ОГЛЯДИ ЛІТЕРАТУРИ

FEATURES OF STRUCTURE AND FUNCTIONS OF DECIDUAL MACROPHAGES IN HEALTHY PREGNANCY AND PREECLAMPSIA*

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Згідно сучасних літературних даних децидуальні макрофаги відіграють суттєву роль як у фізіологічному, так і патологічному перебігу вагітності за рахунок їх пластичності та імуносупресивних властивостей, участі у ремоделюванні тканин та судин, здатності формування місцевого адаптивного імунітету. Але на сьогоднішній день ще відсутня достатня кількість даних щодо особливостей рівнів цитокінів, характеру фенотипових та морфо-функціональних змін макрофагів, співвідношення субпопуляцій децидуальних макрофагів при фізіологічному і патологічному перебігу вагітності, що обмежує розуміння патогенетичної ролі М1 та М2 децидуальних макрофагів при прееклампсії. Лише вірогідною, але не доказаною є думка, що розвиток прееклампсії пов'язаний з дисбалан-сом децидуальних макрофагів під час пізньої фази I триместру та ранньої фази II триместру вагітності з перева-жанням макрофагів фенотипу М1 та подальшим неадекватним ремоделюванням спіральних артерій матки. Не ви-вчена ефективність профілактики прееклампсії шляхом стимуляції диференціації децидуальних макрофагів в сто-рону фенотипу М2. Отримані результати обумовлюють доцільність та актуальність подальшого вивчення етіопатогенезу прееклампсії, вдосконалення знань імунологічних механізмів розвитку даної акушерської патології (з урахуванням особливостей диференціації субпопуляцій децидуальних макрофагів із формуванням фенотипів М1 та М2) та визначають потребу в розробці нових методик раннього формування груп вагітних високого ризику по прееклампсії, шляхів вторинної профілактики захворювання, які б дали можливість розробити ефективну тактику ведення вагітних з прееклампсією, цілеспрямовано направлену на зниження показників материнської і перина-тальної захворюваності та смертності.

Ключові слова: децидуальні макрофаги, цитокіни, прееклампсія, вагітність.

According to modern scholarly data, decidual macrophages play a significant role both in the physiological and patho-logical course of pregnancy due to their plasticity and immunosuppressive properties, participation in the remodeling of tissues and vessels, and the ability to form a local adaptive immunity. The normal course of pregnancy is characterized as a condition of moderate systemic inflammatory process because of activation of the immune system components, in the first place, the innate immunity and vascular endothelium. The development of preeclampsia is characterized by the impairment of placental processes and production of pathologically altered placenta, an excess of proinflammatory cyto-kines that contribute to the development of a systemic inflammatory response. However, there is still not enough data on the peculiarities of cytokine levels, the nature of phenotypic and morphofunctional macrophage changes, the ratio of subpopulations of decidual macrophages in the physiological and pathological course of pregnancy, which limits the un-derstanding of the pathogenetic role of M1 and M2 decidual macrophages in preeclampsia. It is only probable, but not proven, that the development of preeclampsia is associated with an imbalance of decidual macrophages during the late phase of the first trimester and the early phase of the second trimester of pregnancy, with the predominance of macro-phages of the M1 phenotype and subsequent inadequate remodeling of the uterine spiral arteries. The effectiveness of preventing preeclampsia by stimulating the differentiation of decidual macrophages in the direction of the M2 phenotype has not been studied. The obtained results determine the expediency and relevance of further studying the etiopatho-genesis of preeclampsia, improving the knowledge of the immunological mechanisms of this obstetric pathology devel-opment (taking into account the peculiarities of differentiation in subpopulations of decidual macrophages with the for-mation of M1 and M2 phenotypes) and determine the need for the development of new methods for the early formation of high-risk groups for preeclampsia, ways of secondary prevention of the disease, which would enable us to develop effective tactics for the management of pregnant women with preeclampsia, specifically aimed at reducing maternal and perinatal morbidity and mortality.

Key words: decidual macrophages, cytokines, preeclampsia, pregnancy.

