ORIGINAL ARTICLE

MORPHOMETRIC CHARACTERISTICS OF PLACENTA IN WOMEN WITH PREECLAMPSIA AND OBESITY COMPARED TO WOMEN WITH NORMAL BODY WEIGHT

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ABSTRACT

The aim: to investigate the morphometric characteristics of placentas in women with comorbidity of preeclampsia and obesity compared to women with physiological body weight, and to assess the efficacy of the prophylactic therapy course developed to prevent the occurrence of preeclampsia in pregnant women with obesity.

Materials and methods: 25 biopsy samples of placental tissue were taken from women between 37 and 40 weeks of gestation with a physiological body weight and with class II obesity. The women were divided into five groups of five women in each: the 1st group included women with physiological body weight without obstetric and somatic pathology; the 2nd group involved women with physiological body weight, whose pregnancy was complicated with preeclampsia; the 3rd group was made up of women with class II obesity whose pregnancy was complicated with preeclampsia; the 4th group consisted of women with class II obesity, who received the special prophylactic therapy course, and the 5th group included women with class II obesity, who did not receive the prophylactic therapy course.

Results: The analysis of morphometric parameters of placenta samples taken from women with preeclampsia and obesity demonstrates a number of compensatory and adaptive changes in placenta under hypoxic conditions, and the most important of them include a significant decrease in the number and the mean diameter of the terminal villi, the reduction of volume of villious tree, an increase in the diameter of the capillaries of terminal villi. The morphometric parameters and histological structure in placenta samples from women with obesity, who received the special the prophylactic therapy course, as well as in placenta samples of the control group were similar to the gestational normative values.

Conclusions: The morphometric investigation of placenta samples taken from women with comorbidity of preeclampsia and obesity has shown a significant decrease in the mean diameter of the terminal villi and an increase in the diameter of the capillaries of these terminal villi when compared with a group of women with preeclampsia and physiological body weight. The study has also demonstrated the distortion of the percentage ratio of the volume of the intervillous space and the ratio of medium-calibre villi. The combination of these changes indicates a lack of adaptive capabilities in the placenta during preeclampsia under increasing hypoxic condition.

KEY WORDS: preeclampsia, pregnancy, placenta, obesity, prophylactic therapy course

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INTRODUCTION

The incidence of obesity and overweight among pregnant women is continuing to climb from year to year. The number of pregnant women with obesity in economically developed countries reaches 16-38% and is constantly increasing [1]. Obesity seriously impacts on the demographic situation contributing to infertility and morbidity rate since the complex of hormonal and metabolic disorders inherent in this condition often appears as the pathogenetic basis of the reproductive health deterioration in women and as a risk factor of both maternal and neonatal morbidity and mortality [2]. Among the complications compromised by obesity that lead to maternal mortality is preeclampsia (PE), a common and multisystem disorder. However, despite decades of intensive research, data on the PE aetiology, and in particular, in comorbidities, are still limited. The common mechanisms underlying the development of obesity and PE comorbidity and its progression include oxidative stress, systemic inflammatory response syndrome, and placental circulation disorders [3]. These disorders cause morpho-functional disturbances in the components of the mother-placenta-foetus system. Chronic feto-placental insufficiency is associated with various obstetric disorders and almost always leads not only to PE, but also to delayed foetal growth and premature birth [4]. Therefore, the investigation of adaptive and pathological changes in the structure

of the placenta may be particularly beneficial in explaining the causes underlying the PE development under concomitant obesity, as well as in evaluating the efficacy of agents with antioxidant, anti-inflammatory, and angioprotective properties that improve hemomicrocirculation and prevent the PE occurrence.

THE AIM

The aim of the study is to investigate the morphometric characteristics of placentas in women with comorbidity of preeclampsia and obesity compared to women having a physiological body weight, and to assess the efficacy of the prophylactic therapy course developed to prevent the occurrence of preeclampsia in pregnant women with obesity.

