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Prevention of preeclampsia in pregnant women with obesity

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Abstract

Reducing the occurrence of preeclampsia is one of the key tasks in modern obstetrics, especially in pregnant women with concomitant obesity, who are at high risk for preeclampsia, the leading pathogenetic segment of which is endothelial dysfunction. The purpose of this work is to evaluate the effectiveness of the integrated therapeutic and preventive complex (TPC) in order to prevent preeclampsia in pregnant women. These parameters were evaluated using such markers as the concentration of vascular endothelial growth factor (VEGF) in blood serum and the content of circulating endothelial microparticles (CEM) $CD32^{+}CD40^{+}$ in peripheral blood in pregnant women with obesity of varying severity over the course of treatment we proposed. 110 pregnant women were

included in the study: women with physiological body weight (n=26); women with class I obesity (n=42), and women with class II-III obesity. The groups of pregnant women with concomitant obesity were divided into two equal subgroups; one of the subgroups received the TPC (acetylsalicylic acid, calcium supplements, L-arginine, diosmin). The findings obtained demonstrate a significant improvement of endothelial status over the course of the therapy that is manifested with an increase in the serum VEGF concentration and a decrease in the content of $CD32^+CD40^+$ CEM in the peripheral blood. Our clinical assessment of pregnancy course, childbirth and the postpartum period in women with obesity and physiological body weight has shown a decrease in the occurrence of complications due to taking the integrated TPC. We have registered a decrease in the incidence of preeclampsia, placental dysfunction, occurrence of miscarriage, operative delivery and postpartum complications.

Key words: vascular endothelial growth factor; circulating endothelial microparticles $CD32^+CD40^+$; endothelial dysfunction; preeclampsia; pregnancy; obesity.

Introduction

Nowadays, obesity is known as one of the major worldwide challenges and has been recognized as epidemic as almost a third of the world's population is suffering from overweight and obesity [1]. Pregnancy in women with overweight or obesity is associated with a number of maternal and foetal risks, the severity and frequency of which are directly proportional to the severity of obesity [2]. One of the most common complications in pregnant women with concomitant obesity is preeclampsia (PE), and the leading factor in the pathogenesis of its development is endothelial dysfunction (ED) [3]. It has been proven that metabolic factors associated with obesity enhance the risk of PE by affecting different stages of PE pathogenesis including: ED, cytotrophoblast migration and placental ischemia, release of soluble placental factors into the maternal circulation [4]. Given the above peculiarities of the PE pathogenesis in obesity and its consequences, the ED assessment by using such powerful markers as determining the concentration of vascular endothelial growth factor (VEGF) in blood serum and counting circulating endothelial microparticles (CEM) $CD32^+CD40^+$ in plasma blood of pregnant women with concomitant obesity is of a particular clinical significance.

VEGF has been known as a signalling protein produced by cells to stimulate vasculo- and angiogenesis, induced by hypoxia and possesses the properties of endothelial cell mitogen, which promotes survival of endothelial cells, and stimulates the production of a

powerful vasodilator, nitric oxide (NO), associated with gestational vessel dilation characteristic of normal pregnancy [5, 6]. $CD32^{+}CD40^{+}$ CEM has been shown to act as a marker of endothelial damage, and changes in its level point out increased ED progression in pathological conditions or the possibility of its renewal [7, 8].

Nowadays one of the urgent issues is the search for ways to reduce the ED manifestations by impacting certain parts of its pathogenesis, and this is especially relevant for pregnant women with concomitant obesity. There are data on the appropriateness of using semi-synthetic diosmin known as an angioprotector, disaggregant and venotonic in women with preeclampsia and placental dysfunction. Endothelioprotective properties of L-arginine promote its use to prevent the development of PE. The combined use of these medicines has been found out to be effective in the PE prevention, but requires more detailed research in pregnant women with obesity [9, 10].

The purpose of the work is to evaluate the effectiveness of the integrated therapeutic and preventive complex (TPC) in order to prevent preeclampsia in pregnant women with obesity of varying severity.