Introduction

Preeclampsia accounts for a significant proportion in the structure of maternal and perinatal morbidity and mortality, and at present belongs to the most severe complications of pregnancy, delivery and postpartum period [3,13]. The frequency of preeclampsia cases, registered in Ukraine within recent years, in the population of women of reproductive age is 7-16%. Preeclampsia is a complex neurohumoral pathophysiological process, which is manifested by different disorders in the activity of nervous, cardiovascular and endocrine systems, as well as impaired metabolism, immune response and dysfunction of the body in the form of multiple organ and polysystemic failure [4.13].

Recently, the clinical presentation of preeclampsia has a tendency towards the blurring of clinical manifestations, an increase in the proportion of cases of atypical and latent forms of the disease, which in turn is no less dangerous compared with its classical course [3,4,13]. In the modern world, there is no single theory of etiopathogenesis of preeclampsia, which would make it possible to prevent its development. There are more than 30 theories as to the formation and the various aspects of preeclampsia development, each of which, in our opinion, is a separate component in the overall pathogenesis of this disease [3,13,31].

The aim of our research is to summarize the modern ideas presented in the scientific literature as to the peculiarities of differentiation in subpopulations of decidual macrophages in healthy pregnant women and in women with preeclampsia. The present paper is a part of research project of the Department of Obstetrics and Gynecology No.2 for 2017-2022 "The role of chronic infection of the uterus and the lower sections of the genital tract in the formation of obstetric and gynecological pathology" (state registration No.0117U005276).

The leading idea of preeclampsia occurrence is based on the theory of the second wave of trophoblast invasion in the spiral arteries of the uterus (i.e., in their myometric segment). In normal pregnancy, trophoblasts interact with the decidual membrane and with the unique uterine NK-cells, modifying their cytokine repertoire, regulating adhesion of the molecules and matrix metalloproteinases [1.35]. Several proinflammatory (tumor necrotic factor-alpha, gamma-interferon) and anti-inflammatory (interleukins 4 and 10) cytokines, produced in the maternal-fetal interface, affect the trophoblast invasion in the spiral arteries of the uterus in the area of the placental bed [6,23,32]. The inability of trophoblasts to complete the invasion can be a critical factor for the onset of gestosis. Excessive inflammatory response of the mother (in the form of excessive release of proinflammatory cytokines with anti-inflammatory cytokines deficiency) may lead to a defective invasion of trophoblast in the spiral arteries of the uterus, followed by the formation of systemic endothelial dysfunction, which is an important component in the impaired functioning of cells of the vascular bed [1,6,10, 20].

At present, more and more attention is being paid to immunological theory, since the onset of preeclampsia is a process, similar to allograft rejection, which includes the synthesis of antibodies [1,8,9,22]. The hypothesis of switching the immune response, which is the leading concept of changes in regulatory mechanisms during pregnancy, is explained by the indirect influence of T-helper cells type 1 and 2 (Th$_I$, Th$_2$) on the immune deficiency (the so-called "Th$_I$/Th$_2$ paradigm of pregnancy") [11.31]. The major role of this concept is attributed to the action of cytokines. Th$_2$ cytokines (IL-4, IL-5, IL-6, IL-9, IL-10) stimulate trophoblast invasion, and such cytokines as Th$_I$ (TNF-α, IL-2, IL-8, IL-12) limit the given process [11,22,23,40]. However, to date, the functioning mechanisms of cells of the placental endothelium in physiologic and pathologic pregnancy have not been examined.

A significant role in the provision of immunological tolerance belongs to macrophages and monocytes, which account for about 10-15% of the total quantity of cells of the human body [14,15,25].

Macrophages are differentiated from monocytes, that in turn are formed from CD34+-myeloid progenitor cells of the bone marrow, which, circulating in the bloodstream, penetrate the peripheral tissues where different types of tissue macrophages are maturing [17,28].