MATERIALS AND METHODS

For study, 25 biopsy samples of placental tissue were taken from women between 37 and 40 weeks of gestation with a physiological body weight (BMI – 18.5 – 24.9 kg/m^2) and with class II obesity (BMI – 35 – 40 kg/m^2), whose course of pregnancy was complicated with the PE development. The women were divided into five groups of five women in each: the 1st group included women with physiological body weight without obstetric and somatic pathology; the 2nd group involved women with physiological body weight, whose pregnancy was complicated with mild PE; the 3rd group was made up of women with class II obesity whose pregnancy was complicated with mild PE; the 4th group consisted of women with class II obesity, who received a prophylactic therapy course (PTC) we developed for the purpose to prevent PE; and the 5th group included women with class II obesity, who did not receive PTC. The main criteria for inclusion in the study were: spontaneous or induced pregnancy, singleton pregnancy, mild PE, timely delivery. Exclusion criteria were: severe PE, severe extragenital pathology, premature birth, multiple pregnancy, in vitro fertilization, antenatal and intranatal fetal death, manual separation of the placenta.

Since pregnant women with obesity are at risk of the PE occurrence, their pregnancy was under special medical supervision in accordance to the clinical guideline for obstetric care "Hypertensive disorders during pregnancy, childbirth and the postpartum period" (Order of the Ministry of Health of Ukraine No. 151, 01.24.2022). In addition to the recommendations regulated by this order, pregnant women with obesity received the PTC, which we specifically developed. It included a combination of L-arginine and semi-synthetic diosmin taken according to the following scheme over 12 – 16, 22 – 26, and 32 – 36 weeks of gestation. Per oral dose of diosmin, which is produced in the form of tables, was 600 mg per day. L-arginine produced as syrup was taken in a dose of 5 ml three times a day.

For morphometric study, biopsy samples sized 2.0×1.5×1.0 cm were excised from the central, paracentral, and marginal areas of the maternal part of the placenta and then were fixed in a 10% neutral formalin solution. Following the fixation and dehydration with increasing concentrations of ethanol, biopsies were embedded in paraffin blocks. Histological sections cut by a standard microtome at 5 μm thickness were stained with hematoxylin and eosin. The s*ections* were analyzed using an *Olympus BX 41 light micr***o***scope* (Japan) with a digital camera and a set of licensed programs. To obtain stereometric data, we applied the planimetric method and the point count by placing a grid with a 3 μm graticular division at magnification 400×. We carried out morphometric study to evaluate the following parameters in the terminal chorionic villi sized up to 80 μm: the diameter of the terminal villi; diameter of capillaries of terminal villi; the thickness of the syncytiotrophoblast (STB); the volume fraction of the main components of the placenta including stem villi, medium-calibre villi, terminal villi, and intervillous space.

Conducted prospective clinical and statistical analysis of pregnancy and childbirth histories (form No. 096/o) and medical records of newborns (form No. 097/o) approved by the Order of the Ministry of Health of Ukraine «On Amendments to Primary Registration Forms and Instructions for Their Filling», No. 29, 01.21.2016.

The statistical analysis of the findings obtained was performed by the "MedStat" program using the methods of descriptive statistics, calculating the mean sample values (M) and the error of the mean value (m), qualitative indicators given as frequencies and their percentage ratios. The Mann-Whitney U-test was used to assess intergroup differences. Differences at $p<0.05$ were considered as statistically significant for analysis.

RESULTS

The morphometric analysis of histological preparations of placental samples taken from the women with physiological body weight and with class II obesity whose pregnancy was complicated by the mild PE development reveals the deviation in the parameters of the test groups from the respective parameters of the control group (Table I).

The mean diameter of the terminal placental villi in the women with PE and class II obesity was significantly lower compared with the indicators in the group of women with PE and physiological body weight (32.66±1.22 μm

Table I. Comparative characteristics of the main morphometric parameters of the terminal placental villi in the studied groups

Morphometric parameters, μm	Women with physiological body weight, n=5	Women with PE and physiological body weight, n=5	Women with PE and class II obesity, n=5	Women with class II obesity, who received PTC, n=5	Women with class II obesity, who did not received PTC, n=5
Mean d of terminal villi	53,75±2,39	36,52±1,16 p_1	32,66±1,22 p_2, p_3, p_4	53,66±0,11	48,44±0,37 p_6
Mead d of capillaries	11,94±0,35	14,44±0,21 p_1	15,43±0,21 p_2, p_3, p_4	12,42±0,15 p_5	13,9±0,04 p_6
STB thickness	5,96±0,76	5,53±0,41	5,06±0,25 p_2, p_3	6,03±0,58	6,37±1,05 p_6