Materials and methods

This research was carried out in accordance with national and international legislations. Our study included 110 pregnant women who gave written voluntary informed consent to participate in the study according to requirements of the Declaration of Helsinki.

Inclusion criteria for the study were the following: women with physiological body weight and class I-III obesity, singleton pregnancy, III trimester of pregnancy, and absence of severe extragenital pathology.

Exclusion criteria for this study were the following: non-giving consent to participate, overweight (BMI within the range of 25.0-29.9 kg/m^2), multiple pregnancy, the presence of severe extragenital pathology, severe hypertension, diabetes mellitus and gestational diabetes, systemic autoimmune diseases).

The division of pregnant women into groups was carried out based on the BMI values, the class of obesity calculated by height and weight parameters taking into account the gestational age and age of women, according to the table by N. S. Lutsenko [11]. The age of the pregnant women under the study ranged from 21 to 34 years, the average age was 26.4±2.7 years. The participants were divided into 3 groups: Group I (control) included pregnant women (n=26) with physiological body weight (BMI=18.5- 24.9 kg/m^2); Group II involved pregnant women with class I obesity (n=42); Group III included pregnant women with obesity of II and III degree (n=42). The groups of pregnant women with concomitant

obesity (i.e. groups II and III) were subdivided into two subgroups (A and B) with the equal numbers of participants in each. Subgroups IIB and IIIB received the therapeutic and prophylactic complex we elaborated to prevent the PE occurrence. The period of examination of the pregnant women ranged from 36 to 39 weeks of gestation, the average was 37.8±0.9 weeks. We assessed the VEGF concentration in the blood serum and CEM $CD32^+CD40^+$ in the peripheral blood. Blood sampling was performed at maternity welfare clinics and obstetric departments of Poltava city, laboratory investigations were carries out at the Research Institute of Genetic and Immunological Foundations of Pathology and Pharmacogenetics, Ukrainian Medical Stomatological Academy.

The expression level of circulating endothelial microparticles $CD32^+CD40^+$ in venous blood was measured by flow cytofluorometry using murine anti-human monoclonal CD40 antibodies conjugated to FITC (BD Pharmingen, USA) and PE murine anti-human monoclonal CD32 antibodies (BD Pharmingen, USA) by the flow cytometer "EPIX XL-MCL" (Beckman Coulter, USA). Murine IgG labelled with fluorescent dyes were used as control. Data for calculating the absolute number of particles, taking into account the dilution during the measurement, were represented in the form of $A\times10^7$/l.

The serum VEGF concentration was assessed by enzyme-linked immunosorbent assay according to the manufacturer's instructions (Vector-Best, Russia).

The pregnant women with physiological body weight included in the study were under the medical guided counselling in accordance with the Order of the Ministry of Health of Ukraine № 417 (15.07.2011). Since obese pregnant women are at risk for preeclampsia, the course of their pregnancies was managed according to the clinical protocol of obstetric care "Predictors, prevention, diagnosis and treatment of hypertensive disorders of gestation" (01.11.2018), developed by a working group of leading Ukrainian experts in obstetrics. Based on this protocol, pregnant women at risk, including obesity, are prescribed to take acetylsalicylic acid in a dosage of 100 mg/day from the 12^{th} week to 36^{th} weeks of gestation, calcium supplements in a dosage of 1 g/day from the 20th week of gestation, and to add marine products with a high content of polyunsaturated fatty acids to the daily diet. We also considered and implemented the principles of the clinical practice guideline developed by the Canadian hypertensive disorders of pregnancy working group and published by Pregnancy hypertension to provide a reasonable approach to the diagnosis, evaluation, and treatment of the hypertensive disorders of pregnancy [12].

Obese pregnant women who had agreed to receive this pathogenetically grounded complex aimed at preventing PE, took a combination of L-arginine aspartate and

semisynthetic diosmin according to the scheme: from 12 to 16, from 22 to 26, and from 32 to 36 weeks of pregnancy. The dose of diosmin manufactured in tablets was 600 mg per day was taken orally. L-arginine manufactured as syrup was taken in a dose of 5 ml (1 g of the active agent) 3 times a day. This combination of medicines chosen has been known to be applied in obstetric practice [10, 13].