There are two ways to activate macrophages: classic and alternative. The activation of classical path occurs under the conditions of macrophages contact with active T-helper type 1 (Th$_I$) [6,12]. The activated Th$_I$-cell begins to develop a specific spectrum of cytokines, in particular interferon-γ. At the same time, the CD40 ligand is expressed on its membrane. These proteins communicate with the corresponding superficial macrophage receptors and cause its activation. The classically activated macrophage is subjected to changes that substantially increase the protective properties, which are unnecessary for degradation of pathogenic agents and the ability to stimulate the immune response [1,6,21]. Activated macrophages produce a significant amount of active oxygen forms (AOF) and nitrogen oxide (NO). The amplification of synthesis of nitrogen oxide is caused by the enhanced expression of inducible NO-synthase (iNOS). Active forms of oxygen and nitrogen oxide determine the activity of activated macrophages for cytotoxic effects. Moreover, the rate of expression of CD40 and receptors to TNF-α increases on their membrane. Macrophage begins to actively produce TNF-α, which, by autocrine method, affects receptors located on the macrophage surface and enhances its activation [23].

There are 2 phenotypes of activated macrophages: Ml (proinflammatory phenotype) and M2 (immunomodulatory and tissue remodeling phenotype). This distribution corresponds to the classification of activated T-lymphocytes into types (Th1 and Th2), which causes the association of macrophages with a specific phenotype, implementing a targeted path of the immune response [2,29,30,38].

The cells of the M1 phenotype produce a significant amount of IL-12, IL-23, and they are active producers of proinflammatory cytokines (IL-1, FNP-α, IL-6). M1 macrophages act directly as induction effector cells in Th1-type reactions, having strong bactericidal qualities due to the synthesis of AOF, NO and proinflammatory cytokines [6,30,36].

Alternative activation type of M2 combines various forms of macrophages activated nonclassically, due to the action of IL-4, IL-10 or IL-13, immune complexes, vitamin D3, some hormones (in particular, glucocorticoids) [2,23,32]. Some forms of macrophages of the M2-phenotype express a large number of mannose and phagocytic receptors, galactose-type receptors. In the metabolism of arginine, there is a shift towards the development of ornithine and polyamines due to the active action of arginase [18,39]. The considered M2 macrophages play a role in the activation of Th2-type immune responses, in particular, allergic reactions of the reagin

type and immune responses in parasitic invasion. They have an increased phagocytic activity and direct eosinophils to the inflammatory site [27,33,39].

In the modern world, the division of activated macrophages into two categories (M1 and M2) is somewhat arbitrary. One can determine the existence of certain functional states of macrophages, wherein macrophages are localized at one of the poles, actively stimulating the inflammatory process, and at the other – there are macrophages, which amplify tissue regeneration after suppression of inflammation. Macrophages of healthy intact tissues are most likely to be localized between the indicated poles. Macrophages retain the property of an active response to a variety of stimuli affecting them, depending on the primary polarization and the degree of differentiation. This property of macrophages is commonly known as the plasticity of the macrophage phenotype [1,17,19,34,37].

In pregnancy, the system of maternal immunity undergoes exhaustion due to a semi-allogenic fetus. The processes of adaptation of the mother's immune system take place at the local level (maternal-fetal interface). The main role in the immunological processes during pregnancy is played by cells of a number of phagocytes. [9,15] Tolerance of the maternal immune response due to inhibition of the cytotoxic component causes the physiological course of pregnancy. That is, pregnancy is a dynamic and highly controlled immunological process.

The maternal-fetal interface consists of three main components:
• cells of the trophoblast of the fetus;
• decidual stromal cells of the maternal origin;
• maternal immune cells.

Upon completion of the implantation of the embryo and the formation of decidua, the immune cells of the uterus undergo significant changes. In the general population of decidual cells in the first trimester of pregnancy, the amount of leukocytes reaches 40% [1,14]. In the early stages of pregnancy, natural killer (NK) and macrophages become the basic immune cells of the uterus; leukocytes decidua make up about 20-30% of the total number of macrophages. These cells play a universal role in the formation of processes in both innate and acquired immunities [6]. The property of macrophages to effectively react to the influence of microenvironment, changes in the processes of presentation of antigens and cytokine production determines the rate of immunomodulation. Macrophages play a significant role in the formation of fetal tolerance, trophoblast invasion and remodeling of vessels and tissues [12, 17].

