https://doi.org/10.15360/1813-9779-2022-2-37-44

Pathogenetic Approach to Early Preeclampsia and the Feasibility of Pregnancy Prolongation

Larisa D. Belotserkovtseva[1,2], Liudmila V. Kovalenko[1]*, Valery V. Pankratov[2], Vadim N. Zinin[2]

[1] Surgut State University,
Lenin Str., Surgut 628400, Khanty-Mansiysk Autonomous District-Yugra, Russia
[2] Surgut District Clinical Center for Maternity and Childhood Protection,
1/2 Gubkin Str., Surgut 628415, Russia

For citation: *Larisa D. Belotserkovtseva, Liudmila V. Kovalenko, Valery V. Pankratov, Vadim N. Zinin.* Pathogenetic Approach to Early Preeclampsia and the Feasibility of Pregnancy Prolongation. *Obshchaya Reanimatologiya = General Reanimatology.* 2022; 18 (2): 37–44. http://doi.org/10.15360/1813-9779-2022-2-37-44 [In Russ. and Engl.]

Summary

Aim. To evaluate the efficacy of cascade plasma filtration (CPF) for the correction of lipid profile and biochemical markers (sFlt-1, PIGF, sFlt-1/PIGF) in pregnant women with early preeclampsia.

Materials and Methods. A prospective controlled study of 23 CPF procedures was conducted in 11 pregnant women with early preeclampsia at gestational ages 22 to 31 weeks. The evolution of clinical manifestations of preeclampsia (BP, urine output, and proteinuria), laboratory biochemical parameters (protein/creatinine ratio, lipid profile), blood coagulation tests, and thromboelastometry (ROTEM) were assessed. In addition, the effect of CPF on the level of preeclampsia markers (sFlt-1, PIGF, sFlt-1/PIGF ratio) as predictors of endothelial aggression was analyzed. The efficacy of extracorporeal therapy was evaluated based on the duration of pregnancy prolongation.

Results. The use of CPF as an adjunct for the treatment of early preeclampsia had a positive effect on the lipid profile by reducing cholesterol and LDL, which helped to decrease atherogenic aggression on the vascular endothelium. In addition, the extracorporeal therapy promoted reduction of the anti-angiogenic effect of sFlt-1, which was confirmed by a significant decrease in the sFlt-1/PIGF ratio from 515 [347; 750] to 378 [285; 557] (P=0.013). The period of prolongation of pregnancy was longer in the main group (with CPF) and was 19 [5; 26] days, whereas in the comparison group (without CPF) it was 3 [1; 4] days (P<0.001). All newborns were discharged from the hospital in a stable condition. The paper is supplemented with a clinical observation of the effective use of CPF in early preeclampsia.

Conclusion. The use of cascade plasma filtration in the treatment of early preeclampsia to prolong pregnancy could be a promising approach.

Keywords: early preeclampsia; cascade plasma filtration; soluble fms-like tyrosine kinase; sFlt-1; vascular endothelial growth factor; VEGF; lipid profile

Funding. The study was supported by the «Multicenter Research Bioresource Collection «Human Reproductive Health» project 15 BRK.21.008 (Agreement 075-15-2021-1058 dated September 28, 2021), funded by the Ministry of Science and Higher Education of Russia.

Conflict of interest. The authors declare no conflict of interest.

Introduction

Developing effective treatments for early preeclampsia is relevant to obstetric practice. Although surveillance, effective diagnosis and early hospitalization have reduced maternal morbidity and mortality, preterm delivery with extremely low fetal weight leads to postnatal complications and high economic costs. Thus, this problem nowadays requires a pathogenetic approach and modern innovative solutions.

Currently, the mechanism of early preeclampsia is associated with impaired remodeling of the spiral arteries and superficial invasion of the cytotrophoblast into the spiral arteries, which leads to placental ischemia and oxidative stress. Subsequently, the altered placenta produces several aggressive factors (sFlt-1, placental endoglin, etc.) that destroy vascular endothelial cells causing endothelial dysfunction. The latter associates with impaired renal blood flow and decreased glomerular filtration rate resulting in increased production of aldosterone and enhanced glomerular sensitivity to angiotensin. All this leads to abnormal water-compartment distribution, sodium retention, as well as increased permeability of the glomeruli to macromolecules, resulting in clinical manifestations of preeclampsia (hypertension, edema and proteinuria) and organ disorders [1, 2]. As early as in 2003, Maynard et al.

Correspondence to:

Liudmila V. Kovalenko
E-mail: lvkhome@yandex.ru

Адрес для корреспонденции:

Людмила Васильевна Коваленко
E-mail: lvkhome@yandex.ru

demonstrated that the risk of preeclampsia correlated with increased levels of soluble fms-like tyrosine kinase (sFlt-1) and reduced levels of soluble vascular endothelial growth factor (VEGF). In their studies, the authors created a flexible model of preeclampsia by viral transfection of sFlt-1 in pregnant rats, which subsequently led to the development of hypertension, proteinuria, antenatal fetal death and glomerular endotheliosis [3]. Later, another population-based study demonstrated that sFlt-1 levels raised several weeks before the clinical manifestation of the disease (on average, 3 to 4 weeks), thus predicting the development of preeclampsia [4].