Quantitative data are presented in the form of standard deviation and its standard error (M±m). Statistical processing of the findings was performed by the software package «MedStat» (№ MS00019) using standard methods of variation statistics and Student's t-test. The difference was considered statistically significant at $p<0.05$.

Results

Having analyzed the values of ED markers obtained following the TPC course we observed the following changes. There was a significant 1.6-fold growth in the serum VEGF concentration in the women of subgroup IIB compared with the pregnant women of subgroup IIA (234.7±15.4 pg/ml vs. 383.5±13.8 pg/ml, $p<0.0005$) (Fig. 1).

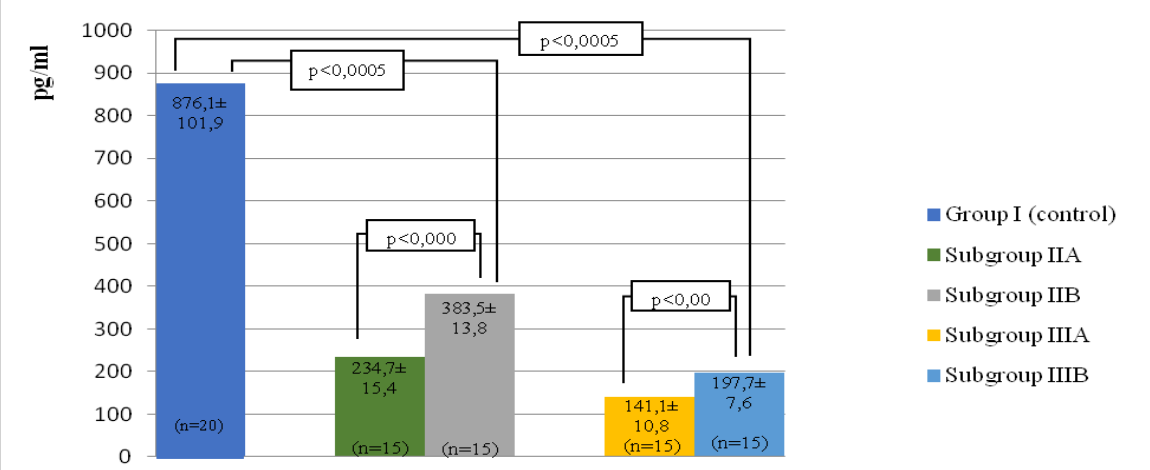

Fig.1 Indicators of VEGF concentration in the serum of pregnant with physiological body weight and obesity of I and II-III class, who did not receive TPS and who received TPC

In contrast to the increase in the level of VEGF concentration in the pregnant women under the study, the number of CEM $CD32^{+}CD40^{+}$ decreased by 1.9 times when comparing these subgroups ($3.28±0.83×10^{7}$/l vs. $1.76±0.27×10^{7}$/l, $p=0.11$) that points out an improvement in the endothelium during the TPC course (Fig. 2).