The enrichment of the decidua macrophage pool is due to the migration of monocytes from the peripheral blood to the endometrium and the decidual membrane under the control of the CCL2 (MCP-1), CCL3 (MIP-1α), CCL5 (RANTE S), CXCL16, M-CSF chemokines, secreted from the decidual tissue cells, natural killers and trophoblast cells. Cytokines interact with VEGF-R1 (Flt-1) receptors on the surface of monocytes, enhancing the expression of integrins (CD11a, CD11b, CD18, CD51), mRNA, TNF-α, IL-1β, MCP-1, IL-8, MIP-1β and stimulate the process of their trans-endothelial migration [25,28]. In the peripheral blood of pregnant women, the level of production of Th1 anti-inflammatory cytokines by monocytes is reduced, due to NF-kB inhibition and increased production of Th2 cytokines. It is considered that the main factor of such changes in the production of cytokines by

monocytes is regulation of their functions due to the effects of hormones [6,11].

Thus, progesterone, estrogens and glucocorticoids increase the synthesis of Th2 cytokines by macrophages (in particular, IL-4, IL-10) [1,6,23]. The level of glucocorticoid hormones with significant immunosuppressive effects in the peripheral blood of pregnant women is elevated. Estrogens, progesterone and glucocorticoids also reduce the activity of COX-2 and the production of NF-kB-dependent proinflammatory cytokines (IL-1, IL-2, IL-3, IL-5, IL-8, IFNγ and TNF-α) by macrophages, stimulate the secretion of anti-inflammatory IL-10 cytokine, which plays a significant role in suppressing local inflammatory processes in pregnancy [1,6,32].

Macrophages of the decidual layer of the uterus are located near the trophoblast, which invades the tissues of the uterus and infiltrates the smooth muscle layer in the wall of the spiral arteries of the uterus. As a result, macrophages are involved in a number of processes that provide the physiological course of pregnancy, including immune tolerance to fetal cells, contribute to trophoblastic reorganization of the spiral arteries, uterine tissues, embryonic and fetal development, and the normal course of labor [19,36].

The property of decidual macrophages to acquire the M2 phenotype causes immune tolerance, which is necessary for the physiological course of pregnancy [12,36]. Acquiring of proinflammatory (M1) or anti-inflammatory (M2) phenotype by macrophages is caused by cellular microenvironment. Throughout the course of pregnancy, the polarity of decidual macrophages varies between the M1 and M2 phenotypes. M1 macrophages predominate during the period of periimplantation [14]. During the early phase of the second trimester of pregnancy, the conversion of macrophages to the mixed M1 / M2 phenotype occurs, as trophoblastic cells are immersed in the stroma of the endometrium and localized therein. During the late phase of the second trimester and the early phase of the third trimester of pregnancy, the M2 phenotype dominates, which prevents the rejecting effect on the fetus. Childbirth can be considered as a proinflammatory process as a result of accumulation of M1macrophages in the tissues of the uterus, which promotes the development of labor activity, adequate for the course of delivery and uterine involution in the postpartum period [29, 30].

Inconsistency of macrophage polarization during pregnancy is associated with involuntary miscarriage, premature birth, placental dysfunction, fetal development delay syndrome, preeclampsia, etc. [1,31].

The issue of the origin of placental macrophages has not yet been unambiguously resolved. There is evidence that placental macrophages are differentiated from the mesenchymal cells of the chorionic villus stroma. After 4-5 weeks of pregnancy, the precursors of placental macrophages are formed in the non-embryonal organs of the hemopoiesis – the yolk sac and the fetal liver. There is an assumption that one of the possible causes of phenotypic and functional heterogeneity of placental macrophages is their different origin [6,19].

Placental macrophages are large (10-40 μm) cells of round, ellipsoid or irregular shape. The nucleus of mature macrophages is localized eccentrically and has a uniform distribution of the chromosomal material – heterochromatin is located under the karyolemma. In the cytoplasm of placental macrophages, there are ribosomes and polysomes, the Golgi complex is not well developed, and the

mitochondria have well-defined cristae. A characteristic feature of mature macrophages is also vacuolation of the cytoplasm, a significant amount of phagosomes, micropinocytotic vesicles and electron-dense granules of lysosomal origin [19]. The signs of maturation of placental macrophages are the increase in the cell size and its vacuolation, caused by the absorption of a large volume of fluid. Different cytoplasmic protrusions are detected on the cellular surface, which are presented as microvilli, lamellipodia that can contact with the extracellular matrix and surrounding cells [12].