Thus, the theory of endothelial dysfunction in the pathogenesis of preeclampsia is currently considered highly plausible, and previous research confirms the validity of the predictive approach in addressing this problem [5–12]. Effective diagnostic models of preeclampsia prediction have been implemented in everyday practice, and this suggests considering prophylactic methods for the prevention and therapy of this pregnancy complication [13–17].

Based on convincing evidence that increased sFlt-1 blood levels are potentially important in the pathogenesis of preeclampsia, the reduction of serum levels of sFlt-1 and other anti-angiogenic factors has been suggested to inhibit further progression of preeclampsia and prolong pregnancy. In this regard, a pilot international study conducted in 2016 deserves special attention. The authors proposed to reduce sFlt-1 by cascade plasma filtration, or DFPP (double filtration plasmapheresis), using negatively charged dextran-sulfate-cellulose columns (PSDS, Kaneka, Japan). The negatively charged columns were assumed to precipitate positively charged sFlt-1 molecules, which would subsequently reduce their aggressive antiangiogenic effect on the vascular endothelium. Cascade plasma filtration was performed in 11 patients with early preeclampsia diagnosed between 23 and 32 weeks of pregnancy. Maternal and neonatal outcomes were analyzed versus a comparison group of 22 pregnant women with early preeclampsia who did not receive extracorporeal therapy. During the study, the authors obtained encouraging results, achieving an 18% (7–28%) reduction in mean sFlt-1 concentrations. In addition, the cascade plasma filtration was associated with an average reduction of urine P/C (protein-to-creatinine) ratio by 44% (indicating improved glomerular filtration) and a decrease in proteinuria. Ultimately, in pregnant women in the main group, labor was delayed by 7–21 days, while in the comparison group, this prolongation averaged 3 days. Neonatal outcomes were also improved. The duration of lung ventilation was reduced from 11 days in the group without extracorporeal therapy to 2 days in pregnant women receiving apheresis therapy [18].

Advancing the pathogenetic approach to early preeclampsia, we should mention another open pilot study conducted in Germany in 2018. Winkler K. et al. questioned the results of earlier research [19]. The authors of the study suggested that clinically significant changes in the lipid profile occur in early preeclampsia. Even in a normal pregnancy, an atherogenic lipid phenotype has been reported, with an increase in triglycerides, low-density lipoproteins (LDL), and very low-density lipoproteins (VLDL). At the same time, preeclampsia causes more pronounced changes in the lipid profile [21–26]. A recent meta-analysis of 24 case-control studies in 2720 women found that high triglyceride levels correlated with the severity of preeclampsia [27]. This finding was further extended and confirmed in five more cohort studies involving 3147 women in the second trimester before the onset of preeclampsia. Hypertriglyceridemia has been shown to precede the onset of preeclampsia and might be considered a predictor of this pregnancy complication [28]. In addition, a recent study proposed a prognostic model based on serum lipoprotein (a). The authors showed that an increase in this marker of more than 40.5 mg/dL in pregnant women with moderate pre-eclampsia can predict severe pre-eclampsia, while serum lipoprotein (a) level of more than 52.5 mg/dL has high sensitivity and specificity for severe pre-eclampsia [29]. Summarizing the results of previous studies, Winkler K. et al. (2018) suggested that impaired low-density lipoprotein metabolism may contribute to endothelial dysfunction and fetoplacental abnormalities in early preeclampsia. Lipid profile correction was performed using cascade plasma filtration in H.E.L.P. apheresis mode. The treatment was administered to 6 pregnant women with early preeclampsia at 24 to 27 weeks' gestation (main group). In the comparison group (gestational age less than 28 weeks), extracorporeal therapy was not performed. Maternal and neonatal outcomes, the changes in lipid profile, and sFlt-1 and PIGF levels were analyzed. Pregnancy prolongation was 15 days in the main group and 6.3 days in the comparison group (P= 0.027). Triglycerides, cholesterol, LDL, and VLDL levels were reduced by more than 40% in the main group. However, the authors did not reveal a significant decrease in sFlt-1 [19].

Thus, currently, there are two main concepts of using different variants of cascade plasma filtration in early preeclampsia. One concept is aimed at reducing the anti-angiogenic effect of sFlt-1 on vascular endothelium, whereas the another one deals with correcting the atherogenic lipid profile. Both concepts hold validity and prove the effectiveness of extracorporeal therapy [18–20]. However, for a more detailed discussion of the problem and providing a

rationale for practical use of the method, larger randomized studies are required.

Material and Methods

We conducted a prospective comparative controlled study that included all patients admitted from December 1, 2019, to October 31, 2020, to the intensive care unit of Surgut Regional Clinical Center for Maternal and Child Health Care, with a referral diagnosis of early preeclampsia (*n*=28). The criteria for the diagnosis of early preeclampsia were gestational age from 22 to 31 weeks, proteinuria ⩾0.3 g/l, and blood pressure >140 mm Hg. The diagnosis was confirmed if Sflt-1/PIGF ratio > 85 pg/mL (biochemical marker of preeclampsia). This helped rule out the diagnosis of early preeclampsia in 6 patients with Sflt-1/PIGF ratio ⩽ 85 pg/ml (comparison group 1). The remaining 22 patients with Sflt-1/PIGF ratio > 85 pg/ml were randomized into 2 groups which included comparison group 2 (*n*=11) who received only conservative therapy without extracorporeal treatment; 3rd group (main, *n*=11) included patients who received conservative treatment and additional cascade plasma filtration (CPF). All CPF sessions were performed upon the written consent of the patients and after approval by the medical team and the ethical committee. Extracorporeal therapy was offered as an alternative method in the integrated management of preeclampsia, including cases where early operative delivery was rejected.