Note:
p_1 – reliability when comparing the indicators between the 1st and 2nd groups, $p<0.05$;
p_2 – reliability when comparing the indicators between the 1st and 3rd groups, $p<0.05$;
p_3 – reliability when comparing the indicators between the 5th and 3rd groups, $p<0.05$;
p_4 – reliability when comparing the indicators between the 2nd and 3rd groups, $p<0.05$;
p_5 – reliability when comparing the indicators between the 1st and 4th groups, $p<0.05$;
p_6 – reliability when comparing the indicators between the 4th and 5th groups, $p<0.05$.

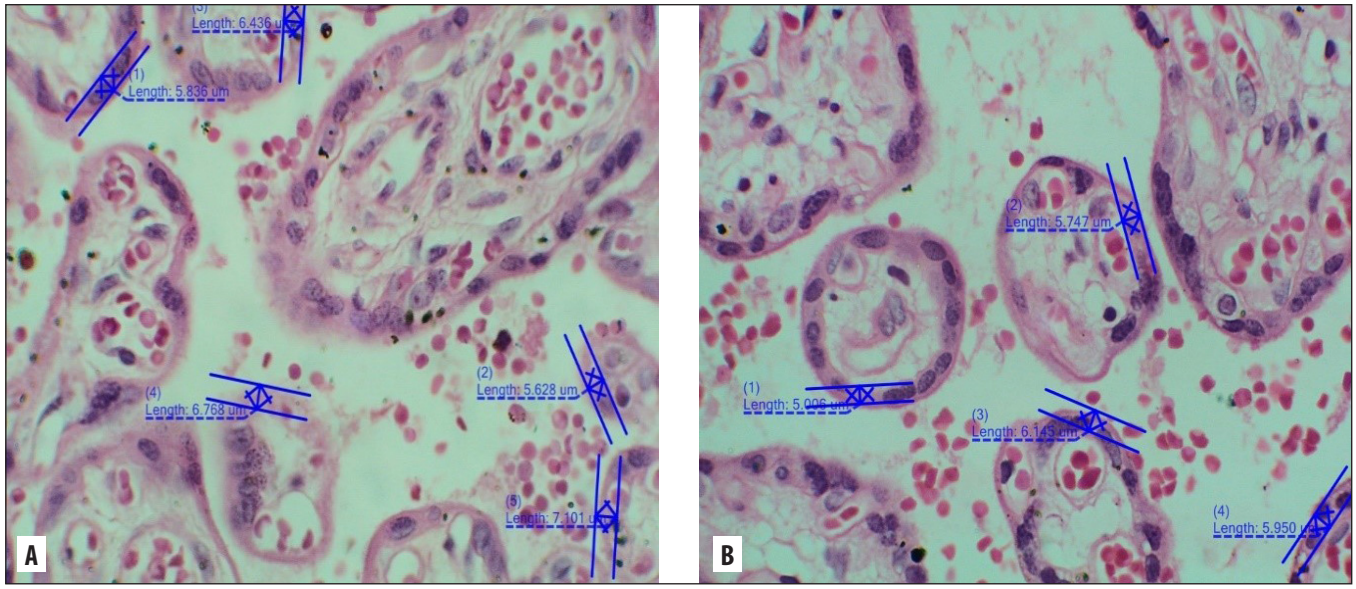

Fig. 1. Placenta biopsy samples taken from women with class II obesity A) who did not receive PTC; B) taken from women who received PTC. The thickness of the syncytiotrophoblast of the terminal villi. Hematoxylin and eosin staining; magnification: x400.

vs. 36.52±1.16 μm, respectively, $p_4<0,01$). A significant decrease of this indicator was observed in the placental samples taken from women with PE and physiological body weight compared with the group of placental biopsies taken from women with physiological body weight and normal course of pregnancy (36.52±1.16 μm vs. 53.75±2.39 μm, $p_1<0.01$). The same tendency was observed when comparing the mean diameter of terminal villi between the placentas of women with PE and class II obesity and the group of women with class II obesity, whose pregnancy was not complicated by the PE course (32.66±1.22 μm vs. 48.44±0.37 μm, $p_3<0.01$). There was a significant decline in the mean diameter of the terminal villi of placentas from women with concomitant class II obesity when compared with the indicators of the control group (48.44±0.37 μm vs. 53.75±2.39 μm, $p_6<0.01$) (Fig. 1). Which indirectly testifies to the connection of a number of pathological changes and deviations of morphometric parameters in placentas from women with moderate preeclampsia and women with obesity, which in turn proves the fact that preeclampsia is manifested by obesity and the feasibility and advantages of prescribing PTC to pregnant women with accompanying obesity for the purpose of prevention of PE.