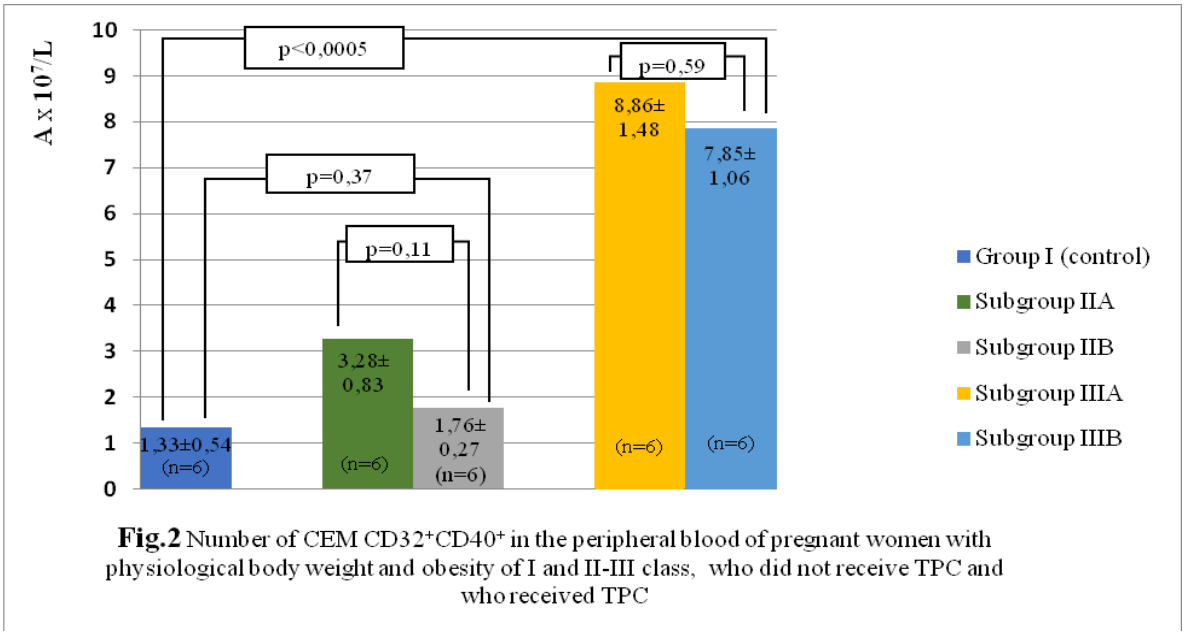

Fig.2 Number of CEM CD32⁺CD40⁺ in the peripheral blood of pregnant women with physiological body weight and obesity of I and II-III class, who did not receive TPC and who received TPC

Comparing the values of serum VEGF concentration in the pregnant women of subgroup IIB and the values of serum VEGF concentration in the pregnant women with physiological body weight demonstrated the improvement of endothelial function, the average VEGF concentration in the pregnant women of subgroup IIB was 2.3 times lower than the average VEGF concentration in the pregnant women with physiological body weight (383.5±13.8 pg/ml vs. 876.1±101.9 pg/ml, $p<0.0005$) (Fig. 1). However, comparing the values of the other marker of ED evaluation, and namely the content of CEM $CD32^+CD40^+$ in the peripheral blood in the pregnant women from subgroup IIB and the content of CEM $CD32^+CD40^+$ in pregnant women with physiological body weight, we observed their maximum approximation ($1.33±0.54×10^7$/l vs. $1.76±0.27×10^7$/l, $p=0.37$) that supports the effectiveness of the therapeutic and prophylactic complex aimed at improving the endothelium (Fig. 2).

The analysis of the dynamic changes in the values of VEGF concentration in the pregnant women with more severe obesity (class II and III) who received TPC and the values of VEGF concentration in those women with the same classes of obesity who did not receive TPC demonstrated a significant increase in the level of VEGF in the serum by 1.4 times in the women who took the TPC course compared with those who did not (141.1±10.8 pg/ml vs. 197.7±7.6 pg/ml, $p<0.005$) (Fig. 1). The assessment of the content of CEM $CD32^+CD40^+$ in the peripheral blood of the pregnant women with obesity II-III degrees shoed a decrease in the corresponding indicator by 12.8% in subgroup IIIB compared with subgroup IIIA, but no statistical significance was observed ($8.86±1.48×10^7$/l vs. $7.85±1.06×10^7$/l, $p>0.05$) (Fig. 2).

Comparing the indicators of the above ED markers (assessment of serum VEGF concentration and calculation of CEM $CD32^+CD40^+$ in peripheral blood) in the pregnant women with physiological body weight and in the pregnant women with concomitant class I-III obesity, who received the TPC, we observed an improvement in the indicators characterizing the endothelium function. However, it can be argued that ED in pregnant women with more severe obesity is less responsive to the therapeutic correction compared with the pregnant women with mild (class I) obesity.