The CPF procedures were performed on a Plasauto Sigma (Asahi, Japan) machine. The whole cycle of extracorporeal therapy consisted of 2 stages. Stage 1 included separation of patient's blood into cells and plasma using «Plasmaflo» TPE column (Asahi, Japan). Stage 2 consisted of processing of the separated plasma using «Cascadeflo» EC-30W filtration column (Asahi, Japan). The volume of processed plasma during treatment ranged from 1000 to 8000 ml. During the course of extracorporeal therapy, the number of CPF sessions was from 1 to 4. One procedure was done in 5 , 2 in 1, 3 in 4, and 4 procedures were performed in 1 pregnant woman. The interval between CPF sessions was 7 to 12 days. All in all, 11 patients in group 3 underwent 23 CPF sessions. Patients in comparison group 2 (without CPF) received standard therapy in ICU according to the protocol for the management of preeclampsia. Obstetrical strategy and timing of delivery were determined by the changes in clinical and laboratory manifestations of preeclampsia and the antenatal status of the fetus. The participants from group 3 (the main group) had clinical assessment of hemodynamic parameters, urine output, doppler study, and laboratory monitoring before and 1.0–1.5 days after CPF. Clinical and laboratory monitoring included measurement of proteinuria, P/C ratio (urine protein/creatinine), total protein, albumin, cholesterol, triglycerides, LDL and VLDL (AU480 «Beckman Coulter» biochemical analyzer, USA). Coagulation parameters such as fibrinogen, von Willebrand factor (FW), and antithrombin-III were measured using the CS-2000i automatic blood coagulation analyzer «Sysmex», Japan. FW was considered as a relative marker of endothelial dysfunction. In parallel with coagulation system, thromboelastometric parameters (ROTEM delta, «TEM Innovations», Germany) such as clotting time (CT), EXTEM (evaluation of platelet hemostasis), maximum clot firmness (MCF), and FIBTEM (evaluation of plasma hemostasis) were evaluated. The levels of fms-like tyrosine kinase-1 (sFlt-1) and placental growth factor (PIGF) before and after CPF session were determined by electrochemiluminescent immunoassay (Roche, Elecsys sFlt-1/PIGF «Cobas®»). The efficacy of the therapy was assessed based on the duration of pregnancy prolongation and the timing of delivery.

Statistica v.10.0, a standard package of applied statistical analysis software, was used for statistical analysis. The Kolmogorov-Smirnov test showed that variables were not normally distributed, so nonparametric statistical methods were used. The results were presented as *Me* [Q1; Q3]. The specific proportion of a parameter in the total set of data was expressed in percents. Differences between mean values in unrelated samples were compared for significance by the Mann–Whitney method; in related samples, they were compared using the Wilcoxon method. Intergroup comparisons of proportions (in %) were made using the χ^2 method. Correlations between quantitative parameters were examined using the rank correlation method. The detected differences were considered significant at $P<0.05$.

Results

All pregnant women in the main group 3 and comparison group 2 exhibited clinical and laboratory manifestations of preeclampsia (ICD codes O13.0 and O14.0). Two patients in group 2 were diagnosed with severe pre-eclampsia within the partial HELLP syndrome and delivered within 8 to 12 hours of their admission to hospital. All pregnant women with pre-eclampsia who underwent fetal Doppler study (*n*=20) at the time of hospital admission had some manifestation of chronic utero-placental insufficiency (CUPI) and 75% (*n*=15) of them had intrauterine growth retardation syndrome (IGRS). In addition, the diagnosis of preeclampsia was confirmed by high levels of anti-angiogenic markers (Sflt-1 and Sflt-1/PIGF ratio). A comparative analysis

Table 1. Comparison of baseline parameters of the comparison groups.

Parameter	Values			*P* (items 1 and 2 using Mann–Whitney test; item 3 using χ^2)		
	Group 1, *n*=6	Group 2, *n*=11	Group 3, *n*=11	1–2	1–3	2–3
1. Age and gestational age *Me* [Q1; Q3]						
Age, years	24.5 [23; 29]	30 [23; 35]	34 [24; 35]	0.25	0.31	0.34
Gestational age, weeks	31 [28; 31]	30 [28; 31]	29 [23; 30]	0.09	0.22	0.23
2. Laboratory parameters *Me* [Q1; Q3]						
Proteinuria, g/l	0.29 [0.25; 0.72]	2.1 [0.48; 4.77]	1.3 [0.58; 1.72]	0.02	0.06	0.11
P/C-ration	3.0 [2.5; 4.1]	43.5 [12.9; 105.0]	23.9 [14.9; 51.8]	0.03	0.04	0.21
Sflt-1, pg/ml	2169 [1892; 5496]	13264 [6887; 15747]	16069 [10316; 16462]	0.0001	0.0002	0.18
PIGF pg/ml	224 [109; 371]	19 [16; 34]	17 [16; 24]	0.02	0.02	0.15
Sflt-1/PIGF	13 [7; 43]	397 [332; 776]	693 [401; 971]	0.0002	0.0001	0.07
3. Doppler study						
Malperfusion grade 1, *n* (%)	—	5 (45.4)	6 (54.5)	—	—	0.71
Malperfusion grade 2, *n* (%)	—	3 (27.3)	3 (27.3)	—	—	0.23
Malperfusion grade 3, *n* (%)	—	1 (9.0)	2 (18.2)	—	—	0.33
CUPI grade 1, *n* (%)	—	4 (36.4)	5 (45.4)	—	—	0.54
CUPI grade 2, *n* (%)	—	2 (18.2)	3 (27.3)	—	—	0.45
CUPI grade 3, *n* (%)	—	1 (9.0)	—	—	—	—

