.3(7.2; 12.2)	13.5(10.4; 16.8)	14.7(9.1; 18)	0.266
	Before delivery (stage III)	22.6 (16.1; 27.7)**	18.1(7.8; 23.4)*	19.1(16.9; 25.8)**	0.003

Notes: * — p<0.017 (Mann-Whitney U test with Bonferroni correction); ** — p<0.017 (Wilcoxon signed-rank test with Bonferroni correction)

Table 6

Comparison of indicators before delivery

Parameter	Groups			Kruskal-Wallis test
	CF, n=16	HP, n=16	Comparison, n=26	
SBP, mmHg	137.5 (133.5; 156)	160 (140; 170)	150 (140; 160)	0.110
DBP, mmHg	87.5 (80; 95) *	100 (90; 110)*	90 (90; 100)	0.033
Proteinuria, g/l	1 (0.35; 3)	0.5 (0.2; 3)	3 (1; 3)	0.137
Platelets, 10^9/l	192 (169.5; 248.5)	207 (167.5; 227.5)	204.5 (142; 221)	0.661
Erythrocytes, 10^{12}/l	3.87 (3.78; 4.07)	3.88 (3.56; 4.13)	4.01 (3.59; 4.18)	0.918
Hemoglobin, g/l	116 (106.3; 128.3)	110 (106.3; 118.8)	115 (105.5; 125.8)	0.556
Leukocytes, 10^9/l	10.8 (8.6; 14.9)	9.4 (7.4; 10.8)	9.9 (8.1; 11.6)	0.261
Proteinemia, g/l	53.1 (47.9; 56.8)	57.2 (52.2; 63.2)	52.8 (49.5; 54.5)	0.746
Albuminemia, g/l	28.3 (27.1; 29.9)	31 (29.5; 33.3)	28.4 (27.5; 29.6)	0.097
Bilirubin, mmol/l	6.2 (4.8; 9.7)	4.6 (6.0; 6.7)	5.2 (3.7; 8)	0.426
ALT, IU/L	19.9 (14.3; 26.6)	16.2 (10.7; 18.3)	20 (15.6; 29.9)	0.062
AST, IU/L	25.7 (19.3; 35.1)	23.1 (18.5; 28.3)	25.9 (22.7; 35.6)	0.554
LDH, IU/l	474 (329,5; 529,3)	326 (258,3; 428)**	484 (411; 635)	0,001
Alkaline phosphatase, IU/L	203 (182; 223,3)	229 (193,5; 289)	310 (215; 370) **	0,003
Creatinine, μmol/l	81 (69,3; 100,3)	76 (60,5; 84,5)	75 (68; 92)	0,192
Urea, mmol/l	4,1 (3,5; 5,5)	4,1 (2,9; 6,7)	5,5 (4,1; 6,7)	0,259

Notes: * – p<0.017 between groups; Mann–Whitney U test with Bonferroni correction; ** – p<0.017 compared with other groups; Mann–Whitney U test with Bonferroni correction; ALT — alanine aminotransferase; AST — aspartate aminotransferase; DBP — diastolic blood pressure; BMI — body mass index; LDH — lactate dehydrogenase; SBP — systolic blood pressure

More significant differences from the clinical point of view were revealed when assessing the intragroup dynamics of laboratory parameters. In contrast to the study groups, the Comparison group showed a statistically significant increase in the levels of ALT (p=0.048), AST (p=0.012), LDH (p=0.002), and alkaline phosphatase (p=0.002). Figures 7–9 show the dynamics of liver function indicators in the CF, HP and Comparison groups upon inclusion in the study and before delivery, depending on the duration of pregnancy prolongation.

Taking into account the duration of observation, the analysis of intragroup dynamics of laboratory data revealed a statistically significant deterioration in liver function in the Comparison group compared with the therapeutic apheresis groups.