At the same time, the capillaries of terminal villi in placenta samples taken from women with PE and class II obesity had a larger diameter than in the group of women with PE and physiological body weight (15.43±0.21 μm vs. 14.44±0.21 μm, $p_4<0.01$). An increase in the diameter of the capillaries of terminal villi was also found

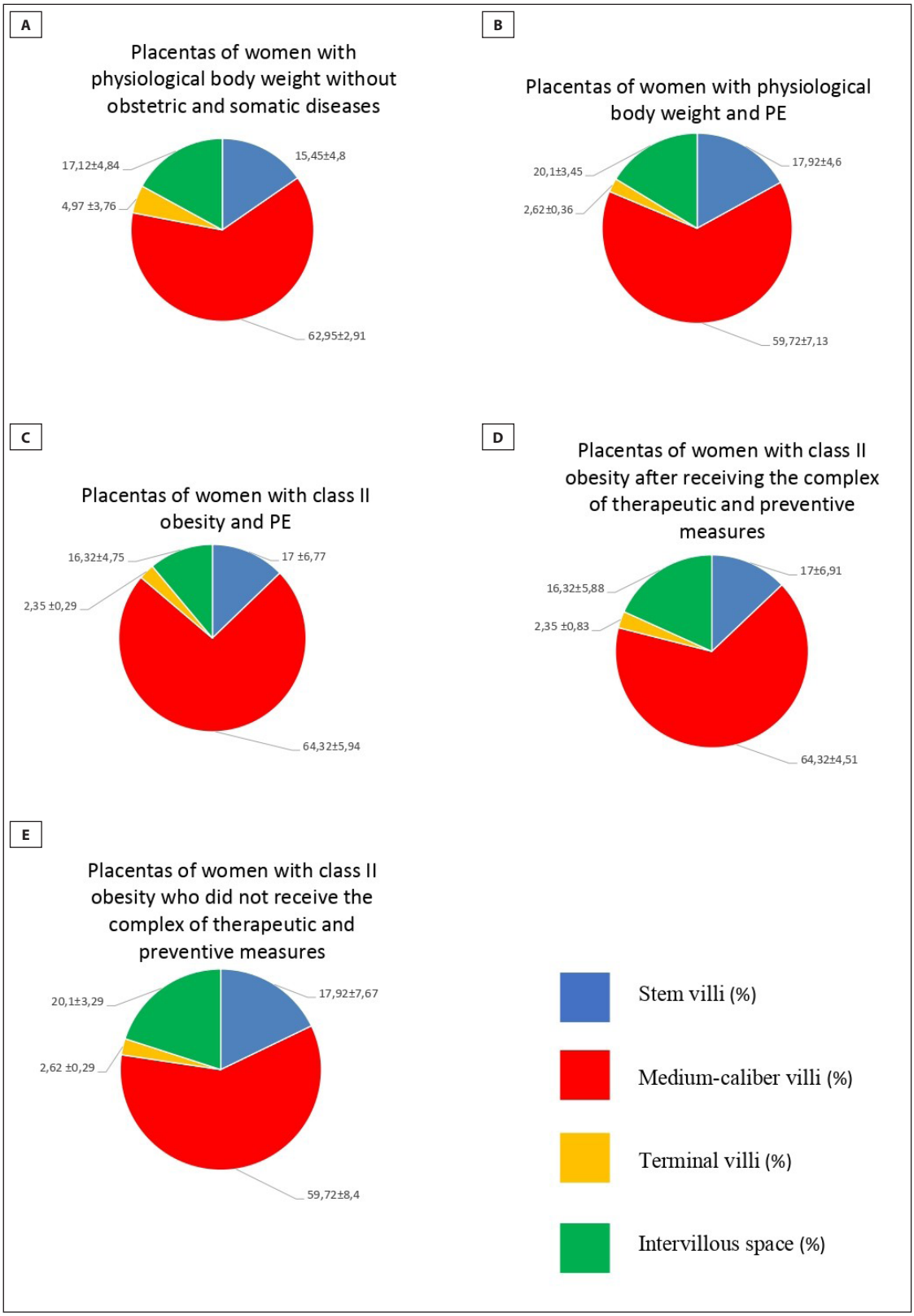

Fig. 2. Comparative characteristics of the relative volume of the main placental components in the studied groups A) Placentas of women with physiological body weight without obstetric and somatic diseases; B) Placentas of women with physiological body weight and PE ; C) Placentas of women with class II obesity and PE; D) Placentas of women with class II obesity after receiving the complex of therapeutic and preventive measures; E) Placentas of women with class II obesity who did not receive the complex of therapeutic and preventive measures.

in placenta samples from women with PE and physiological body weight, compared to the placenta samples from women of the control group (14.44±0.21 μm vs. 11.94±0.35 μm, p_1<0.01). There was a similar pattern found when comparing the indicators between the 3rd group and the 5th group (15.43±0.21 μm vs. 13.9±0.04 μm, p_3<0.01). An increase in the diameter of the capillaries of the placental terminal villi is seen in women with class II obesity compared to the control group (13.9±0.04 μm vs. 11.94±0.35 μm, p_6<0.01) (Table I).

The mean thickness of STB was slightly greater in the placenta samples from women with PE and physiologi-

cal body weight compared with the indicators in the group of women with PE and class II obesity (5.53±0.41 μm vs. 5.06±0.25 μm, respectively, p>0, 05). When comparing the indicators of the mean thickness of STB between the group of women with PE and physiological body weight and the indicators of the control group, we observed a tendency to their decline, but no significant difference was determined (5.53±0.41 μm vs. 5.96±0.76 μm, respectively, p>0.05). A significant decrease of this indicator was revealed in the group of women with PE