Note. CUPI — chronic utero-placental insufficiency.

of the laboratory manifestations of preeclampsia and the Doppler results in the comparison groups is presented in Table 1, which shows that the baseline data in Groups 2 and 3 is comparable.

In 8 out of 11 pregnant women with preeclampsia, temporary stabilization of hemodynamic parameters, an increase in urine output, as well as a decrease in proteinuria and P/C ratio were seen after the first CPF session, which suggested an improvement in glomerular filtration. Lipid profile changes in pregnant women with early preeclampsia were particularly noteworthy. Almost all patients had an atherogenic lipid profile (elevated total cholesterol, triglycerides, LDL and VLDL). After CPF, a decrease in all studied lipid profile parameters was observed. In addition, the reduction in total cholesterol and LDL was significant, which confirms the high efficiency of lipoprotein apheresis in correcting the atherogenic profile. The changes in coagulation tests and ROTEM also merit attention. Initially all pregnant women with early preeclampsia had high levels of von Willebrand factor (FW), which was considered as a relative marker of severe endothelial dysfunction. Furthermore, many authors now consider reduced antithrombin III (AT-III) to be a significant and independent criterion of preeclampsia severity, and a decrease in AT-III level in women with hypertension in pregnancy down to the lower limit of normal may be a predictor of early pre-eclampsia development [30–31]. No baseline low AT-III values (less than 70%) were found. Meanwhile, there was a significant decrease of AT-III associated with CPF sessions, which can be explained by extracorporeal clearance. For this reason, AT-III concentrate was administered at a dose of 500–1000 IU in 2 out of 23 clinical cases with an AT-III decrease less than 70%. Assessing the effect of CPF on the blood coagulation system, we conclude that after the extracorporeal therapy the hemostatic potential (as indicated by changes in coagulation tests and thromboelastometry) is reduced. A significant decrease was obtained for the levels of fibrinogen, FW, AT-III, as well as the maximum clot firmness (MCF FIBTEM). Besides, our earlier observations demonstrated loss of protein fractions, primarily albumin, when performing CPF at 40–80% of the circulating plasma volume. Therefore, after each CPF session 100–200 ml 20% albumin was administered. These results can be regarded in two ways. On the one hand, there is an impact of extracorporeal circuit (loss of protein fractions, dilution effect, residual effect of heparin). On the other hand, we cannot rule out the so-called «apheresis component», as the technology of CPF on Plasauto Sigma device implies patient's plasma drainage in order to prolong the work of Cascadeflo filtration column. On average, we conducted one CPF procedure with 150–300 ml of plasma drainage which can be considered as a low-volume plasmapheresis. Analysis of the changes in Sflt-1 and PIGF revealed a positive, although minor, effect of CPF. Only in 5 out of 23 CPF sessions there was an increase in Sflt-1 after extracorporeal therapy. This fact was considered as an additional criterion for early operative delivery. Nevertheless, we obtained a significant decrease in the Sflt-1/PIGF ratio from 515 [347; 750] pg/ml to 378 [285; 557] pg/ml (*P*=0.013). The changes in the laboratory parameters associated with CPF are presented in Table 2.

The efficacy of the extracorporeal therapy was also evaluated based on a comparative analysis of pregnancy prolongation period. All pregnant

Table 2. Changes in laboratory parameters associated with CPF, *Me* [Q1; Q3].

Parameter	Before CPF (*n*=11)	After CPF (*n*=11)	*P*-value (Wilcoxon)
Total cholesterol, mmol/l	6.18 [5.4; 6.7]	3.87 [3.2; 5.1]	0.001
Triglycerides mmol/l	2.77 [2.3; 3.25]	2.48 [2.1; 3.1]	0.36
LDL, mmol/l	3.98 [2.6; 4.4]	2.65 [2.0; 3.2]	0.002
VLDL, mmol/l	1.34 [1.0; 1.6]	1.13 [0.9; 1.4]	0.24
Proteinuria, g/l	1.3 [0.5; 1.7]	0.54 [0.4; 1.3]	0.66
P/C ratio	23.9 [14.9; 51.8]	18.7 [12.6; 46.7]	0.75
Total protein, g/l	55 [50; 57]	50 [47; 54]	0.04
Albumin, g/l	31 [28; 35]	31 [29; 33]	0.75
Fibrinogen, g/l	3.4 [2.8; 4.1]	2.78 [2.6; 3.2]	0.001
FW, %	251 [202; 283]	195 [171; 213]	0.001
Antitrombin III, %	84 [73; 95]	77 [70; 90]	0.007
CT EXTEM, s	60 [55; 67]	62 [58; 72]	0.13
MCF FIBTEM, mm	20 [18; 21]	14 [11; 16]	0.001
Sflt–1, pg/ml	10798 [7984; 16069]	8947 [6652; 12817]	0.21
PIGF, pg/ml	19 [15–27]	21 [16; 27]	0.23
Sflt-1/PIGF ratio	515 [347–750]	378 [285; 557]	0.013

Table 3. Pregnancy outcomes after cascade plasma filtration.