Fig. 7. Dynamics of liver function indicators in the cascade plasma filtration group (Wilcoxon signed-rank test)

Notes: АЛТ — alanine aminotransferase; АСТ — aspartate aminotransferase; ЛДГ — lactate dehydrogenase; ЩФ — alkaline phosphatase

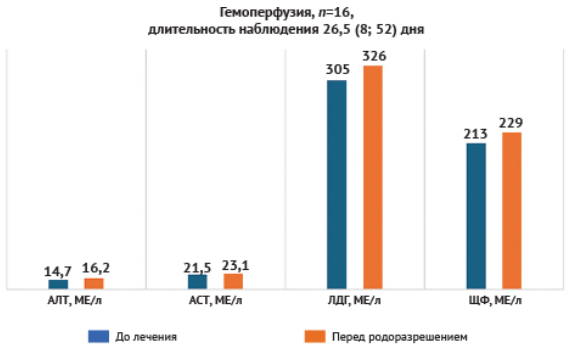

Fig. 8. Dynamics of liver function indicators in the hemoperfusion group (Wilcoxon signed-rank test)

Notes: АЛТ — alanine aminotransferase; АСТ — aspartate aminotransferase; ЛДГ — lactate dehydrogenase; ЩФ — alkaline phosphatase

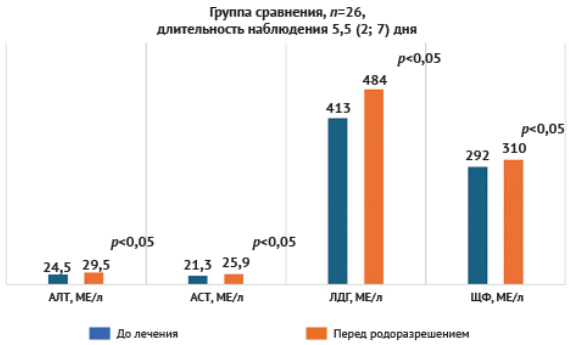

Fig. 9. Dynamics of liver function indicators in the comparison group (Wilcoxon signed-rank test)

Notes: АЛТ — alanine aminotransferase; АСТ — aspartate aminotransferase; ЛДГ — lactate dehydrogenase; ЩФ — alkaline phosphatase

In the CF group (see Fig. 7), a statistically significant increase in the lactate dehydrogenase (LDH) level was also noted during the observation period; however, in this group the duration of observation was statistically significantly longer than in the Comparison group. No increase in other studied liver function indices was observed over time in the CF group. In the HP group, liver function indices remained stable throughout the observation period (Fig. 8). Such intragroup dynamics of liver functional activity parameters indicate rapid progression of its dysfunction in the Comparison group against the background of standard PE therapy.

The dynamics of renal function parameters also indicate a more rapid deterioration during standard therapy (Fig. 10).

Fig. 10. Intragroup dynamics of renal function indicators depending on the duration of pregnancy prolongation (Wilcoxon signed-rank test)

In contrast to the study groups, in the Comparison group, with a statistically significantly shorter term of pregnancy prolongation, an increase in the level of creatinine and urea is noted. Rapidly progressive deterioration of renal function is evidenced by a statistically significant increase in the level of proteinuria over a short observation period in the Comparison group, in contrast to the therapeutic apheresis groups (Fig. 11).

Fig. 11. Dynamics of protein metabolism indicators during observation (Wilcoxon signed-rank test)

Rapid progression of kidney damage in the Comparison group was accompanied by a statistically significant loss of the protein fraction of the blood. Such dynamics over a short observation period also additionally confirms the development of liver failure with a decrease in synthetic function. In the therapeutic apheresis groups, a statistically

significant decrease in the level of protein fractions in the blood by the time of delivery was also noted. However, taking into account the duration of pregnancy prolongation, the absence of laboratory signs of MOF progression, these changes can be considered clinically insignificant. The decrease in total protein and albumin concentrations in the therapeutic apheresis groups may be due to hemodilution associated with the maximum increase in circulating blood volume in the third trimester of pregnancy.