To evaluate the course of pregnancy and labour in the women under the study, we combined subgroups IIB and IIIB into a group of pregnant women with class I-III obesity who took the TPC course and subgroups IIA and IIIA into a group of pregnant women with class I-III obesity who did not take the TPC course. The groups were equivalent in terms of the presence of extragenital pathology. In addition to concomitant obesity, a significant proportion of extragenital pathology was represented by vegetative-vascular dystonia, anaemia, thyroid pathology (mostly diffuse non-toxic goitre) and chronic gastritis in remission.

Assessing the course of pregnancy in the women we studied demonstrated a significant decrease in the incidence of miscarriage (early and late) in the groups of pregnant women with obesity who took the TPC course compared with the pregnant women who refused it: 14.3% vs. 33.2% cases ($p<0,05$), (Table 1). There was also a 1.8-fold reduction in the risk of preterm labours in obese pregnant women who took the TPC course compared to the pregnant women with concomitant obesity without the therapy. Moreover, the occurrence of this complication among the pregnant women who took the therapy approached to the values typical of pregnant women with physiological body weight (Table. 1).

Having analyzed the results obtaines, we observed the improvement in the course of gestation in the women with concomitant obesity, who took the TPC, due to the better functioning of the fetoplacental complex. The occurrence of placental dysfunction according to ultrasound scan finding in the pregnant women during the TPC course was 1.5 times lower compared to the pregnant women who did not take the TPC; the occurrence of slow blood circulation in the umbilical arteries was registered 4 times less compared to the relevant group, but no statistical significance was found out ($p=0.16$) (Table 1). Intrauterine growth retardation (IUR) diagnosed on the basis of the criteria specified in the Order of the Ministry of Health of Ukraine № 782 (29.12.2005) occurred only in 4.8% of cases of the obese pregnant women who did not take the TPC course and was not registered in the group of

pregnant women with physiological body weight or in the group of pregnant women who received the TPC course (Table 1).

Table 1 - Occurrence rate of complications during pregnancy, childbirth and the postpartum period in women with concomitant obesity when taking the TPC course

Complications	Control group, (n=26)	Pregnant women with class I-III obesity		P_1	P_2
		Who received no therapeutic and prophylactic complex (n=42)	Who received the therapeutic and prophylactic complex (n=42)		
Risk of spontaneous miscarriage	4 (15.4%)	14 (33.3%)	6 (14.3%)	0.03	0.58
Risk of preterm labour	3 (11.5%)	7 (16.7%)	4 (9.5%)	0.26	0.55
Placental dysfunction	4 (15,4%)	14 (33,3%)	9 (21,4%)	0,16	0,39
Slow blood circulation in umbilical arteries	0	4 (9,5%)	1 (2,4%)	0,18	0,62
IUR	0	2 (4,8%)	0	0,24	-
BPF 7 scores and below	0	4 (9,5%)	2 (4,8%)	0,34	0,38
Fetal distress during gestation	0	1 (2,4%)	1 (2,4%)	0,75	0,62
Gestational hypertension	0	2 (4,8%)	1 (2,4%)	0,5	0,62
Preeclampsia	0	5 (11,9%)	2 (4,8%)	0,22	0,38
Uterine inertia	2 (7,7%)	10 (23,8%)	6 (14,3%)	0,2	0,34
Induced labours (including failures)	0	6 (14,3%)	2 (4,8%)	0,13	0,38
Fetal distress during the labour	0	2 (4,8%)	1 (2,4%)	0,5	0,62
Forceps and vacuum extraction	0	3 (7,1%)	0	0,12	-
Bleeding in III period of labour	0	2 (4,8%)	0	0,25	-
Manual separation and removal of placenta	0	3 (7,1%)	0	0,12	-
Cesarian section	0	12 (28,6%)	10 (23,8%)	0,4	0,005
Anemia	3 (11,5%)	9 (21,4%)	4 (9,5%)	0,11	0,55
Uterine subinvolution	0	3 (7,1%)	0	0,12	-

Note: p1 - reliability when comparing the indicators of the group of pregnant women with class I-III obesity who took the PTC course and who refused it;

p2 - reliability when comparing the indicators of the control group and the group of pregnant women with class I – III obesity who took the TPC course.