Patient	Gestational age at the time of treatment initiation (weeks, days)	Sflt-1/PIGF*		CPF volume, ml (number of sessions)	Gestational age at the moment delivery (weeks, days)	Prolongation period duration (days)
		Before CPF	After CPF			
A	30 weeks and 4 days	293	208	1000 (1)	34 weeks and 2 days	26
B		971	405	3000 (3)	26 weeks and 1 days	21
C	31 weeks and 1 day	693	871	1200 (1)	31 weeks and 6 days	5
D	23 weeks and 6 days	347	251	3000 (3)	27 weeks and 6 days	28
E	28 weeks and 2 days	1482	1409	1500 (1)	28 weeks and 5 days	3
F	27 weeks	750	268	2500 (2)	29 weeks and 5 days	19
G	22 weeks and 4 days	401	291	4500 (3)	28 weeks	38
H	28 weeks and 2 days	569	913	1800 (1)	28 weeks and 6 days	4
I	27 weeks and 2 days	998	352	8000 (4)	30 weeks	19
K	27 weeks and 4 days	154	285	1500 (1)	28 weeks and 1 day	4
L	25 weeks and 3 days	443	236	6000 (3)	28 weeks and 1 day	19

Note. * — change in Sflt-1/PIGF ratio from the baseline at the moment of treatment initiation until minimal value during the whole course of CPF.

women underwent cesarean section due to clinical and laboratory deterioration of preeclampsia. In two cases, additional manifestations of subcompensated utero-placental insufficiency were observed. The pregnancy prolongation period was longer in the main group and reached 19 [5; 26] days, while in the comparison group it was 3 [1; 4] days (P<0.001). All neonates were discharged from the hospital in a stable condition. The pregnancy outcomes, changes in biochemical markers of preeclampsia (Sflt-1/PIGF ratio), and the main parameters of extracorporeal therapy are presented in Table 3. Achieving a lower Sflt-1/PIGF ratio after CPF sessions was associated with an increase in the pregnancy prolongation period (R=–0.61; P=0.02). We also found a direct and significant relationship between the number of CPF sessions and the duration of pregnancy prolongation period (R=0.61; P=0.01). The results demonstrate the effectiveness of CPF for prolongation of pregnancy in early preeclampsia.

Clinical observation of the use of CPP in early preeclampsia

To illustrate our findings, we present a clinical case on observation of prolongation of early preeclampsia in a patient who underwent 4 CPF procedures.

Patient V., 33 years old, was admitted to Surgut Regional Hospital Center for Maternal and Child Health Care on 04.08.2020 with the diagnosis of 2nd pregnancy at 27 weeks' gestation. Preeclampsia of moderate severity. Fetal breech presentation. Chronic utero-placental insufficiency (grade 1A malperfusion, grade 1 intrauterine growth retardation). Hypertension stage 2, risk 2. Before her admission to the hospital, she received inpatient treatment for preeclampsia in the Nefteyugansk Regional Hospital (methyldopa, nifedipine, magnesium sulfate) with no apparent effect. The systolic blood pressure persisted at 150–160 mm Hg, progressing edema was seen. The patient had a history of full-

Table 4. Changes in lipid profile and preeclampsia markers associated with CPF procedures.

Parameter	Changes in parameters at different gestational ages (weeks, days)							
	27 weeks, 2 days		27 weeks, 6 days		28 weeks, 3 days		29 weeks, 1 day	
	CPF №1		CPF №2		CPF №3		CPF №4	
	before	after	before	after	before	after	before	after
Total cholesterol, mmol/l	6.6	3.7	—	3.31	—	3.04	—	2.78
Triglycerides, mmol/l	2.47	2.36	—	1.91	—	1.88	—	2.1
LDL, mmol/l	4.47	2.62	—	2.09	—	2.01	—	2.29
VLDL, mmol/l	1.12	1.07	—	0.87	—	0.84	—	0.95
Sflt-1, pg/ml	16462	14529	11546	9625	11016	10809	12683	12817
PIGF, pg/ml	16.49	28.5	21.23	27.3	19.7	21.6	25.4	29.86
Sflt-1/PIGF ratio	998	509	543	352	559	500	495	429

term delivery in 2018 (fetal weight was 2,700 g). On admission, the patient complained of headache, severe edema (+++) and hypertension up to 140/80–150/90 mm Hg. On laboratory examination, proteinuria was 0.35 g/l (daily protein loss was 1.5 g/l), serum ALT was 68 units, AST was 66 units, total protein was 57 g/l. Other biochemical parameters were normal, coagulation studies were normal for the gestational age. Atherogenic lipid profile was found (increased cholesterol, triglycerides, LDL and VLDL). Atherogenic index of plasma was 3.68 (normal reference 2.0–3.0). The markers of preeclampsia were were measured: Sflt-1 was 16462 pg/ml, PIGF was 16.49 pg/ml, and Sflt-1/PIGF ratio was 998. Treatment with antihypertensives and magnesium sulfate in the ICU for 2 days was not effective, hypertension and edema persisted. Due to the obstetric status, chronic utero-placental insufficiency, and the lack of treatment efficacy, after a course of dexamethasone 24 mg/day to prevent fetal respiratory distress, the patient was offered an early surgical delivery at 27 weeks' gestation + 2 days, which she refused. In order to prolong pregnancy and as an adjunct to the integrated therapy of preeclampsia, four CPF sessions were performed. A total of 8000 ml of plasma (2,000 ml per one session of CPF) were processed during the entire course of extracorporeal therapy. The changes in lipid profile and preeclampsia markers of the patient are presented in Table 4.

