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Modulation of the Maternal Immune System During Physiological and Miscarriage-Related Pregnancies

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Abstract The article provides a detailed analysis of the immune mechanisms that support physiological pregnancy and the pathogenetic aspects of miscarriage. The immunological basis of these conditions includes changes in uterine NK cells, a decrease in the number of macrophages and myeloid suppressor cells, an increased Th1/Th2 ratio, and a decreased Treg/Th17 ratio.

Keywords Miscarriage, Maternal immunity, NK cells, Th cells, Cytokines

1. Introduction

Spontaneous miscarriage is defined as termination of pregnancy in the first 20 weeks of pregnancy, two or more miscarriages are designated as habitual spontaneous miscarriage [1]. This pregnancy complication occurs in 12-15% of pregnant women worldwide, with about 80% of miscarriages occurring during the first trimester of pregnancy [2]. As the number of miscarriages increases, the risk of losing future pregnancies increases dramatically. Multiple miscarriages pose a serious threat to a woman's fertility and health. Each subsequent miscarriage can damage the uterine mucosa, which leads to a violation of the reciprocity of the endometrium with a complication of the relationship at the uterine-fetal interface [3]. A habitual miscarriage negatively affects a woman's emotional sphere, causes psychological stress in the family and conflicts between couples [4,5].

The cause of miscarriage may be chromosomal abnormalities, immunological, anatomical, thrombotic pathologies, and environmental factors [6,7]. In about 50% of cases, the causes of miscarriage remain unknown [8]. Despite the diversity of the etiology of miscarriage, maternal immunity has been actively considered a key link in its pathogenesis in recent years.

The purpose of the study: to study the role of factors of nonspecific immune protection in the pathogenesis of early pregnancy miscarriage.

2. Materials and Methods

To write this review, a literary analysis of articles on the websites PubMed, Medline, WHO and Medscape was conducted.

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The mother's immune system as the basis for maintaining and preserving pregnancy

A successful pregnancy requires a difficult balance in the relationship between mother and fetus. This balance is maintained by modulating the maternal immune system, and the main mediators of these relationships are immune cells and cytokine signaling pathways. Cell-mediated immune factors that have been studied in maternal peripheral blood and in uteroplacental tissues include natural killer cells (NK), neutrophils, macrophages, and T lymphocytes [9].

NK cells are large and granular lymphocytes without antigenic T or B cell receptors [10]. There are two types of NK cells: CD56dim/CD16+ (pNK) and CD56bright/CD16 −(uNK) [10]. pNK cells are present in peripheral blood and have stronger cytotoxic properties than uNK. uNK cells are classified into eNK cells (endometrial) and dNK cells (decidual) [11]. eNK cells account for up to 30% of the total number of endometrial lymphocytes and are more widely distributed in the superficial and deep layers of the endometrium during implantation and early pregnancy. dNK cells make up 70% of the total number of decidual lymphocytes and are distributed in the deep layers of the endometrium, persisting even in late pregnancy [9].

NK cells play an important role in maintaining pregnancy and secrete cytokines that stimulate placenta formation, angiogenesis, and fetal growth. uNK cells contribute to the remodeling of the spiral artery by producing angiogenic growth factors at an early stage of pregnancy, such as interleukin-8 (IL-8), angiopoietin-1/2, and vascular endothelial growth factor (VEGF) [12,13]. dNK cells also produce a number of matrix metalloproteinases (MMPs), which can lead to destruction of the extracellular matrix [14]. In addition, dNK cells prevent excessive trophoblast invasion in the late stages by expressing cytokines such as transforming growth factor β (TGF-β), tumor necrosis factor α (TNF-α) and interferon γ (IFN-γ) [15].

Decidual macrophages account for about 10-20% of the total number of decidual leukocytes in early pregnancy [16]. Depending on the exposure factor, macrophages can differentiate into M1 or M2 polarization states. M2 macrophages produce anti-inflammatory cytokines such as IL-10 and TGF-β. Macrophages promote decidual tissue remodeling and angiogenesis, support trophoblast invasion by inhibiting T cell activation, promote tissue repair, support immune homeostasis, and prevent excessive manifestation of inflammatory reactions [17]. M1 macrophages produce pro-inflammatory cytokines such as IL-1b, IL-6, and TNF-α, which are involved in regulating the immune response, while their excessive content initiates increased inflammation [17].