and class II obesity compared to the indicators in the group of women with class II obesity (5.06±0.25 μm vs. 6.37±1.0 μm, respectively, p_3<0.01). A smaller thickness of STB was found in the placentas of women in the control group than in the placentas of women with II degree obesity (5.96±0.76 μm vs. 6.37±1.0 μm, respectively, p_6<0.02).

The morphological study of the volume fraction of the main placenta components demonstrates that the volume of stem villi in placentas makes up 12.42±6.67% in women with comorbidity of PE and class II obesity, 17.0± 4.6% in women with PE and physiological body weight; this indicator in the reaches 17.92±7.67% in group of women with class II obesity and 15.45±4.8% in the control group. The percentage of medium-calibre villi in the placentas of women with comorbidity of PE and class II obesity is 71.32±5.94%, and 59.72±7.13% in women with physiological body weight, whose pregnancy was complicated by the PE. The percentage of medium-calibre villi in the placentas of women with class II obesity is 59.72±8.4%, and in women with a physiological body weight and a normal course of pregnancy is 62.95±2.91%. The volume of placental terminal villi makes up 2.62±0.29% in women with the comorbidity of PE and obesity, 2.35±0.36% in women with PE and physiological body weight, 2.62 ±0.29% in women with class II obesity; this indicator in the control group is 4.97±3.76%. The indicators of the relative volume of the intervillous space are significantly lower in the placentas in the groups of women with PE and concomitant obesity and in women with PE and physiological body weight (16.32±4.75% and 20.1±3.45%, respectively, p<0.05); in the placenta samples of women with class II obesity, this indicator is at the level of 20.1±3.29%, and in the placentas of the control group it equals to 17.12±4.84% (Fig. 2).

Having analyzed the findings of the morphometric study of placenta samples from women with class II obesity, who received PTC, we can suggest that they are comparable to the control group and approaching the normal gestational parameters (Fig. 2).