Early operative delivery was performed on August 25, 2020, at 30 weeks' gestation due to the lack of treatment effect (persistent hypertension despite using 3 antihypertensive drugs, daily protein loss 0.41–1.5 g/l) and worsening of Doppler parameters (chronic utero-placental insufficiency with 3 grade malperfusion, 2 grade intrauterine growth retardation). A female fetus was born weighing 800 g with Apgar score of 6–7. The newborn stayed in the intensive care units for 82 days and was discharged in stable condition. Thus, the period of pregnancy prolongation was 19 days from the initiation of extracorporeal therapy.

Conclusion

The addition of cascade plasma filtration to the treatment of early preeclampsia is a promising approach to prolong pregnancy.

Cascade plasma filtration is effective for lipid profile correction (total cholesterol, triglycerides, LDL, VLDL).

Cascade plasma filtration as a part of the complex treatment of early preeclampsia reduces sFlt-1 and sFlt-1/PIGF ratio and helps to prolong pregnancy by 19 [5; 26] days.

References

1. *Tkachenko O., Shchekochikhin D., Schrier R.W.* Hormones and hemodynamics in pregnancy. *Int J Endocrinol Metab.* 2014; 12 (2): e14098. DOI: 10.5812/ijem.14098.
2. *Turpin C.A., Sakyi S.A., Owiredu W. KBA., Ephraim R.KD., Anto E.O.* Association between adverse pregnancy outcome and imbalance in angiogenic regulators and oxidative stress biomarkers in gestational hypertension and preeclampsia. *BMC Pregnancy and Childbirth.* 2015; 15: 189. DOI: 10.1186/s12884-015-0624-y.
3. *Maynard S.E, Min J.Y., Merchan J., Lim K.H., Li J., Mondal S., Libermann T.A., Morgan J.P., Sellke F.W., Stillman I.E., Epstein F.H., Sukhatme V.P., Karumanchi S.A.* Excess placental soluble fms-like tyrosine kinase 1 (sFlt1) may contribute to endothelial dysfunction, hypertension, and proteinuria in preeclampsia. *J Clin Invest.* 2003; 111 (5): 649–658. DOI: 10.1172/JCI17189.
4. *Levine R.J., Maynard S.E., Qian C., Lim K.H., England L.J., Yu K.F., Schisterman E.F., Thadhani R., Sachs B.P., Epstein F.H., Sibai B.M., Sukhatme V.P., Karumanchi S.A.* Circulating angiogenic factors and the risk of preeclampsia. *N Engl J Med.* 2004; 350: 672–683. DOI: 10.1056/NEJMoa031884.
5. *Heydarian M., McCaggrey T., Florea L., Yang Z., Ross M.M., Zhou W., Maynard S.E.* Novel splice variants of sFlt-1 are upregulated in preeclampsia. *Placenta.* 2009; 30 (3): 250–255. DOI: 10.1016/j.placenta. 2008.12.010.
6. *Sela S., Itin A., Natanson-Yaron S., Greenfield C., Goldman-Wohl D., Yagel S., Keshet E.* A novel human-specific soluble vascular endothelial growth factor receptor-1: cell type-specific splicing and implications to vascular endothelial growth factor homeostasis and preeclampsia. *Circ Res.* 2008; 102 (12): 1566–1574. DOI: 10.1161/CIRCRESAHA.108.171504.
7. *Souders C.A., Maynard S.E., Yan J., Wang Y., Boatright N.K., Sedan J., Balyozian D., Cheslock P.S., Molrine D.C., Simas T.A.M.* Circulating levers of sFlt-1 splice variants as predictive markers for the development of preeclampsia. *Int J Mol Sci.* 2015; 16 (6): 12436–12453. DOI: 10.3390/ijms160612436.
8. *Thomas C.P., Andrews J.I., Raikwar N.S., Kelley E.A., Herse F, Dechend R., Golos T.G., Liu K.Z.* A recently evolved novel trophoblast-enriched secreted form of fms-like tyrosine kinase-1 variant is up-regulated in hypoxia and preeclampsia. *J Clin Endocrinol Metab.* 2009; 94 (7): 2524–2530. DOI: 10.1210/jc.2009-0017.
9. *Whitehead C.L., Palmer K.R., Nilsson U., Gao Y., Saglam B., Lappas M., Tong S.* Placental expression of a novel primate-specific splice variant of sFlt-1 is upregulated in pregnancies complicated by severe early onset preeclampsia. *BJOG.* 2011; 118 (10): 1268–1271. DOI: 10.1111/ j.1471-0528.2011.02962.x.
10. *Jebbink J., Keijser R., Veenboer G., van der Post J., Ris-Stalpers C., Afink G.* Expression of placental FLT-1 transcript variants relates to both gestational hypertensive disease and fetal growth. *Hypertension.* 2011; 58 (1): 70–76. DOI: 10.1161/HYPERTENSIONAHA.110.164079.