Despite the fact that the comparison of clinical blood test parameters did not reveal statistically significant intergroup differences at the stages of the study, intragroup comparison over time revealed significant changes in individual parameters in all study groups (Table 7). In the group of patients who underwent CF and HP for the purpose of prolonging pregnancy, a statistically significant decrease in the number of erythrocytes was noted; and in the HP group it was accompanied by a decrease in the hemoglobin level.

The number of red blood cells and the level of hemoglobin in patients from the therapeutic apheresis groups did not go beyond the reference values for the third trimester of pregnancy by the time of delivery. The decrease in the number of erythrocytes and hemoglobin in patients from these groups can be associated with a statistically significantly longer period of pregnancy prolongation from inclusion in the study compared to the Comparison group, and a physiological decrease in these parameters against the background of hemodilution. In contrast to the therapeutic apheresis groups, despite the short observation period, the Comparison group showed a statistically significant decrease in the platelet count, which can also be regarded as a sign of progression of PE severity. No changes in the level of leukocytes were observed during the observation period in any of the groups.

The use of therapeutic apheresis methods allowed statistically significant and safe prolongation of pregnancy without deterioration of the uteroplacental blood flow. When the patients were included in the study groups (stage I), no intergroup differences were found in the incidence of uterine blood flow abnormalities, assessed by the pulsation index of the uterine artery. By the time of delivery (stage III), the incidence of uteroplacental blood flow abnormalities in the Comparison group was statistically significantly higher than in the other two groups (Table 8).

Table 7

Intragroup dynamics of clinical blood test parameters

Parameter		Group		
		CF, n=16	HP, n=16	Comparison, n=26
Platelets,10^9/l	Before treatment	204 (166.5; 270.5)	215.5 (196.5; 243)	230.5 (153;281)*
	Before delivery	192 (169.5; 248.5)	207 (167.5; 227.5)	204.5 (142;221)*
Erythrocytes, 10^{12}/l	Before treatment	4.07 (3.84; 4.28)*	4.08 (3.7; 4.36)*	4.0 (3.7; 4.3)
	Before delivery	3.87 (3.78; 4.07)*	3.88 (3.56; 4.13)*	4.01 (3.59; 4.18)
Hemoglobin, g/l	Before treatment	120 (106.5; 128)	114.5 (109; 123)*	120.5 (109; 126)
	Before delivery	116 (106.3; 126.3)	110 (106.3; 118.8)*	115 (105.5; 125.8)
Leukocytes,10^9/l	Before treatment	9.4 (7.6; 12.4)	9.9 (7.2; 11.3)	9.4 (7.9; 10.9)
	Before delivery	10.8 (8.6; 14.9)	9.4 (7.4; 10.8)	9.9 (8.1; 11.6)

Notes: * — p<0.05, Wilcoxon signed-rank test

Table 8

Incidence of uteroplacental blood flow abnormalities at the stages of the study

Group	Stage I		χ^2 (Pearson), p	Stage II		χ^2 (Pearson), p
	Abnormalities	No abnormalities		Abnormalities	No abnormalities	
CF, n=16	10	6	2.351 *p*=0.308	6	10	9.014 *p*=0.011
HP, n=16	6	10		6	10	
Comparison, n=26	15	11		20*	6*	

Notes: * — p<0.017 compared with other groups, Pearson's chi-square test

At the same time, when studying the intragroup dynamics of changes in uterine blood flow, no statistically significant differences were obtained at the time of delivery (Table 9).

Table 9

Comparative analysis of intragroup dynamics of uteroplacental blood flow

Group	McNemar's test	95% CI for the difference in relative frequencies
CF, n=16	0.219	-0.52; 0.24
HP, n=16	1.00	-0.24; 0.24
Comparison, n=26	0.226	-0.04; 0.43

Note: CI – confidence interval

More significant changes were revealed in the study of fetal blood flow. With an initial absence of differences in the incidence of increase in the pulsatility index of the umbilical artery, this indicator statistically significantly increased compared to the initial value in the Comparison group, and was higher than in the other two groups before delivery (Tables 10, 11).

