ORIGINAL ARTICLE

CHARACTERISTICS OF CD68$^+$ AND CD163$^+$ EXPRESSION IN PLACENTA OF WOMEN WITH PREECLAMPSIA AND OBESITY

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ABSTRACT

The aim: To study the peculiarities of CD68+ and CD163+ macrophage expression in the placentas of women with obesity who developed preeclampsia by applying immunohistochemical method.

Materials and methods: The study included 20 placentas taken from women who delivered full-term live-birth babies. The women were divided into 4 groups of 5 individuals each: women with physiological body weight (1st group); women with class II obesity (2nd group); women with physiological body weight and preeclampsia (3rd group); women with class II obesity, who developed preeclampsia (4th group).

Results: The analysis of the expression level of CD68$^+$ and CD163$^+$ decidual macrophages shows the predominance of CD68$^+$ pro-inflammatory profile over CD163$^+$ anti-inflammatory profile in women of all groups. Evaluation of CD68$^+$ and CD163$^+$ expression levels of Kashchenko-Hofbauer cells in the stroma of the terminal villi of the placenta shows that the expression level of CD68$^+$ macrophages is significantly higher in women with obesity and preeclampsia than in the control, or in women with obesity or preeclampsia. There was a reverse tendency to the polarization shift in Kashchenko-Hoffbauer cells in the stroma of the terminal villi towards the predominance of CD163$^+$ macrophages over CD68$^+$ macrophages in all groups of women.

Conclusions: The imbalance in anti-inflammatory and pro-inflammatory profile of placental macrophages with a predominance of the latter can lead to the development of preeclampsia.

KEY WORDS: preeclampsia, pregnancy, M1 and M2 macrophages, obesity

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INTRODUCTION

Obesity is becoming an increasingly common disease globally. Nowadays experts estimate that the percentage of European women suffered overweight is 6-37% [1]. The prevalence of coronary heart diseases is also rising in women of childbearing age and moreover, currently, more than one in five pregnant women go through it. Maternal obesity is related to increased morbidity and mortality rate of both mothers and foetuses. Obesity provokes the development of antenatal risks, including preeclampsia (PE). An increase in gravida body mass index (BMI) from 35 kg/m^2 and above causes a 30% build-up in the risk of PE development [2]. However, the mechanisms underlying the increased risk of obesity and PE in pregnant women are still insufficiently studied.

The leading factors contributing to obesity are known to include low-grade inflammation, endothelial dysfunction (ED), and immune system hyperactivity. Obesity is accompanied by local (adipose tissue, placenta and vascular endothelium) and systemic (circulating plasma factors) manifestations of increased inflammatory response. Disorders of placental development in pregnant women with result from the accumulation of lipids in the form of non-esterified fatty acids and high levels of circulating pro-inflammatory mediators (TNF-α, IL-1β, IL-6, CRP) [3], which, in turn, trigger dysregulation of trophoblast invasion, oxidative stress, the rise of local inflammation and migration of activated immune cells into the tissue at the maternal-foetal interface. These placental lesions often witness the PE course. The connection between maternal obesity and PE is considered to involve immune cells in the maternal adipose tissue and the placenta that contributes to more severe placental disorders.

Macrophages are cells of the innate immune system; they maintain homeostasis in the placenta by regulating the processes of placentation, angiogenesis and tissue remodelling; they provide immune tolerance in the mother-foetus system. There are two main subpopulations of macrophages: classically activated pro-inflammatory M1 type (CD68) and alternatively activated anti-inflammatory M2 type (CD163) [4, 5]. These phenotypes are different by their functions, switching stimuli, gene expression profiles and, as a consequence, they respond differently to external factors. Now the impairment of the M1 / M2 macrophage polarisation is considered as one of the key factors promoting the development and progression of obesity [6]. It has been proven the imbalance between the M1 / M2 macrophage ratio in the placenta is observed during pregnancy with intrauterine growth retardation [5], as well as in PE [7, 8]. However, the role of M1 and M2 macrophages and

the process of their polarization in the placenta in women with obesity and PE are still unclear and require further study. This will deepen knowledge about the pathogenetic mechanisms of the conditions and promote their targeted therapy.