The mean diameter of the terminal placental villi from women with class II obesity, who received PTC is 53.66±0.11 μm that is higher than in the placentas of women who did not receive PTC (53.66±0.11 μm vs. 48 ,44±0.37 μm, respectively p<0.01). The diameter of the placental capillaries in women who took the course of PE prevention is 12.42±0.15 μm that is similar to the respective indicators in the control group. The mean thickness of STB is smaller in women who received PTC compared to that in women who did not receive PTC during the pregnancy (6.03±0.58 μm vs. 6.37±1.05 μm, respectively p>0.05) (Table I). The morphometric study of the volume fraction of the main components of the placenta demonstrated that the volume of stem placental villi in women with class II obesity, who received PTC, makes up 12.92±6.91%. The percentage of medium-calibre villi in the placentas of women who took PE prevention is 66.1±4.51%, and the volume of terminal villi in this group is 2.8±0.83%. The indicator of the volume fraction of the intervillous space in the placentas of women who received PTC equals to 18.27±5.88% (Fig. 2).

Thus, the terminal placental villi in women with class II obesity and normal body weight, whose pregnancy was complicated by the mild PE development differ from those in women with physiological body weight and a normal course of pregnancy by a number of morphometric parameters including the diameter of the villi and their capillaries, STB thickness, changes in the parameters of the volume fraction of the main components of the placenta. It is worth to point out the morphometric placenta indicators of women with class II obesity, who received PTC during pregnancy, approach to the normal gestational parameters and can be comparable with the indicators of women with a physiological body weight and a normal course of pregnancy. The placentas from women with obesity who took PTC during the pregnancy have been found to show minor deviations of morphometric indicators and moderately expressed compensatory and adaptive reactions that correspond to normal gestational indicators. This proves the efficacy and feasibility of prescribing PTC to pregnant women with obesity in order to prevent the PE development.

DISCUSSION

In mild PE, premature placental aging accompanied with pronounced involutive-dystrophic processes can develop as opposed to the placental development during normal pregnancy that leads to fibrinoid necrosis and sclerosis of terminal villi with the subsequent occurrence of local ischemic infarctions of the placenta tissue [5]. Disorders of the normal histological structure of the placenta resulted from defective (delayed or early

maturation) maturation of chorionic villi are especially pronounced when PE develops in women with obesity.

A number of morphological changes detected in the placenta samples taken from women with mild PE demonstrate the impaired villi development and growth with an increasing angiogenic pattern, a decrease in the size of terminal villi, a reduced volume of the villous tree, which includes stem, intermediate and terminal villi. These changes are caused by the development of uteroplacental hypoxia and, as a consequence, malperfusion of the intervillous space [6]. Similar changes most likely cause lower indicators of placenta mass in pregnant women with obesity [7]. Since the main cause for the reduction in uteroplacental blood circulation in early-onset PE is considered to be the slowing down of the second wave of trophoblast invasion following 16 weeks of gestation, it is the incomplete invasion of cytotrophoblast into the uterine tissue that leads to incomplete transformation of the spiral arteries and a decreased inflow of maternal blood to the placenta with the further development of uteroplacental hypoxia [8]. Under pre-placental and utero-placental hypoxia, the extensive angiogenesis with vascular branching needed to increase the area for gas exchange of the villous tree is seen. The activation of pro-angiogenic factors is considered the main mechanism that triggers compensation processes in the villous tree of the placenta during hypoxia. Vascular endothelial growth factor (VEGF), placental growth factor (PlGF) and their receptors (VEGFR-1 and VEGFR-2) play the exceptionally important role in the formation of fetoplacental angiogenesis. Their balanced interaction determines the processes of vascularisation in villi in the early stages of pregnancy and the final formation of their capillary network, therefore, the development of either early-onset or late-onset PE is accompanied by a different degree of expression of angiogenic growth factors [9, 10]. The use of PTC we developed enables us to act on the term of PE manifestation that can be explained by both the PTC constituent components and the scheme of its medication regimen. According to our recommendations, the 1st PTC course lasts from the 12th to the 16th week of gestation as the process of interstitial cytotrophoblast invasion begins from the 16th to the 18th week of gestation. Impairment of this process is subsequently accompanied by the destruction of the elastomuscular components of vessels and their replacement with fibrinoid that results in deterioration of contractility of the placental vessels [11]. Therefore, the use of semi-synthetic diosmin, which has capillary protective, anti-edematous, anti-fibrinolytic, and anti-inflammatory effects, can prevent these adverse processes. And given the fact that the development of early-onset and late-onset PE is manifested with different expression of angiogenic growth factors, the use L-arginine, which is able to reduce the concentration of antiangiogenic growth factors and promote angiogenesis, which is essential for increasing the area of gas exchange of the villous tree, seems to be quite appropriate [12-15]. Hence, the balanced interaction of the medicines promotes the processes of vascularisation of the villi in the early stages of pregnancy and the final formation of their capillary network and thus helps to prevent early-onset PE.