Placental macrophages can be located both freely in the middle of collagen fibers, and inside special chambers, which are likely to be the remnants of stromal channels. According to the transmission and scanning electron microscopy, the ability of macrophages to move in stromal channels and migrate through their walls was detected [12,19]. In general, the only population of cells that provide immune functions of the stroma of tissues of the placenta are macrophages, which account for about 40% of the total number of cells.

The normal course of pregnancy is characterized as a condition of moderate systemic inflammatory process as a result of activation of the immune system components, in the first place, the innate immunity and vascular endothelium. Systemic changes in preeclampsia can be considered as an excessive manifestation of the same processes – "excessive inflammation", which is due to activation and endothelial dysfunction, disorder of the clotting system of the blood, etc. [1,4]. Despite the systemic nature of this process, local mechanisms that are realized in the placenta play a primary role in the etiology of preeclampsia [5]. The development of preeclampsia is characterized by a two-stage process: the first stage is the impairment of the placental processes that cause hypoxic changes in the placenta; The second stage is the production of pathologically altered placenta, an excess of proinflammatory cytokines that contribute to the development of the systemic inflammatory response [16,26].

Under conditions of complication of the second trimester of pregnancy with preeclampsia, the decidual phenotype of macrophages changes in the direction of the M1 phenotype, whereas normally the M2 phenotype must prevail at this gestation period [12, 18]. In preeclampsia, apoptotic trophoblasts are localized near the walls of the arteries, there is a decrease in the trophoblast invasion to the spiral arteries of the uterus within the placental area. Increased apoptosis of trophoblast cells can cause changes in the inflammatory nature, which further contributes to the destruction of trophoblastic cells, which results in blockage of intravascular invasion of normal trophoblast [1,7]. The development of preeclampsia can also lead to a powerful inducer of macrophage differentiation of GM-CSF, since increasing its content in the preeclamptic decidual membrane enhances the concentration of proinflammatory cytokines TNF-α and IL-1β [23]. Upon completion of phagocytosis of necrotic and aponecrotic trophoblasts, macrophages and dendritic cells continue to synthesize proinflammatory cytokines, reinforcing the inflammatory response [16].

To date, a significant number of hypotheses have been suggested as to the nature of placental signal formation regarding generalization of the systemic inflammatory response and initiation of systemic endothelial dysfunction. These signaling components include cell debris and microparticles of placental genesis, vascular factors, renin-angiotensin system components, and various cytokines, in particular INF-γ, TNFα and others [1,32].

In parallel with other cells of the utero-placental complex, decidual macrophages can also be a source of these signals, including proinflammatory cytokines and vascular origin factors [16]. In the development of preeclampsia, utero-placental macrophages may alter the levels of M-CSF, GM-CSF, IL-15 in the placenta. The clinical course of preeclampsia may be due to disturbances in the balance of pro- and anti-angiogenic factors by shifting towards the antiangiogenic ones [1,35]. The development of preeclampsia is also accompanied by an increase in the amount of soluble receptor sVEGFR1 (sFlt-1) and endoglin, as well as a decrease in the expression of the VEGFR1 ligand in the maternal circulatory system [1,9]. Placental macrophages have the ability to produce both these and other angiogenesis mediators, therefore, one can make assumptions about the involvement of these cells in the imbalance of angiogenic factors in the development and progression of preeclampsia. The disturbed balance of VEGF and sVEGFR1, caused by macrophages, is likely to play a significant role in the pathogenesis of preeclampsia. The modulating influence of hypoxia on changes of morphofunctional properties of monocytes and macrophages is also possible [25].

In preeclampsia, the microphragments of syncytiotrophoblast can be considered as a factor of pathological changes of the placenta with the processes of systemic inflammation, since the increase of their number in the system of maternal circulatory circulation is detected. The formation of such particles is also observed in the processes of apoptosis. With the pregnancy complication, preeclampsia increases apoptosis of trophoblast cells, since local hypoxia is a trigger for the synthesis of proapoptic factors [2,10]. Taking into account the probable significance of placental macrophages in regulating apoptosis processes of trophoblast cells and the involvement of macrophages in phagocytosis of the trophoblast debris, one can make an assumption regarding the importance of the effect of these cells on the processes of implementing the systemic effects, which are observed in preeclampsia [21].