THE AIM

The aim of this study is to investigate the peculiarities of CD68+ and CD163+ macrophage expression in the placenta of women with obesity, who developed preeclampsia by applying immunohistochemical method.

MATERIALS AND METHODS

The study included 20 placentas taken from women who delivered full-term live-birth babies at Poltava Clinical Maternity Hospital from 2019 – 2020. The women were divided into 4 groups of 5 individuals each: women with physiological body weight (1st group); women with class II obesity (2nd group); women with physiological body weight and PE (3rd group); women with class II obesity, who developed PE (4th group). The participants gave informed consent to personal data collection and processing as well as to examination of the placenta after delivery. The study design was approved by the Commission on Bioethics, Poltava State Medical University (Minutes № 170, 24.01.2019).

The diagnosis of class II obesity was confirmed by BMI values ranging from 35 to 40 kg/m^2; the PE diagnosis was established and confirmed according to the criteria of the Society of Obstetricians and Gynaecologists of Canada (SOGC) 2014, Canada [9]. Inclusion criteria: singleton pregnancy, timely delivery, women with physiological body weight and class II obesity, PE. Exclusion criteria: multiple pregnancy, premature birth, severe extragenital pathology.

The morphological material was fixed in 10% neutral buffered formalin, dehydrated in alcohols and embedded in paraffin. For histological verification, 6-9 pieces were excised from the organ (central, paracentral, peripheral parts of the placenta). To study the structure of the placenta, histological preparations were stained with hematoxylin-eosin. The sections were examined under microscope followed by photographing (x200, x400; Axio Lab.A1, Zeiss, Germany).

The expression of CD68+ and CD163+ macrophages was investigated in all samples by using immunohistochemical streptavidin peroxidase method. Paraffin sections, 4 μm thick, were deparaffinized and dehydrated, antigens were recovered in citrate buffer in the microwave oven, and endogenous peroxidase was blocked. Further, the sections were incubated at 4°C overnight with murine monoclonal antibodies anti-CD68 (1:25, clone PG-M1, REF PD M065-S, Diagnostic BioSystems, USA) and anti-CD163 (1:100, clone 10D6, REF Mob460-01, Diagnostic BioSystems, USA). Afterwards, the sections were treated in two steps with the Mouse/Rabbit PolyVue™ HRP/DAB Detection System (Diagnostic BioSystems, USA), with visualization by chromogen; the nuclei were counterstained with Mayer's haemalaun. We used Antibody Diluent buffer as a negative control instead of primary antibodies, and lymph node tissues were used as a positive control. Quantitative indicators were obtained by counting immunopositive CD68+ and CD163+ cells over the entire field of view with a large magnification lens ×40 (high power field, HPF) of placenta. We took into account all obtained quantitative individual data from all fields of view with calculating the mean value. The sections were examined under microscope followed by photographing (x200, x400; Axio Lab. A1, Zeiss, Germany)

Analyses were performed using Prism 5.0 (GraphPad, CA, USA). P-values <0.05 were considered to indicate statistical significance. Normally distributed data were reported using the means with standard deviations, categorical variables were reported using counts and proportions. Comparisons between the groups were performed using parametric T-test and nonparametric methods: $\chi 2$ Fischer exact test, Spearman´s correlation test.

RESULTS

The analysis of CD68+ and CD163+ decidual macrophage expression showed (Fig. 1) the level of pro-inflammatory CD68+ placental macrophages in pathological pregnancy in contrast to pregnancy of women with physiological body weight (7.96±0.23%) was significantly higher in women with obesity (10.64±1.01%, p = 0.03), in women with physiological body weight and PE (11.04±0.87%, p = 0.009), and in women with obesity and PE (19.2±1.48%, p = 0.00008). The CD68+ level in placental decidua was significantly higher in women with obesity and PE than in women with obesity without PE (19.2±1.48% vs. 10.64±1.01%, respectively; p = 0.0004).