Decrease in the parameters of a biophysical profile of the foetus (BPF) to 7 scores and lower was found twice less often in the pregnant women with concomitant obesity during the TPC course comparing with the occurrence in the pregnant women with obesity without receiving the TPC (9.5% vs. 4.8% respectively), no decrease in the BPF parameters was observed in the pregnant women with physiological weight (Table 1). Foetal distress during the pregnancy confirmed by ultrasound scanning by BPP score fall to 4 points and below occurred only in the women with class II-III obesity; this allowed us to suggest that pregnant women with more severe obesity are less responsive to the medication applied compared to with the pregnant women with class I obesity.

The use of the TPC we elaborated demonstrates its effectiveness through lowering the number of cases of gestational hypertension and 2.5-fold reducing the PE occurrence in the women with obesity who received the course compared with the pregnant women who refused taking this TPC course. PE cases manifested twice less common in the subgroup of pregnant women with class I obesity who took the TPC (4.8% of cases vs. 9.5%, respectively) and three times less common in the subgroup in the pregnant women with class II-III obesity who took the TPC course compared with the subgroups without the therapeutic correction (4.8% vs. 14.3%, respectively). Cases of early (up to 34 weeks) and severe PE occurred only in the subgroup of the pregnant women with class II-III obesity, who did not receive the therapy. PE, which nevertheless manifested after the TPC course, occurred in women with full-term pregnancy and was classified as moderate that had a more favourable effect on the condition of newborns and parturients.

The labour course in the women with obesity who received TPC was characterized by a decrease in the occurrence of uterine inertia cases almost twice (compared to the pregnant women with obesity without taking the therapy) and make up to 23.8% and 14.3% of cases respectively ($p=0.2$), and was diagnosed only in 7.7% of parturients in the control group (Table 1).

Occurrence of such complications as gestational hypertension, PE, IUR, foetal distress and the development of such pathological conditions as slowed blood flow in the umbilical arteries and decreased BPF according to ultrasound findings led to the growth of operative delivery cases in the group of pregnant women with concomitant obesity. Induced labours were three times less common in the pregnant women with concomitant obesity who completed the TPC complex, i.e. 4.8% of cases vs. 14.3% of cases in the group without the therapy ($p=0.13$). Foetal distress during the childbirth was found as less common in obese parturients who received the TPC course, and the use of foetal vacuum extractor or obstetric

forceps was needed only in the cases of obese parturients who did not take the TPC course (Table 1). Caesarean section was significantly more often performed on for the pregnant women with concomitant obesity compared with the pregnant women with physiological body weight ($p<0.005$). The frequency of Caesarean section tended to decrease in the pregnant women with concomitant obesity who took the TPC course compared with the pregnant women with obesity without receiving the therapy (Table 1).

Bleeding in the third period of labour, manual removal of placenta as well as uterine subinvolution was registered only in the parturients with obesity who did not receive the TPC course (Table 1). Postpartum anaemia occurred more than twice in the obese women who did not receive the therapy comparing to the women with obesity who took the TPC course (21.4% vs. 9.5% of cases, respectively ($p=0.11$).

Discussion

The results obtained by assessing the ED severity using such markers as the serum VEGF concentration and the content of CEM $CD32^{+}CD40^{+}$ in peripheral blood in the pregnant women with obesity of varying severity following the course of the pathogenetically grounded complex of therapeutic and prophylactic measures aimed at preventing preeclampsia demonstrated the improvement of endothelial function.

Recent studies have proven that arginine transport in the maternal organism is significantly reduced during pregnancy, and the antiangiogenic properties of sFlt-1 (whose concentration predominates in PE) are explained by the inability to stimulate arginine transport and, thus, to generate NO [14]. Therefore, the prescription of L-arginine is pathogenetically appropriate and has been supported by our own results showing a significant increase in the VEGF concentration in the subgroups, which took the TPC course.