11. *Palmer K.R., Kaitu'u-Lino T., Cannon P, Tuohey L., De Silva M.S., Varas-Godoy M., Acuna S., Galaz J., Tong S., Illanes S.E.* Maternal plasma concentrations of the placental specific sFlt-1 variant, sFlt-1 e15a, in fetal growth restriction and preeclampsia. *J Matern Fetal Neonatal Med.* 2017; 30 (6): 635–639. DOI: 10.1080/14767058.2016.1182975.
12. *Palmer K.R., Kaitu'u-Lino T., Hastie R., Hannan N.J., Ye L., Binder N., Cannon P, Tuohey L., Johns T.G., Shub A., Tong S.* Placental-specific sFlt-1 e15a protein is increased in preeclampsia, antagonizes vascular endothelial growth factor signaling, and has antiangiogenic activity. *Hypertension.* 2015; 66 (6): 1251–1259. DOI: 10.1161/HYPERTENSIONAHA.115.05883.
13. *Verlohren S., Herraiz I., Lapaire O., Schlembach D., Moertl M., Zeisler H., Calda P., Holzgreve W., Galindo A., Engels T., Denk B., Stepan H.* The sFlt-1/PlGF ratio in different types of hypertensive pregnancy disorders and its prognostic potential in preeclamptic patients. *Am J Obstet Gynecol.* 2012; 206 (1): 58.e1-8. DOI: 10.1016/j.ajog.2011.07.037.
14. *Stepan H., Herraiz I., Schlembach D., Verlohren S., Brennecke S.,Chantraine F, Klein E., Lapaire O., Llurba E., Ramoni A., Vatish M., Wertaschnigg D., Galindo A.* Implementation of the sFlt-1/PlGF ratio for prediction and diagnosis of pre-eclampsia in singleton pregnancy: implications for clinical practice. *Ultrasound Obstet Gynecol.* 2015; 45 (3): 241–246. DOI: 10.1002/uog.14799.
15. *Серов В.Н., Кан Н.Е., Тютюнник В.Л.* Прогностическое значение отношения растворимой fms-подобной тирозинкиназы-1 к плацентарному фактору роста у беременных с преэклампсией. *Акушерство и гинекология.* 2016; 6: 5–10. DOI: 10.18565/ aig.2016.6.5-10 [*Serov V.N., Kan N.E., Tyutyunnik V.L.* Prognostic value of the ratio of soluble fms-like tyrosine kinase-1 to placental growth factor in pregnant women with preeclampsia. *Obstetrics and Gynecology / Akusherstvo i Ginecologiya.* 2016; 6: 5–10. DOI: 10.18565/ aig.2016.6.5-10].
16. *Холин А.М., Муминова К.Т., Балашов И.С., Ходжаева З.С., Боровиков П.И., Иванец Т.Ю., Гус А.И.* Прогнозирование преэклампсии в 1-м триместре беременности: валидация алгоритмов скрининга на российской популяции. *Акушерство и гинекология.* 2017; 8: 74–84. https://dx.doi.org/10.18565/aig.2017.8.74-84 [*Kholin A.M., Muminova K.T., Balashov I.S., Khodzhaeva Z.S., Borovikov P.I., Ivanets T.Yu., Gus A.I.* Prediction of preeclampsia in the 1st trimester of pregnancy: validation of screening algorithms in the Russian population. *Obstetrics and Gynecology/ Akusherstvo i Ginecologiya.* 2017; 8: 74–84. https://dx.doi.org/10.18565/ aig.2017.8.74-84]
17. *Ходжаева З.С., Холин А.М., Шувалова М.П., Иванец Т.Ю., Демура С.А., Таличкина И.В.* Российская модель оценки эффективности теста на преэклампсию sFlt-1/PIGF. *Акушерство и гинекология.* 2019; 2: 52–58. https://dx.doi.org/10.18565/aig.2019.2.52-58 [*Khodzhaeva Z.S., Kholin A.M., Shuvalova M.P, Ivanets T.Yu., Demura S.A., Telichkina I.V.* Russian model for evaluating the effectiveness of the sFlt-1/PIGF preeclampsia test. *Obstetrics and Gynecology/ Akusherstvo i Ginecologiya.* 2019; 2: 52–58. https://dx.doi.org/10.18565/aig.2019.2.52-58]
18. *Thadhani R., Hagmann H., Schaarschmidt W., Roth B., Cingoez T., Ananth Karumanchi S., Wenger J., Lucchesi K.J., Tamez H., Lindner T., Fridman A., Thome U., Kribs A., Danner M., Hamacher S., Mallmann P., Stepan H., Benzing T.* Removal of soluble Fms-like tyrosine kinase-1 by dextran sulfate apheresis in preeclampsia. *J Am Soc Nephrol.* 2016; 27 (3): 903–913. DOI: 10.1681/ASN.2015020157.
19. *Winkler K., Contini C., König B., Krumrey B., Pütz G., Zschiedrich S., Pecks U., Stavropoulou D., Prömpeler H., Kunze M., Markfeld-Erol F.* Treatment of very preterm preeclampsia via heparin-mediated extracorporeal LDL-precipitation (H.E.L.P.) apheresis: The Freiburg preeclampsia H.E.L.P.-Apheresis study. *Pregnancy Hypertens.* 2018; 12: 136–143. DOI: 10.1016/j.preghy.2018.04.007.