The shift of decidual macrophage polarization towards the predominance of CD68+ pro-inflammatory profile over CD163+ anti-inflammatory profile was observed in women of the control group (7.96±0.23% vs. 3.92±0.48%, respectively; p = 0.0006), in women with physiological body weight and PE (11.04±0.87% vs. 5.16%, respectively, p = 0.0006), and in women with obesity and PE (19.2±1.48% vs. 4,72±0.18%, respectively; p = 0.000001).

Evaluation of the CD68+ and CD163+ expression level of Kashchenko-Hofbauer cells in the stroma of the placental terminal villi demonstrates (Fig. 2) the CD68+ expression level is significantly higher in women having obesity and PE (11.4±0.42%) than in women with physiological body weight (7.96±0.41%, p = 0.0004), or in women with obesity (8.6±0.35%, p = 0.04), or in women with PE (10.08±0.53%, p = 0.04). Similarly, the CD163+ expression level in the stroma of the terminal villi is also significantly higher in women with obesity and PE (19.0±0.85%) than in women with physiological body weight (16.24±0.67, p = 0.03).

We noted the reverse tendency of shifting Kashchenko-Hofbauer cell polarization in the stroma of the placental terminal villi towards the predominance of the CD163+ anti-inflammatory profile over the CD68+ pro-inflammatory profile in the groups of women with physiological body

Table I. Expression of placental CD68+ and CD163+ macrophages in the fields of view in the experimental groups

Fields of view in placenta	Women with physiological body weight, (n=5)		Women with class II obesity, (n=5)		Women with physiological body weight, whose pregnancy is complicated by PE, (n=5)		Women with class II obesity whose pregnancies are complicated by PE, (n=5)	
	CD68+,%	CD163+,%	CD68+,%	CD163+,%	CD68+,%	CD163+,%	CD68+,%	CD163+,%
Decidua	7,96±0,23	3,92±1,08[4] p4=0,0006	10,64±1,01[1] p_1=0,03	9,12±0,7[1] p_1=0,003	11,04±0,87[5] p_5=0,009	5,16±0,64[4,6] p_4=0,0006 p_6=0,003	19,2±1,48[2,3] p_2=0,000008 p_3=0,0004	4,72±0,18[3,4] p_3=0,003 p_4=0,000001
Villous stroma in terminal villi	7,96±0,41	16,24±0,67[4] p4=0,000006	8,6±0,35	14,8±1,18[4] p_4=0,001	10,08±0,53[5,6] p_5=0,01 p_6=0,047	16,0±0,51[4] p_4=0,00004	11,4±0,42[2,3] p_2=0,0004 p_3=0,04	19,0±0,85[2,3,4,7] p_2=0,03 p_3=0,02 p_4=0,0004 p_7=0,02
Cells in blood vessels	2,4±0,43	3,24±0,35	3,96±0,72	2,08±0,56	3,36±0,47	4,52±0,57[6] p_6=0,03	4,44±0,72[2] p_2=0,04	1,64±0,34[2,4,7] p_2=0,01 p_4=0,02 p_7=0,002
Fibrosis of the villi	2,74±0,17	2,12±0,68	4,44±0,48[1] p_1=0,01	5,36±0,67[1] p_1=0,009	3,08±0,46	3,72±0,55	4,52±0,5[2] p_2=0,009	6,8±0,97[2] p_2=0,004

Note: the numbers indicate a statistically significant difference at $p<0.05$

[1] comparison between the indicators of the control group and the group of women with class II obesity;

[2] comparison between the indicators of the control group and the group of women with class II obesity and PE;

[3] comparison between the indicators of the group of women with class II obesity and the group of women with class II obesity and PE;

[4] comparison between values of CD68+ and CD163+ macrophages.

[5] comparison between the indicators in the control group and in the group of women with physiological body weight and PE;

[6] comparison between the indicators in the group of women with physiological body weight and PE and the group of women with class II obesity;

[7] comparison between the indicators in the group of women with physiological body weight and PE and the group of women with class II obesity whose PE pregnancy.

weight (16.24±0.67% vs. 7.96±0.41%, respectively; p = 0.000006), physiological body weight and PE (16.0±0.51% vs. 10.08±0.53%, respectively; p = 0.00004), with obesity (14.8±1.18% vs. 8.6±0.35%, respectively; p = 0.001), and obesity with PE (19.0±0.85% vs. 11.4±0.42%, respectively; p = 0.0004).