Neutrophils are an important component of the innate immune system, the activation of which leads to phagocytosis, cytokine secretion, and the generation of reactive oxygen species to effectively neutralize pathogens. From the early stages of pregnancy, the neutrophil content is actively increasing. During pregnancy, the production of cytokines increases, which enhance the formation of neutrophils in the bone marrow: granulocyte colony-stimulating factor (G-CSF) and granulocyte-macrophage colony-stimulating factor (GM-CSF). During pregnancy, neutrophils express CD15 more than CD10, which is especially noticeable in the third trimester [18]. At the same time, there is an increase in the population of myeloid-derived suppressor cells (MDSCs), including mature and immature monocytic or granulocytic cell phenotypes with immunosuppressive functions. It is assumed that the increase in the number of MDSCs plays a key role in maintaining an immunosuppressive environment and immunotolerance during pregnancy. A decrease in MDSC levels is associated with an increased risk of miscarriage [19].

T-lymphocytes make up 3-10% of immune cells and are a key component of the adaptive immune system. CD4+T cells are a vital component of the immune system and have different subtypes (Treg and Th1/2/17 cells) depending on their functions and secreted cytokines. Th1 cells produce pro-inflammatory cytokines (IL-1b, IL-2, IL-6, IL-8, tumor necrosis factor α (TNF-α), interferon γ (IFN-γ)), through which they induce a cell-mediated cytotoxic response, whereas Th2 cell cytokines are anti-inflammatory cytokines (IL-4, IL-5, IL-10, IL-13), which are responsible for humoral immunity and immune tolerance [20].

In recent years, in addition to subpopulations of Th1 and Th2 cells, more complex subpopulations of regulatory T cells (Treg) and Th17 cells have played an important role in the successful regulation of pregnancy [21]. Th17 cells produce the pro-inflammatory interleukin IL-17, a cytokine that, by interacting with Th1 cells, can participate in the immunopathology of miscarriage [22]. On the contrary, Treg cells form immune tolerance, as a result of which the mother's body does not react to the fetus as to a semi-allograft, which is important for implantation and further growth of the embryo [23].

Pregnancy can be conditionally divided into three immunological stages, depending on the predominance of a pro-inflammatory or anti-inflammatory immune background [24]. The first trimester of pregnancy occurs against a background of weak pro-inflammatory activity. Invasion of the blastocyst into the endometrium of the uterus causes damage to the underlying maternal tissue. For optimal hematological support, the trophoblast of the blastocyst displaces the uterine endothelium and smooth muscle arteries of the mother during the secondary phase of embryonic development. The inflammatory stage is important for cleaning the wound from the remains of the fetal egg and dead tissues and preparing the damaged tissue for healing and vasculogenesis. It occurs immediately after injury and is characterized by the production of pro-inflammatory cytokines and chemokines. These mediators attract immune cells to the site of injury and stimulate the production of more signaling molecules. During implantation, the mother's immune system promotes immunological adaptation to the fetus, and many other physiological changes occur in it, including endocrine modulation [25]. The same cytokines that play a role in modulating the immunological balance during implantation also play a role in the formation of the placenta [21].

In the second trimester of pregnancy, the anti-inflammatory link begins to prevail, and cytokines released during this phase contribute to the establishment of immunological tolerance to the fetal allograft, promote coordination of the function of the fetoplacental complex, which stimulates fetal growth and development. Further, the final phase is characterized by absolute anti-inflammatory dominance, at the end of which an increased pro-inflammatory response is noted, creating conditions for the onset of labor [25].