The appropriateness of using the TPC, which components increase the NO level in endothelial cells, normalize the balance between vasopressors and vasodilators, as well as restore regional blood circulation, is supported in the reports of other researchers [9, 10, 12, 15]. As L-arginine has a pronounced effect on the state of vascular tone of both uterine arteries and umbilical arteries, it contributes to the normalization in the maternal-placental-foetal hemodynamics [16].

The favourable effects of semi-synthetic diosmin as a component of the TPC are explained by its angioprotective and anti-inflammatory properties that is especially important in PE and obesity (because these conditions are characterized by systemic inflammatory response syndrome) and have been proven by some scientists [10, 17] and confirmed in our

work by the approximation of values of the content of CEM $CD32^+CD40^+$ in the subgroups of pregnant women with obesity to the values in the control group.

Known as a phleboprotector and venotonic, diosmin can reduce the symptoms of chronic venous insufficiency, promotes renewal of vascular elasticity, relieves oedema and reduces thrombosis. The powerful anti-inflammatory effect of this natural flavonoid has been experimentally proven in rats [18], and applied in the therapy of pregnant women it confirms its effectiveness in preventing fetoplacental insufficiency, normalization of Doppler parameters and in turn reduces the occurrence of operative delivery and postpartum complications.

Diosmin in combination with acetylsalicylic acid and micronized progesterone for prophylactic purposes (in pregnant women with twins whose pregnancies were achieved through assisted reproductive technology (ART), using the method of intracytoplasmic sperm injection (ICSI) and frozen embryos transfer) resulted in the improvement of obstetric and prenatal outcomes: a significant reduction in the PE incidence, premature birth, IUR and foetal distress. Estimation of the ratio of sFlt-1 / PlGF concentration in the second trimester of pregnancy, according to the data of the researchers, reflected the effectiveness of this method because the PlGF level in the study group was higher (186.5±12.3 vs. 154.2±10.7; $p<0.05$), and the sFlt-1 level was lower (1523.1±40.3 vs. 1835.3±33.6; $p<0.05$) [19]. The growth in the VEGF concentration ranging from 60 to 80% is identical to PlGF, as well as a lowering in the PE incidence of PE and other perinatal complications have also been highlighted in our studies.

The combined use of L-arginine and semisynthetic diosmin demonstrates its effectiveness in the comprehensive prevention and treatment of pregnant women with PE and IUR, and also provides a positive effect on obstetric and perinatal outcomes in the pregnant women with obesity that is consistent with results obtained by other researchers [10, 13].

Conclusion

1. The algorithm for applying the pathogenetically grounded integrated therapeutic and prophylactic complex (acetylsalicylic acid, L-arginine, calcium drugs) and semisynthetic diosmin we developed for pregnant women with concomitant obesity has been proven to lead to decrease in signs of endothelial dysfunction based on the changes in the values of such endothelial dysfunction markers as the concentration of vascular endothelial growth factor in blood serum and the content of circulating endothelial microparticles $CD32^+CD40^+$ in the blood plasma of pregnant women with obesity of varying severity. There is a 1.6-fold increase in the VEGF concentration in the serum of the pregnant women with class I obesity, who

received the therapy aimed at improving the endothelium condition compared with the pregnant women with class I obesity, who did not receive the therapy ($p<0.0005$), and in 1.4 times in the women of class II-III obesity who received the therapy compared with those, who did not ($p<0.005$).

2. The prescription of the treatment and prevention complex to pregnant women with concomitant obesity in order to prevent preeclampsia demonstrates its effectiveness and appropriateness, as evidenced by a 2.5-fold reduction in the occurrence of preeclampsia in women with obesity who received the therapy and the no cases of severe and early preeclampsia.

Prospects for further research.

Further investigating the role of endothelial dysfunction in preeclampsia is of great clinical importance in order to determine the pathogenetic segments in the development of this complication to improve pharmacological correction, especially in groups at high risk of preeclampsia, which includes women with obesity.

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