In the analysis of the studied biopsies of placental areas selected after the labor in women with preeclampsia, we found an increase in the infiltration of CD68+ cells, associated with the M1 phenotype, to the walls of the spiral arteries of the myometrium, as well as the level of activation of these cells [29].

An increase in the number of decidual CD68+ cells was observed due to the fact that macrophages that are involved by chemoattractants of MCP-1 (whose production is stimulated by proinflammatory TNFα and IL-1β cytokines), induce apoptosis of trophoblast cells and inhibit its migration, impeding the adequate rebuilding of the uterine vessels [16,32] At the same time, there was a decrease in the expression of CD163 level, which is one of the M2 activation markers [24]. Probably, the imbalance in the ratio of macrophage phenotypes in the direction of the shift to proinflammatory M1 has a direct effect on the pathogenesis of preeclampsia.

The revealed changes in the balance of decidual macrophages in preeclampsia indicate one of the probable molecular-cellular mechanisms of the occurrence of this obstetric pathology, since the impaired invasion by the extravillous trophoblast of the spiral arteries of the uterus and their inadequate transformation are the key links in the emergence of unsatisfactory perfusion of the

placental tissues with further development of systemic manifestations of preeclampsia [4.9].

The complication of the second trimester of pregnancy with preeclampsia is accompanied by a decrease in the expression of several markers of the villous chorion genes, which determine the activation of the M2 type macrophages: the receptor FR-β folate (basic macrophage transporter of folic acid and its derivatives), the scavenger receptor CD163, mannose receptor CD206 [24,37] The obtained data testify to the decrease in the number of placental macrophages in the preeclamptic placenta, and the shift in their differentiation in favor of the pro-inflammatory phenotype M1. These disorders can be one of the main pathophysiological mechanisms of the development of preeclampsia.

Conclusions

Summarizing the studied literature data, it can be noted that at this stage there is every reason to believe that decidual macrophages play an essential role both in the physiological and pathological course of pregnancy due to their plasticity and immunosuppressive properties, participation in the remodeling of tissues and vessels in the early stages of pregnancy, and the ability to form a local adaptive immunity. The development of preeclampsia is probably caused by inadequate remodeling of the uterine spiral arteries due to the imbalance of decidual macrophages during the late phase of the first and the early phase of the second trimester of pregnancy, due to the predominance of macrophages of M1 phenotype [14].

In addition, decidual macrophages are likely to be a significant link in the emergence of other complications of pregnancy, including miscarriage, placental dysfunction and delayed fetal development [19].

However, to date, there is still insufficient systematic research data, which impedes the formation of a coherent and objective concept to describe the role of decidual macrophages in the processes of gestation. The features of cytokine synthesis, the character of phenotypic and morphofunctional changes of macrophages in the physiological and pathological course of pregnancy are insufficiently studied, which limits the understanding of the pathogenetic role of decidual macrophages in preeclampsia. The effectiveness of preventing preeclampsia by stimulating the differentiation in subpopulations of decidual macrophages to the M2 phenotype [1,16] has not been studied.

The obtained results determine the expediency and relevance of further studying the etiopathogenesis of preeclampsia, improving the knowledge of the immunological mechanisms of the development of this obstetric pathology (taking into account the peculiarities of differentiation in subpopulations of decidual macrophages with the formation of phenotypes M1 and M2) and determine the need for the development of new methods for early formation of high-risk groups for preeclampsia, ways of secondary prevention of the disease, which would enable us to develop effective tactics for the management of pregnant women with preeclampsia, specifically aimed at reducing maternal and perinatal morbidity and mortality.