The analysis of the CD68+ and CD163+ expression level in sites of fibrotic changes in the placental terminal villi showed (Table I) that the levels of CD68+ and CD163+ macrophages in women of the control group were lower than in women with obesity (p = 0.01; p = 0.009, respectively) or in the women having obesity and PE (p = 0.009; p = 0.004, respectively). No shift in the M1 / M2 macrophage polarization was found in fibrotic areas of the placenta in any of the studied groups. A significantly higher expression level of the anti-inflammatory profile of CD163+ mononuclear cells in the blood vessels of the terminal villi was found in women with physiological body weight and PE compared with the women with class II obesity (p = 0.002).

The assessment of the CD68+ and CD163+ monocyte expression level in the capillaries of the placental terminal villi showed (Table I) significantly higher values of both cell types in women with obesity and PE than in women of the control group (p = 0.04; and p = 0.01, respectively). The level of CD163+ monocytes was significantly lower in women with physiological body weight than in women with PE (p = 0.03), as well as in women with PE compared to women with obesity and PE (p = 0.02). At the same time, only in women with obesity and PE the polarization of M1 / M2 monocytes shifted towards the probable predominance of the pro-inflammatory CD68+ profile over the anti-inflammatory CD163+ profile (p = 0.008).

DISCUSSION

Thus, we have found out the differentiated immunophenotype of placental macrophages, which play different region-specific roles during pregnancy under the conditions of obesity, preeclampsia or comorbidity between obesity and PE.

Obesity is characterized by chronic low-grade inflammation and ED. During pregnancy, obesity acts as an independent pregravid trigger of cascade processes in the placenta, and in particular, increased inflammation and ischemic-induced vascular dysfunction. The inflammatory response to placental ischemia is even suggested to be more intense in pregnant women with obesity due to the activation of immune mechanisms involving macrophages. Our findings have revealed a high expression level of both pro-inflammatory CD68+ and anti-inflammatory CD163+ macrophages in the decidua and in sites of fibrotic changes in the placental terminal villi in women with class II obesity, but without a significant polarization of M1 / M2 macrophages in the tissues. However, there has been revealed a polarization shift toward the predominance of the anti-inflammatory CD163+ Kashchenko-Hofbauer cell pool in the terminal chorionic villi in women with class II obesity. Today, the role of placental macrophage polar-