Thus, the use of therapeutic apheresis in patients with early-onset PE allowed prolongation of pregnancy without deterioration of fetal blood flow; whereas the use of standard therapy not only failed to prevent the progression of fetal blood flow abnormalities, but also, against the background of a decrease in systemic arterial pressure, led to their progression. The main indications for delivery in the Comparison group, in contrast to patients in the therapeutic apheresis groups, were indications from the fetus (Table 12).

The indication for emergency delivery was statistically more often deterioration of the fetal condition in the Comparison group compared to the CF group - OR (odds ratio) 6.75 95% CI (confidence interval) [1.65; 27.5], p = 0.007. The frequency of delivery in the HP group due to indications on the part of the fetus compared to the Comparison group was 2.89 times less frequent, but did not reach a statistically significant difference, OR 2.89 95% CI [0.79; 10.53], p = 0.107. There were also no differences in indications for delivery between the CF group and the HP group: OR 0.42 95% CI [0.09; 1.92], p=0.268.

Table 10

Incidence of fetal blood flow abnormalities at the stages of the study

Group	Stage I		χ^2 (Pearson), p	Stage II		χ^2 (Pearson), p
	Abnormalities	No abnormalities		Abnormalities	No abnormalities	
CF, n=16	7	9	5.401 *p*=0.292	3	13	9.014 *p*=0.011
HP, n=16	2	14		3	13	
Comparison, n=26	1	14		17*	9*	

Notes: * — p <0.017 compared with other groups, Pearson's chi-square test

Table 11

Comparative analysis of intragroup dynamics of fetal blood flow

Group	McNemar's test	95% CI for the difference in relative frequencies
CF, n=16	0.218	-0.52; 0.02
HP, n=16	1.00	-0.14; 0.27
Comparison, n=26	0.012	0.07; 0.37

Note: CI – confidence interval

Table 12

Comparative analysis of indications for emergency delivery

Group	Indications for delivery		χ^2 (Pearson), p
	From the mother	From the fetus	
CF, n=16	12	4	8.096 *p*=0.017
HP, n=16	9	7	
Comparison, n=26	8	18*	

No statistically significant intergroup differences in the height and weight of children at birth were found (Table 13).

There were also no statistically significant differences between the groups in the severity of fetal acidosis at birth, and the resuscitation assessment according to the Apgar scale at 5 minutes after birth. The resuscitation assessment of newborns in the first minute was statistically significantly higher in the CF group compared to the Comparison group. More pronounced differences were revealed in a comparative analysis of the duration of treatment in the neonatal intensive care unit (NICU) and in the department of pathology of premature babies (DPPB): newborns in the Comparison group required a statistically significantly longer duration of treatment in these departments compared to the other groups.

An important indicator of the fitness of the respiratory system at birth is the newborn's need for surfactant and invasive respiratory therapy.

In the groups of patients who prolonged pregnancy by performing CF and HP procedures, the newborns' need for surfactant at birth was statistically significantly lower than in the Comparison group (Fig. 12).

No statistically significant differences in the surfactant requirements of newborns were found between the CF and HP groups.

No statistically significant intergroup differences were found in the duration of invasive respiratory therapy for newborns (Fig. 13).

Table 13

Comparative analysis of neonatal outcomes

Parameter	Groups			Kruskal-Wallis test
	CF, n=16	HP, n=16	Comparison, n=26	
Apgar 1	7 (6; 7) *	6 (6; 7)	6 (5; 6.25) *	0.049
Apgar 5	8 (7; 8)	7.5 (7; 8)	7 (7; 8)	0.146
Height, cm	41 (33.5; 45)	42 (39.3; 45.8)	40 (34.8; 42)	0.404
Weight, g	1650 (952.5; 2162.5)	1700 (1332.5; 2137.5)	1400 (1090; 1770)	0.436
pH a. umbilicalis	7.32 (7.29; 7.39)	7.28 (7.42; 7.32)	7.32 (7.22; 7.38)	0.160
Lactate, mmol/l	2.3 (1.2; 3.68)	1.6 (1.2; 2.7)	2.8 (1.6; 4.2)	0.125
NICU, bed/days	5 (0.5; 12)	5 (2.25; 11.5)	12 (8.5; 16.8)**	0.019
DPPB, bed/days	7 (0; 13.5)	8 (0; 16.5)	15 (7.0; 22)**	0.046