References

1. Abdullaeva NK Neuroimmune aspects of pre-eclampsia. Russian bulletin of obstetrician-gynecologist. 2014.T.14 (5). 18-21 pp.
2. Ailamazyan EK, Stepanova OI, Sel'kov SA, Sokolov DI Cells of the immune system of the mother and cells of the trophoblast: "constructive cooperation" in order to achieve a common goal. Bulletin of the Russian Academy of Medical Sciences. 2013; 11: 12-21 pp.
3. Obstetrics: National guide. Ed. Ailamazyan AK, Kulakova, VI, Radzinsky VE, Savel'eva GM M.: GEOTAR-MEDIA. 2015. 1200 pp.
4. Batman SK Hypertensive disorders in pregnancy. Preeclampsia Eclampsia Methodical instructions. Krasnodar, KSMU, 2017. 30 p.
5. Ventskovskaya IB, Aksonova AV, Lagoda NM Morphological features of placenta in preeclampsia according to histochemistry. Health of a woman. 2016.6. 73-76 p.
6. Drannik GN Clinical immunology and allergology: a manual for students, internists, immunologists, allergists, doctors. 4 th ed., sup. Kiev, 2010. 552 pp.: il.
7. Dubovaya AA Heavy preeclampsia: features of angiogenic status. Dis... Candidate of med. sciences Stavropol, 2016. 153 pp.
8. Ziganshina MM Identification of antibodies that bind to invitro endothelial cells in serum of women with physiological pregnancy and pre-eclampsia. Bulletin of Experimental Biology and Medicine. 2015. T. 159, No. 4. 467-471 p.
9. Ivanets TYu, Alekseeva ML, Goncharova EA, Khodjaeva ZS, Vavina OV Markers of pre-eclampsia in the 1st and 2nd trimesters of pregnancy. Problems of reproduction. 2012. 3. 83-87 p.
10. Kerkeshko GO, Korenevsky AV, Sokolov DI, Sel'kov SA The interaction of extracellular microvesicles of trophoblast with cells of the immune system and endothelium in the pathogenesis of preeclampsia. Medical Immunology. 2018 20 (4). 485-514 p.
11. Kudryashova AV, Sotnikova NYu, Panova IA Differentiation of memory cells in the population of T-helper with uncomplicated pregnancy and preeclampsia. Journal of women's diseases. 2013. 2. 110-116 pp.
12. Lyamina SV, Malyshev IYu, Chesnokova NP, Morozova, O.L. Polarization of macrophages in the modern concept of forming an immune response. Fundamental research. 10.10.2013. 930-935 p.
13. Makatsaria AD, Bitsadze VO, Chervenaka FA Pregnancy high risk. M.: Medical Information Agency LLC.2015. 920 p.
14. Mustafina LR, Logvinov SV, Yuriev SYu Dynamics of changes in the numerical density of placental macrophages when urogenital infection in early pregnancy. Morphology. 2015, No. 2. 54-58 s.
15. Panova IA, Kudryashova AV, Malyshkina AI, Khlipunova, DA, Rokotyanskaya EA Expression of cellular adhesion molecules by phagocytes as a criterion for differential diagnosis of hypertensive pregnancy disorders. Obstetrics and Gynecology 2015; 7. 33-37 p.
16. Pozdnyakov IM, Shirinskaya AV Level of leptin, pro- and anti-inflammatory cytokines during pregnancy, complicated by various forms of arterial hypertension. Cytokines and inflammation. 2015. T. 14, No. 1. 75-79 p.
17. Sarbaeva NN, Ponomareva YuV, Milyakova MN Macrophages: a variety of phenotypes and functions, interaction with alien materials. Genes & Cells. 2016 1 (XI). 9-17 with
18. Sakhno LV, Shevely EYa, Tikhonova MA, Ostanin AA, Chernykh YeR Molecular mechanisms of immunosuppressive activity of M2 macrophages. Immunology. 2016. 37 (6). 311-315 p.
19. Sokolov DI, Sel'kov SA Decidual macrophages: role in the immunological dialogue of the mother and the fetus. Petersburg: Research Institute of Obstetrics and Gynecology. 2014. 113-117 pp.
20. Trunova LA Infringement of cytokine regulation in the pathogenesis of pre-eclampsia. Russian Immunology Journal. 2015. T. 9. 16-21 pp.
21. Abumaree MH, Chamley LW, Badri M, El-Muzaini MF Trophoblast debris modulates the expression of immune proteins in in macrophages: a key to maternal tolerance of the fetal allograft. J Reprod Immunol. 2012.94(2).-131-141 p.
22. Bartmann C, Segerer SE, Rieger L, Kapp M, Sutterlin M. Quantification of the predominant immune cell populations in decidua throughout human pregnancy. Am. J. Reprod. Immunol. 2014. Vol. 71, N 2. 109-119 p.