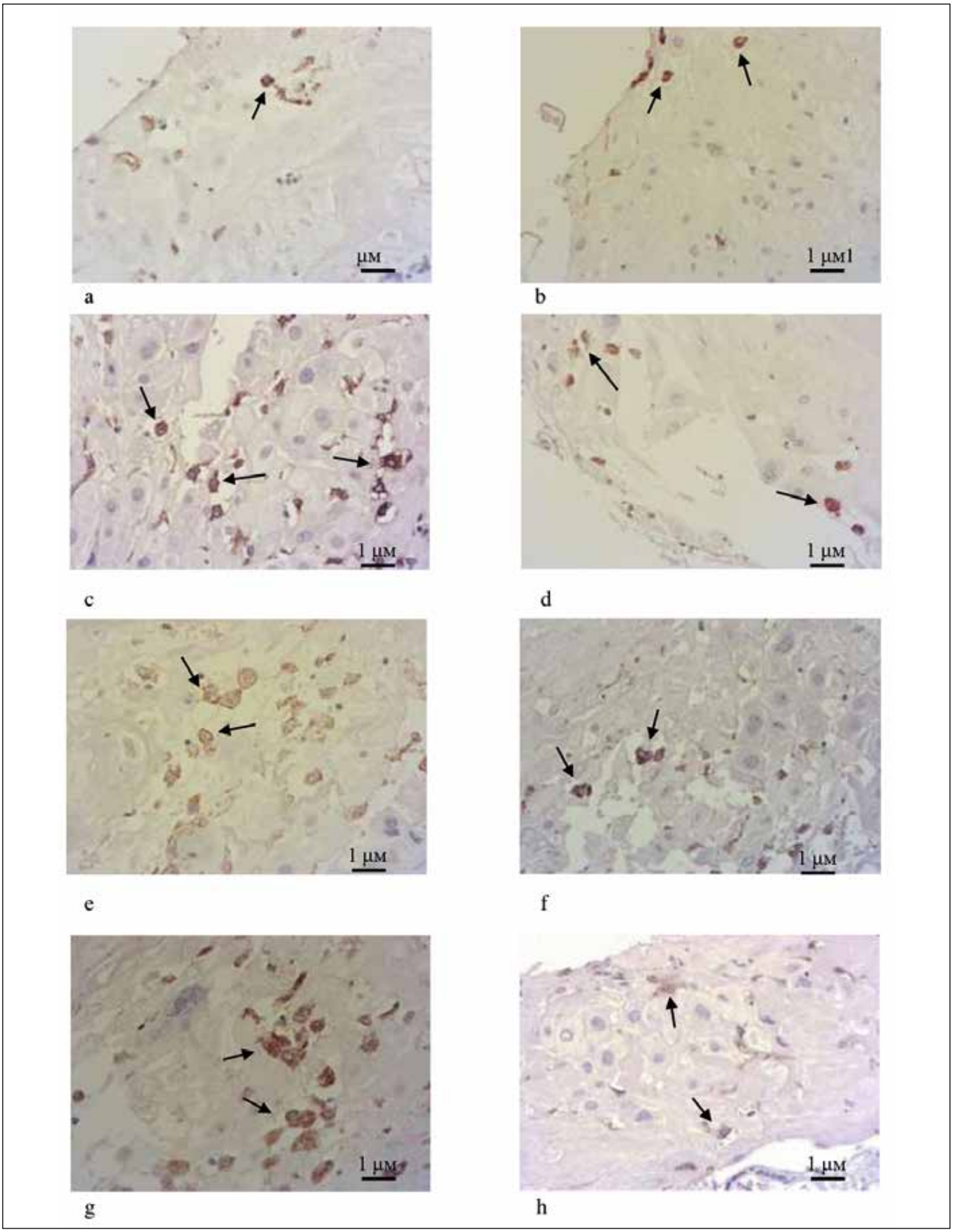

Fig. 1. Expression of CD68+ (a, c, e, g) and CD163+ (b, d, f, h) macrophages in the placental decidua in women with physiological body weight (a, b); women with physiological body weight and preeclampsia (c, d); women with class II obesity and preeclampsia (e, f); women with class II obesity (g, h); hematoxylin staining, magn. x400.