Notes: * - p <0.017 between groups; Mann-Whitney U test with Bonferroni correction;** - p <0.017 compared with other groups; Mann-Whitney U test with Bonferroni correction; NICU – neonatal intensive care unit; DPPB – department of pathology of premature babies

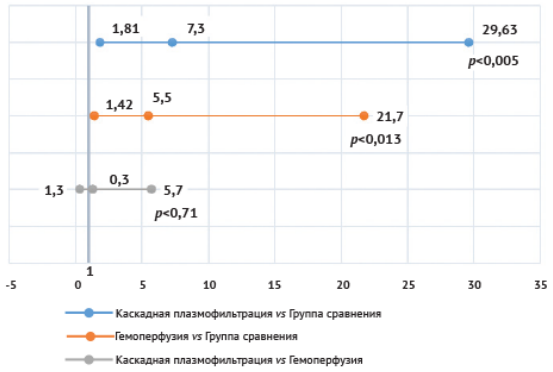

Fig. 12. Comparative intergroup assessment of surfactant requirements (confidence interval for the odds ratio)

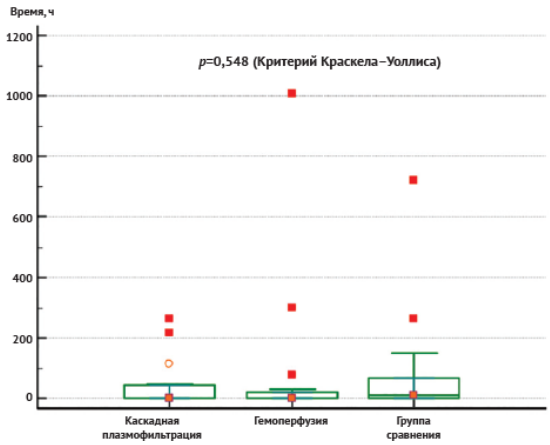

Fig. 13. Between-group comparison of invasive respiratory therapy duration in neonates

However, from a clinical point of view, the duration of invasive respiratory therapy in the Comparison group was longer (Table 14).

Table 14

Duration of invasive respiratory therapy in newborns, hours

Groups	Q_{25}	*Me*	Q_{75}	*Max*
CF, n=16	0	0	44	264
HP, n=16	0	0	18.5	1008
Comparison, n=16	0	10.5	65	720

In the group of patients who underwent standard therapy for early-onset PE before delivery, 3 cases of purulent-septic complications in the postpartum period were registered: 2 cases of postpartum endometritis, and 1 case of seroma of the postoperative suture. In the therapeutic apheresis groups, no complications were observed in the postoperative period. The hospital bed-day in the postpartum period in patients from the CF and HP groups was statistically significantly less than 5 (5; 6) days, p=0.0002 and 5 (4; 6.5) days, p=0.008, respectively, compared to the Comparison group - 7 (6; 7) days.