20. *Wang Y., Walli A.K., Schulze A., Blessing F., Fraunberger P., Thaler C., Seidel D., Hasbargen U.* Heparin-mediated extracorporeal low density lipoprotein precipitation as a possible therapeutic approach in preeclampsia. *Transfus Apher Sci.* 2006; 35 (2): 103–110. DOI: 10.1016/j.transci.2006.05.010.
21. *Sattar N., Bendomir A., Berry C., Shepherd J., Greer I.A., Packard C.J.* Lipoprotein subfraction concentrations in preeclampsia: pathogenic parallels to atherosclerosis. *Obstet. Gynecol.* 1997; 89 (3): 403–408. DOI: 10.1016/S0029-7844 (96)00514-5.
22. *Hubel C.A., Lyall F., Weissfeld L., Gandley R.E., Roberts J.M.* Small low-density lipoproteins and vascular cell adhesion molecule-1 are increased in association with hyperlipidemia in preeclampsia. *Metabolism.* 1998; 47 (10): 1281–1288. DOI: 10.1016/s0026-0495 (98)90337-7.
23. *Winkler K., Wetzka B., Hoffmann M.M., Friedrich I., Kinner W., Baumstark M.W., Zahradnik H.-P., Wieland H., März W.* Triglyceride-rich lipoproteins are associated with hypertension in preeclampsia. *J. Clin. Endocrinol. Metab.* 2003; 88 (3): 1162–1166. DOI: 10.1210/jc.2002-021160.
24. *Enquobahrie D.A., Williams M.A., Butler C.L., Frederick I.O., Miller R.S., Luthy D.A.* Maternal Plasma Lipid Concentrations in Early Pregnancy and Risk of Preeclampsia. *Am J Hypertens.* 2004; 17 (7): 574–581. DOI: 10.1016/j.amjhyper.2004.03.666.
25. *Sanches S.E., Williams M.A., Muy-Rivera M., Qiu C., Vadachkoria S., Bazul V.* A Case-Control Study of Oxidized Low Density Lipoproteins and Preeclampsia Risk. *Gynecol Endocrinol.* 2005; 21 (4): 193-199. DOI: 10.1080/09513590500154019.
26. *Dallinga-Thie G.M., Kroon J., Boren J., Chapman M.J.* Triglyceride-rich lipoproteins and remnants: targets for therapy? *Curr. Cardiol. Rep.* 2016; 18 (7): 67. DOI: 10.1007/s11886-016-0745-6.
27. *Ray J.G., Diamond P., Singh G., Bell C.M.* Brief overview of maternal triglycerides as a risk factor for pre-eclampsia. *BJOG.* 2006; 113 (4): 379–386. DOI: 10.1111/j.1471-0528.2006.00889.x.
28. *Gallos I.D., Sivakumar K., Kilby M.D., Coomarasamy A., Thangaratinam S., Vatish M.* Pre-eclampsia is associated with, and preceded by, hypertriglyceridaemia: a meta-analysis. *BJOG.* 2013; 120 (11): 1321–1332. DOI: 10.1111/1471-0528.12375.
29. *Konrad E., Güralp O., Shaalan W., Elzarkaa A.A., Moftah R., Aleman D., Malik E., Soliman A.A.* Correlation of elevated Levels of lipoprotein (a), high-density lipoprotein and low-density lipoprotein with severity of preeclampsia: a prospective longitudinal study. *J Obstet Gynaecol.* 2020; 40 (1): 53–58. DOI: 10.1080/01443615.2019.1603214.
30. *Матковский А.А, Александров И.В., Беломестнов С.Р., Быков А.С., Жилин А.В., Куликов А.В.* Уровень антитромбина III у женщин с гипертензивными расстройствами во время беременности. *Тромбоз, гемостаз и реология.* 2017; 1 (69): УДК 616-089.1: 618.3: 616.16. 30. [*Matkovsky A.A., Alexandrov I.V., Belomestnov S.R., Bykov A.S., Zhilin A.V., Kulikov A.V.* The level of antithrombin III in women with hypertensive disorders during pregnancy. *Thrombosis, hemostasis and rheology/Tromboz, Gemostaz, Rheologiya.* 2017; 1 (69): UDC 616-089.1:618.3:616.16]
31. *Пылаева Н.Ю., Шифман Е.М., Пономарева Е.Г., Османова Э.С.* Антитромбин III — эволюция от антикоагулянта к маркеру тяжелых форм преэклампсии. *Анестезиология и реаниматология.* 2020; (6): 57–62. DOI: 10.17116/anaesthesiology202006157. [*Pylaeva N.Yu., Shifman E.M., Ponomareva E.G., Osmanova E.S.* Antithrombin III — evolution from anticoagulant to a marker of severe preeclampsia. Russian Journal of Anaesthesiology and Reanimatology. 2020; (6): 57–61. (In Russ.). https://doi.org/10.17116/anaesthesiology202006157]

Received 14.06.2021
Accepted 25.10.2021