The following alterations including a decrease in the diameter of the terminal villi and an increase in the diameter of their capillaries, an increase in the STB thickness, a reduction of the volume fraction of the stem and terminal villi, a growth in the percentage ratio of medium-calibre villi and a decrease in the volume fraction of the intervillous space indicate a deteriorating placental circulation and a decrease in the intervillous perfusion that initiates the development of adaptation and compensation processes. A significant deviation of the morphometric parameters of the terminal villi from the control level suggests the fact of insufficiency of compensatory and adaptive reactions in the placenta during mild PE under increasing hypoxic conditions. Hypovascularisation (reduction in the number of vessels and their mean diameter), the STB thinning, increase in syncytiocapillary membranes, impairment of the differentiation of the vascular-stromal component in the villous chorion and increased fibrin deposition in the epithelium of these villi along with hypofunction of the terminal villi have also been revealed by other scientists in cases of delayed fetal growth, and in cases complicated with PE that evidences the failure of compensatory changes at the stage of chronic placental insufficiency [16]. Thinning of the cellular trophoblast of the chorion we found in the groups of women with mild PE is in good agreement with the reports of other scientists and can be found in other pathological conditions, besides anaemia [17]. The positive changes we obtained after applying PTC in the percentage ratio of the volume fraction of the main components of the placenta support previous findings in the literature that point out a significant growth in the area of capillaries of terminal villi and syncytiocapillary membranes in the placentas of women who received L- arginine aspartate [18].

The analysis of the morphometric parameters of the small-calibre arteries of the placenta in anaemia demonstrates an increase in the outer diameter of these vessels that evidenced a pronounced decrease in the permeability of small-calibre vessels, which are under greater functional stress compared to larger arteries and are the first and

more pronounced to be affected in various pathological conditions [19]. These authors confirm the damage to a significant number of endotheliocytes that leads to their dysfunction, a decrease in the synthesis of nitric oxide (NO), blockade of NO synthase, activation of NO degradation processes that is accompanied by spasm and narrowing of blood vessels. The latter worsens blood supply to organs, maintains and intensifies hypoxia, which is complicated by oedema, dystrophy, necrobiosis of tissues and cells (under significant damage to endotheliocytes, the degree of morphological changes in the placenta is more pronounced) that yet again proves the need to use a combination of an NO donor and an angioprotector, which are the constituent agents of PTC we propose.

CONCLUSIONS

The morphometric investigation of placenta samples taken from women with comorbidity of mild preeclampsia and obesity has shown a significant decrease in the mean diameter of the terminal villi (32,66±1,22 μm vs. 36,52±1,16 μm, $p<0,01$) and an increase in the diameter of the capillaries of these villi (15,43±0,21 μm vs. 14,44±0,21 μm, $p<0,01$) when compared with a group of women with preeclampsia and physiological body weight. The study has also demonstrated the distortion of the percentage ratio of the volume of the intervillous space (16,32±4,75% and 20,1±3,45%, respectively) and the ratio of medium-calibre villi (64,32±5,94% and 59,72±7,13%, respectively). The combination of these changes indicates a lack of adaptive capabilities in the placenta during preeclampsia under increasing hypoxic condition.

The prophylactic therapy course, which combines L-arginine aspartate and semi-synthetic diosmin to reduce the occurrence of preeclampsia and other complications during pregnancy than may develop as a consequences of placental dysfunction under obesity, has been proven to reduce the structural, functional, and dystrophic changes of the placenta and bring the respective indicators in proximity to the normal values.

PROSPECTS FOR FURTHER INVESTIGATION

The easy of use, accessibility, and convincing positive results of the described method of pharmacological correction enables us to recommend this PTC for enhancing the effectiveness of the PE prevention in pregnant women with obesity thus preventing the incidence of obstetric and prenatal complications.

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Conflict of interest:
The Authors declare no conflict of interest.

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