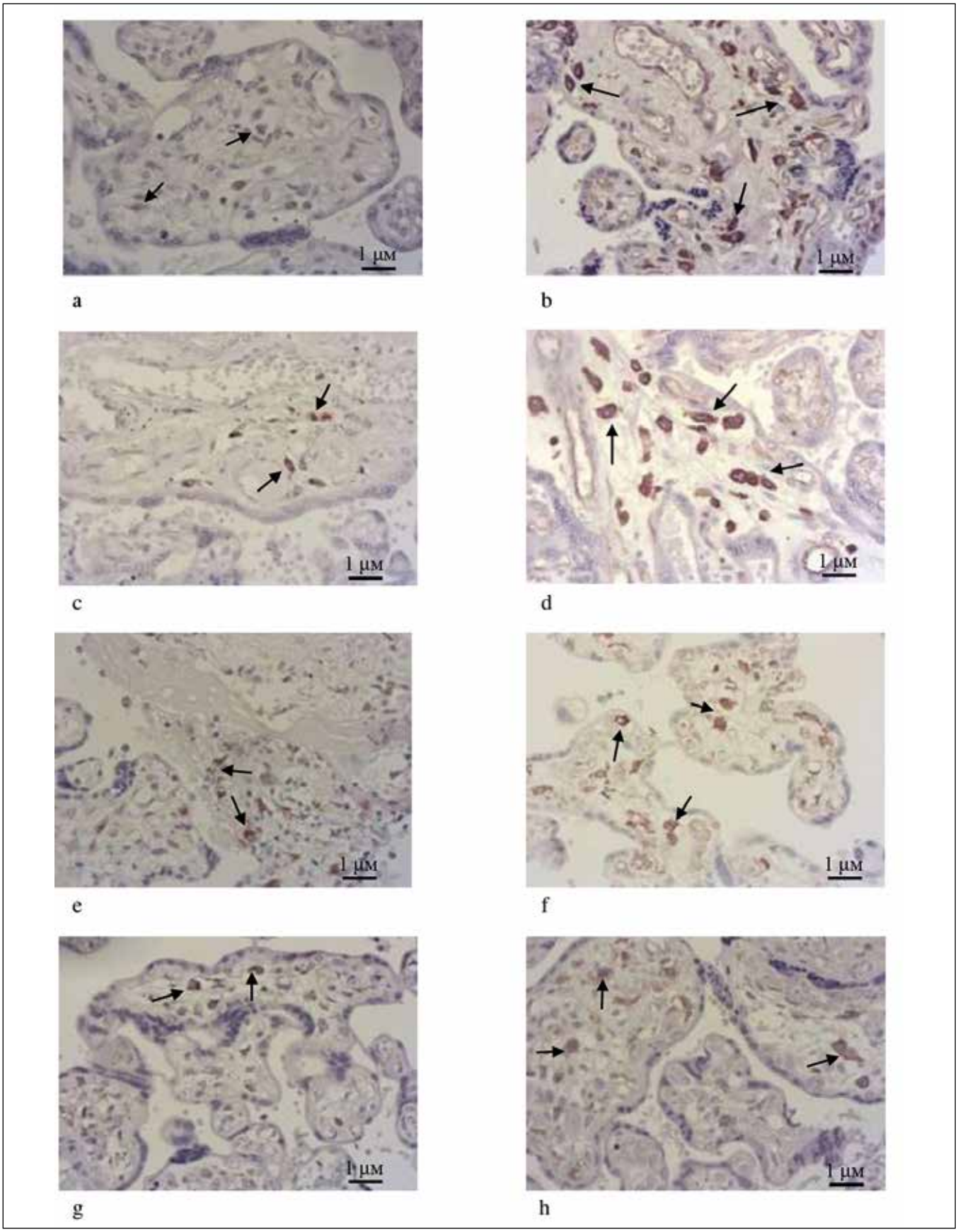

Fig. 2. Expression of $CD68^+$ (a, c, e, g) and $CD163^+$ (b, d, f, h) macrophages in the stroma of the placental terminal villi in women with physiological body weight (a, b); women with physiological body weight and preeclampsia (c, d); women with class II obesity and preeclampsia (e, f); women with class II obesity (g, h); hematoxylin staining, magn. x400.

ization in obesity is still obscure. Special attention should be paid to decidual macrophages involved in remodelling the uterine vascular wall because of their importance in maintaining placentation and pregnancy, as well as to Kashchenko-Hofbauer cells, which regulate placental vasculo- and angiogenesis and manifest a pro-angiogenic phenotype [10]. Previously, Challier J.C. et al. (2008) [6] reported high levels of $CD14^+$, $CD68^+$, $CD11c^+$ resident decidual macrophages, which correlated with the level of pro-inflammatory markers IL-6 and CRP in pregnant women with obesity, in contrast to normal weighing pregnant women. Our results are consistent with the data of other authors [11,12], who found a high frequency of fibrin deposits in placental villi in women with obesity that interferes with perfusion and exchange of gases / nutrients in the intervillous space, and results in chronic placental insufficiency, as well as high level of M2 Kashchenko-Hofbauer cells in the villous stroma and decreased levels of M1 macrophages in the decidua. It may indicate the increasing need in regulatory macrophage phenotypes rather than in a pro-inflammatory phenotype to maintain maternal tolerance to an immunologically semi-allogenic foetus, regulatory functions, and tissue remodelling. This functionally divergent activity of macrophages can be explained by switching on a successful mechanism to compensate increased inflammatory state in pregnant women with obesity in the third trimester.