Immunological aspects of the formation of miscarriage in early pregnancy

Increased activation of pro-inflammatory cytokines leads to disruption of the embryo implantation process, placental dysfunction, and miscarriage [26]. TNF-α is a key pro-inflammatory cytokine that induces the inflammatory process. TNF-α promotes trophoblast invasion by increasing the production of IL-17 by endometrial stromal cells. Moreover, TNF-α plays an important role in implantation by inducing the production of VEGF by trophoblast cells [27]. However, excessive TNF-α production disrupts the balance of Th1/Th2 immune cells, which changes the endometrial environment, causes excessive apoptosis of embryonic and endometrial cells, which leads to failure of embryo implantation and the threat of miscarriage [28]. It is noteworthy that TNF-α levels are significantly increased in cases of repeated miscarriage compared with primary miscarriage. This difference may be related to the initial sensitization to the antigens of the embryo during a previous pregnancy, which may cause a manifest manifestation of a humoral or cytotoxic reaction to these antigens in subsequent pregnancies [20].

IFN-γ regulates the expression of IL-6, monocyte chemoattractant protein (MCP)-1 and macrophage colony-stimulating factor (M-CSF) in early pregnancy. IFN-γ promotes implantation by developing vessels at the implantation site and maintaining decidual tissues during

placental development [20]. A significant increase in IFN-γ expression leads to spontaneous abortion [29]. IFN-γ suppresses the production of GM-CSF, which is necessary for the progression of pregnancy. In addition, IFN-γ affects the expression of proteins involved in embryo adhesion to the endometrium [30].

Transforming growth factor β (TGF-β) is considered a multifunctional cytokine, controls the cytokine network, and supports maternal immune tolerance [31]. TGF-β plays an important role in decidualization and stimulation of implantation. The level of TGF-β1 is significantly higher in women with a successful pregnancy compared to patients with repeated pregnancy loss [32,33]. At the same time, an increased level of TGF-β1 can inhibit trophoblast invasion by increasing the expression of kisspeptin [34].

IL-1β, as a fast-reacting proinflammatory cytokine, initiates inflammation by activating NK and T cells. IL-1β may promote the expression of matrix metalloproteinases (MMPs), thus participating in the regulation of trophoblast invasion [35]. In addition, IL-1β promotes blood clotting. IL-1β leads to an increase in the number of proteins that increase platelet stability, and thus forms a prothrombotic state. This condition is fraught with the formation of microthrombi at the uteroplacental interface, which is one of the important links in the pathogenesis of miscarriage in early pregnancy [36,37].

IL-6 stimulates inflammatory reactions and at the same time suppresses TNF-α expression [38]. This pleiotropic cytokine plays a dual role during pregnancy, supporting both pro-inflammatory and anti-inflammatory responses. IL-6 enhances decidualization and increases endometrial susceptibility to signaling molecules [35]. An increase in IL-6 levels and its positive correlation with Th17 have been reported in patients with habitual miscarriage [21]. Similarly, IL-6 has been shown to positively correlate with the number of repeated miscarriages, while IL-10 is negatively correlated [26].

IL-10 suppresses the immune Th1 response by reducing the expression of TNF-α, IFN-γ, and IL-1β and supports immunological tolerance by promoting embryo development [39]. In patients with miscarriage, the level of IL-10 in the blood was lower than in women with a physiological course of pregnancy [40].

It is noteworthy that the aberrant cytokine Th1 or Th2 alone cannot determine pregnancy outcomes. Pregnancy is regulated by the complex interaction of a network of cytokines, and in this context, the ratio of Th1/Th2 cells is important in maintaining pregnancy. A number of studies have found a significant increase in the ratio of Th cells producing IFN-γ/IL-4, IFN-γ/IL-10, TNF-α/IL-4 and TNF-α /IL-10 in patients with miscarriage compared with healthy pregnant women [41,42].

In recent years, the role of Treg/Th17 cell imbalance in the pathogenesis of miscarriage has been widely discussed [22,43]. Treg cells modulate immune responses, inhibit the activation and proliferation of cytotoxic immune cells that can potentially target fetal antigens, control inflammation, and support maternal vascular adaptation, which ultimately promotes decidual invasion and adequate vasculogenesis [43]. A decrease in the level of Treg cells in the blood and an increase in the content of Th17 cells during miscarriage were revealed [44].