DISCUSSION

Based on the obtained results, it is possible to speak about the possibility of safe prolongation of pregnancy in early-onset preeclampsia using therapeutic apheresis of such pathogenetically significant factors of preeclampsia as soluble fms-like tyrosine kinase-1 (sFlt-1) and neutrophil extracellular traps, the accumulation of which leads to the progression of endothelial dysfunction and the development of preeclampsia. Previously conducted pilot studies have shown the potential of various therapeutic apheresis options for prolonging pregnancy in early-onset preeclampsia. In all the cases, the authors associated the positive effects with the elimination of pathological molecules that cause endothelial damage. For example, Y. Wang et al. in 2006 published the results of a comparative study of the use of apheresis of very low density lipoproteins in patients with early development of preeclampsia, which showed that the removal of their various fractions was accompanied by a decrease in inflammatory activity, blood viscosity, and contributed to the prolongation of pregnancy by 17.7 (3–49) days [25]. The assumption about the possibility of prolonging pregnancy in early-onset preeclampsia by removing lipoproteins is based on the fact that the development of early-onset preeclampsia is associated with significant changes in the lipid profile. The lipid profile takes on an atherogenic phenotype with an increase in triglycerides, low-density lipoproteins, and very low-density lipoproteins [40–45]. Currently, it has been proven that high triglyceride levels correlate with the severity of preeclampsia [46, 47]. In our study, we did not perform lipid profile analysis before and after therapeutic apheresis, but taking into account the characteristics of the Evaflux 2A20 fractionator used in the study, the pore size of which allows large molecules with a molecular weight of more than 90 Da to be retained, we assume that larger lipoprotein molecules were also removed along with sFlt-1. K. Winkler et al. (2018) suggested that endothelial dysfunction and fetoplacental disorders in early-onset preeclampsia were associated with activation of lipid peroxidation and impaired low-density lipoprotein metabolism. The use of cascade filtration using heparin-induced lipoprotein precipitation in 6 pregnant women with early-onset preeclampsia at a gestational age of 24–27 weeks allowed us to prolong pregnancy by up to 15 days, which was statistically significant compared to the Comparison group - 6.3 days (p = 0.027). The content of triglycerides, cholesterol, low-density lipoproteins and very low-density lipoproteins in the main group was reduced by more than 40%. At the same time, the authors did not reveal a statistically significant decrease in sFlt-1 [28]. On the other hand, R. Thadhani et al. (2011; 2016) showed a significant decrease in sFlt-1, and a significant prolongation of pregnancy, depending on the number of cascade filtration procedures performed using a dextran sulfate-based fractionator. In this study, the researchers also managed to statistically significantly reduce the duration of respiratory therapy in neonates [26, 27]. In our study, when using cascade filtration with the Evaflux 2A20 fractionator, we also noted a statistically significant decrease in the sFlt-1 level after the completion of 2 procedures, in contrast to hemoperfusion. Subsequently, the concentration of sFlt-1 increased again to the initial level; however, the removal of this antiangiogenic factor and, possibly, atherogenic lipoproteins, allowed prolonging pregnancy by 32.5 (5.5; 72.5) days, and improving neonatal outcomes: statistically significantly, compared with the Comparison group, reducing the need for surfactant, the number of intensive care bed days, and the duration of treatment in the department of pathology of premature babies.

In contrast to cascade filtration, hemoperfusion was not accompanied by a decrease in sFlt-1. Nevertheless, we achieved pregnancy prolongation by 26 (8; 52) days without deterioration of

uteroplacental and fetal blood flow, a significant decrease in the need of newborns for surfactant, duration of treatment in neonatal intensive care, and the department of premature babies. This result is probably associated with the elimination of neutrophil extracellular traps, the decrease in the level of which was statistically significant after hemoperfusion sessions, and remained statistically significantly lower than in the other groups by the time of delivery.

In addition to selective methods of therapeutic apheresis, attempts are being made to use plasma exchange with replacement by donor plasma to prolong pregnancy in early-onset preeclampsia. A. Iannaccone et al. (2023) published the results of the largest single-center study, in which 20 patients with early preeclampsia and a gestational age of 23.75±2.26 weeks underwent 95 sessions of therapeutic plasma exchange. Unfortunately, the authors did not indicate the volumes of plasma apheresis and plasma substitution. Comparison with the control group showed a decrease in the sFlt-1/PlGF ratio and another studied antiangiogenic factor, soluble endoglin (sEng). The duration of pregnancy in the treatment group was statistically significantly longer, and amounted to 8.25±5.97 days versus 3.14±4.57 days (p=0.004). The fetal survival rate after 25 weeks of gestation was 100%, while in the control group it was 88%. At birth before 25 weeks of gestation, neonatal mortality in the therapeutic plasma exchange treatment group was 63.6%, while in the control group it was 100% [31].