23. Calleja-Agius J, Jauniaux E, Muttukrishna S., Calleja-Agius, J. Placental villous expression of TNFα and IL-10 and effect of oxygen tension in euploid early pregnancy failure. Am. J. Reprod. Immunol. 2012. Vol. 67, N 6. 515-525 p.

24. Etzerodt A, Berg R, Plovsing R, Andersen M, Bebien M, Habbeddine M, Lawrence T Soluble ectodomain CD163 and extracellular vesicle-associated CD163 are two differently regulated forms of 'soluble CD163' in plasma. Sci Rep. 2017; 7: 40286.

25. Faas MM, Spaans F, de Vos P Monocytes and macrophages in pregnancy and preeclampsia. Front. Immunol. 2014;30 (5). 298 p.

26. Ferguson KK, McElrath TF, Chen YH Longitudinal profiling of inflammatory cytokines and C-reactive protein during uncomplicated and preterm pregnancy. Am. J. Reprod. Immunol. 2014. Vol. 72, N 3. 326-336 p.

27. Gomez-Lopez N, StLouis D, Lehr MA Immune cells in term and preterm labor. Cellular and Molecular Immunology. 2014. 11, № 6. 571-581 p.

28. Haldar M, Murphy KM Origin, development, and homeostasis of tissue-resident macrophages. Immunol. Rev.2014. 262, №1. 25-35 p.

29. Italiani P, Boraschi D From monocytes to M1/M2 macrophages: phenotypical vs. functional differentiation. Front. Immunol. 2014. 113-117 p.

30. Jetten N, Verbruggen S, Gijbels MJ Anti-inflammatory M2, but not pro-inflammatory M1 macrophages promote angiogenesis in vivo. Angiogenesis. 2014. 17, № 1. 109-118 p.

31. LaMarca B, Cornelius D, Wallace K Elucidating immune mechanisms causing hypertension during pregnancy. Physiology (Bethesda).2013.28 (4). 225-233 p.

32. Lau SY, Guild S., Barrett CJ Tumor necrosis factor-alpha, interleukin-6, and interleukin-10 levels are altered in preeclampsia: a systematic review and meta-analysis. Am. J. Reprod. Immunol. 2013. 70, № 5. 412-427 p.

33. Mantovani A, Biswas SK, Galdiero MR Macrophage plasticity and polarization in tissue repair and remodelling. J. Pathol. 2013. 229, № 2. 176-185 p.

34. Murray PJ Macrophage activation and polarization: nomenclature and experimental guidelines. Immunity. 2014. 41. 14-20 p.

35. Palm M, Axelsson O, Wernroth L Involvement of inflammation in normal pregnancy. Acta Obstet. Gynecol. Scand. 2013. 92, № 5. 601-605 p.

36. Svensson-Arvelund J, Ernerudh J The role of macrophages in promoting and maintaining homeostasis at the fetal-maternal interface. Am. J. Reprod. Immunol. 2015. Vol. 74, N 2. 100-109 p.

37. Tang Z, Buhimschi IA, Buhimschi CS, Tadesse S, Norwitz, E, Niven-Fairchild T. et al. Decreased level of folate receptor-β and reduced numbers of fetal macrophages (Hofbauer cells) in placentas from pregnancies with severe pre-eclampsia.Am. J. Reprod. Immunol. 2013. Vol. 70, N 2. 104-115 p.

38. Van den Bossche J, Baardman J, de Winther M Metabolic characterization of polarized M1 and M2 bone marrow-derived macrophages using real-time extracellular flux analysis department of medical biochemistry, experimental vascular biology. Academic medical center; Amsterdam, 2015. 24 p.

39. Young OM, Tang Z, Niven-Fairchild T Toll-like receptor-mediated responses by placental Hofbauer cells (HBCs): a potential pro-inflammatory role for fetal M2 macrophages. Am. J. Reprod. Immunol. 2015. Vol. 73, N 1. 22-35 p.

40. Zenclussen AC Adaptive immune responses during pregnancy. Am. J. Reprod. Immunol. 2013. Vol. 69, N 4. 291-303 p.