Inadequate trophoblast remodelling of the uterine spiral arteries resulted from excessive activation of the maternal immune response and placental angiogenesis is reported as a key feature of PE course. The exact mechanisms underlying placental lesions in PE have not been elucidated yet. The findings obtained from women with physiological body weight and PE in contrast to women in the control group showed a high level of pro-inflammatory profile of $CD68^+$ decidual macrophages and Kashchenko-Hofbauer cells in the terminal villi of the chorion. At that, there was a polarization shift towards the predominance of M1 pro-inflammatory pool of $CD68^+$ decidual macrophages, and vice versa M2 anti-inflammatory pool of $CD163^+$ Kashchenko-Hofbauer cells in the stroma of the placental terminal villi in women with physiological body weight and PE. Our data are consistent with the results of the report [13] that also reveal a high level of $CD68^+$ decidual macrophages in the placenta of women with PE. Other authors have shown that macrophages are phenotypically different in pregnant women with PE, as the ratio between $CD163^+$ / $CD14^+$ and $CD206^+$ / $CD68^+$ reduces in the decidua [14]. Moreover, a decrease in the number of $CD206^+$ macrophages in uterine tissue was found out in the PE model in rats [15]. Therefore, there is suggestion that the polarization shift towards the anti-inflammatory type M1 is observed in PE. In vitro studies have demonstrated that enhanced production of TNF-α by macrophages intensifies the expression of MMP-1, MMP-3 and MMP-9 matrix metalloproteinases in decidual cells, thus interfering with the normal stepwise process of trophoblast invasion [16]. As M2 macrophages produce proteases necessary for the degradation of the extracellular matrix surrounding the spiral arteries [17], a decrease in the number of decidual M2 cells may also lead to impaired vascular remodelling.

At present, the concept of dysfunction of the maternal immune cells is considered as an underlying cause of inflammation and ED under obesity that is critical for the establishment of intraplacental circulation. Thus, our study has showed the shift in polarization toward the predominance of M2 anti-inflammatory pool of $CD163^+$ Kashchenko-Hofbauer cells in the chorionic villi stroma, and vice versa a shift in the polarization of macrophages / monocytes toward the M1 pro-inflammatory pool of $CD68^+$ cells in the decidua and capillaries of the stroma.

Some authors report a high level of MCP-1 synthesis in the placenta in obesity that triggers the infiltration and accumulation of $CD14^+$ and $CD68^+$ macrophages [18, 6], and the latter are intensively producing pro-inflammatory cytokines IL-1, TNF-α. High levels of pro-inflammatory cytokines TNF-α and IL-6 in the circulation are also observed in PE [19]. Phenotypic and genotypic similarity between $CD14^+$ placental and circulating monocytes were found out in pregnant women with obesity. They are the circulating monocytes that can produce TNF-α and ROS, as well as adhere to syncytiotrophoblast cells and damage the trophoblast barrier [20], opening the way for cellular infiltration and promoting the further spread of inflammation at the maternal-foetal interface. Thus, the comorbidity between obesity and preeclampsia is accompanied by the impairment of compensatory mechanisms involving the polarization processes of M1 / M2 macrophages / monocytes in the placenta [21] that determines the development of further dysregulation of uteroplacental circulation and the occurrence of perinatal complications.

PROSPECTS FOR FURTHER INVESTIGATION

Monocytes and tissue macrophages are extremely important cell types involved in the PE pathogenesis. This provides a good starting point for further research of using them as PE predictors, macrophage reprogramming for therapeutic purposes, as well as the elaboration of therapeutic modes to restore the normal differentiation of subpopulations of decidual macrophages.

CONCLUSIONS

1. In the placentas of women with obesity and preeclampsia there has been found out a significant predominance of decidual M1 macrophages over decidual macrophages of the M2 phenotype compared with the placentas of women with physiological body weight.
2. The imbalance in anti-inflammatory and pro-inflammatory profile of placental macrophages with a predominance of the latter can lead to the development of preeclampsia

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