The major concern in early-onset preeclampsia is adverse neonatal outcomes. In a multicenter study conducted from 2008 to 2011 at 25 U.S. hospitals that included 8,334 preterm births (23.0–36.9 weeks of gestation), the neonatal mortality rate was 1.4%. Overall, 657 (7.9%) neonates had serious morbidity. Mortality was noted to decrease rapidly with each subsequent week of gestation. This decrease in mortality was accompanied by an increase in serious neonatal morbidity, which peaked at 54.8% at 25 weeks of gestation. As the incidence of mortality and serious neonatal morbidity decreased, minor neonatal morbidity increased, peaking at 81.7% at 31 weeks of gestation. The overall incidence rate began to decline only after the 32nd week of pregnancy. It was noted that among children born from 26 to 32 weeks, each additional week of pregnancy reduced the subsequent duration of hospitalization in neonatal intensive care by at least 8 days [22].

A comparative analysis of the incidence and outcomes of early- and late-onset preeclampsia by S. Lisonkova and K.S. Joseph (2013) showed that despite the fact that early-onset preeclampsia is significantly less common than late-onset preeclampsia – 0.38 and 2.72% of the total number of pregnancies, respectively, – it leads to a high risk of fetal death (OR 5.8, 95% CI [4.0–8.3] versus OR 1.3, 95% CI [0.8–2.0], respectively). The odds ratio for perinatal death/severe neonatal morbidity was 16.4, 95% CI [14.5–18.6] for early-onset preeclampsia and 2.0, 95% CI [1.8–2.3] for late-onset preeclampsia [23].

CONCLUSION

Each additional week of pregnancy increases neonatal survival while reducing the incidence of severe pathology, and the duration of hospitalization in neonatal intensive care. These data necessitate the search for methods of prolonging pregnancy as close to full-term pregnancy as possible that are safe for the mother.

As presented above, the safest and pathogenetically justified methods are probably therapeutic apheresis, among which the most promising are selective methods of removing certain molecules whose role was proven in the pathogenesis of preeclampsia. Such molecules include antiangiogenic factors (sFlt-1, sEng), products of neutrophil activation and destruction (neutrophil extracellular traps, intracellular neutrophil enzymes, inflammation mediators), and atherogenic lipoproteins. A large number of different sorption and filtration columns require further study from the point of view of the possibility of removing factors that contribute to the progression of preeclampsia.

FINDINGS

1. Cascade filtration and hemoperfusion statistically significantly reduce the concentration of sFlt-1 in the blood (p<0.017), and the level of neutrophil extracellular traps (p<0.017), respectively, and can significantly slow the progression of multiple organ failure in patients with early-onset preeclampsia.

2. The use of therapeutic apheresis in early-onset preeclampsia statistically significantly prevents the progression of uteroplacental and fetal blood flow abnormalities, in contrast to standard therapy (p=0.011).

3. The use of therapeutic apheresis methods allows for safe and statistically significant prolongation of pregnancy complicated by early development of preeclampsia to late preterm and early full-term terms in relation to the data of the Comparison group (p<0.017).

4. Therapeutic apheresis in early-onset preeclampsia statistically significantly improves the neonatal resuscitation assessment (p=0.049), reduces the need for surfactant (p=0.005 compared with the CF group, and p=0.013 compared with the

HP group), and the duration of treatment in the neonatal intensive care unit (p=0.019).

5. The use of therapeutic apheresis to prolong pregnancy in early-onset preeclampsia is not accompanied by complications during pregnancy and in the early postpartum period, and reduces the duration of hospitalization of the mother (p=0.008 compared with the CF group, and p=0.008 compared with the HP group, statistically significant in both cases).

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