Th17 cells have a special effect due to their ability to regulate inflammation depending on the situation. The pro-inflammatory nature and its stimulation of progesterone secretion emphasize the lability of Th17 and pregnancy outcomes. However, other studies report that Th17 levels remain constant during pregnancy, and the Treg/Th17 ratio decreases closer to childbirth [44]. Similarly, another study showed that the number of Treg cells constantly decreases during pregnancy, while Th17 levels do not change significantly [45]. The pro-inflammatory properties of Th17 cells in combination with the immunoregulatory ability of Treg cells create a balance that is key for both immune tolerance and protection against pathogens [22].

A number of studies have investigated the possible role of IL-17 as a pro-inflammatory mediator in spontaneous miscarriage. At the same time, it is reported that IL-17 affects the rate of trophoblast invasion and reduces its death, which is an important point in successful implantation [43]. In another study, it was found that the level of IL-17 in the peripheral blood of women with physiological pregnancy was higher than in patients with miscarriage. This indicates the need for further research to clarify the effect of IL-17 on implantation and pregnancy outcomes.

IL-7 stimulates the development of Th17 cells from naive T cells [46] and their differentiation. IL-7 then inhibits Treg cell differentiation, and subsequently disrupts the Treg/Th17 balance towards Th17 activation [47], which contributes to the formation of miscarriage [46]. The significantly increased expression of IL-7 in the decidual membrane of women with spontaneous miscarriage indicates that IL-7 probably plays an important role in enhancing the proinflammatory immune response at the uteroplacental interface [46].

Hormone-mediated cytokine regulation during pregnancy

It is known that the successful course of pregnancy depends on the level of the hormone progesterone, synthesized at the beginning of pregnancy by the corpus luteum of the ovary, and then by the placenta. In addition, adequate levels of estradiol and chorionic gonadotropin and their complex interactions at the mother-placenta-fetus interface with a number of factors of nonspecific immune protection are important for the progression of pregnancy and fetal growth [48].

Female steroid hormones estradiol and progesterone induce the activity of anti–inflammatory cytokines and reduce the pro-inflammatory response. Progesterone enhances the production of cytokines of the anti-inflammatory cytokines IL-4, IL-5, leukemia inhibitory factor and M-CSF in the decidual membrane, while simultaneously suppressing the synthesis of IFN-γ and TNF-α and cytokines produced by Th17 cells, such as IL-17A and IL-23 in the blood [49]. However, Th17 cells do not always have a negative effect on pregnancy, since, depending on the established cytokine

environment, they are able to differentiate into either Th17/Th1 cells or Th17/Th2 cells. The Th2 shift caused by progesterone promotes the transition of Th17 cells to Th17/Th2 cells and stimulates the production of IL-17A, IL-17F, and IL-4 by T helper cells, which is important for embryo implantation [50]. It is reported that the production of IL-17 together with IL-4 can promote embryo implantation and growth [51].

The immunotolerogenic effect of progesterone is manifested in an increase in the phagocytic capacity of trophoblasts and an increase in the expression of anti-inflammatory cytokines such as TGF-β by trophoblasts [52]. A decrease in progesterone levels leads to a decrease in the number of MDSCs, which is associated with an increased bias towards the production of Th1 cytokines and early miscarriage [53]. These studies clearly emphasize the important immunoregulatory role of progesterone at the fetoplacental level.

Estradiol during pregnancy plays a role in modulating the balance of Th1/Th2 cytokines, promotes the attraction and activation of Treg cells, and thereby supports the immune tolerance of the mother to the fetus [49]. The immunomodulatory effect of estradiol is dose-dependent. Although estradiol increases the production of IFN-γ and IL-12 before ovulation outside pregnancy, during pregnancy it increases the levels of IL-6 and IL-10, reducing the ratio of IFN-γ/IL-10, which shows its role in regulating the cytokine balance in favor of the Th2-type immune response [53].

3. Conclusions

Pregnancy is a difficult coordinated condition, where the mother's immune system is considered an important link. The immunological basis of this condition includes uterine NK cells, macrophages and myeloid suppressor cells, a balance in the content of Th1/Th2 and Treg/Th17. A change in the immunotolerant relationship between mother and fetus can lead to defects in implantation and placentation and is a key aspect of the pathogenesis of early pregnancy miscarriage.

REFERENCES

[1] Youssef A, Vermeulen N, Lashley EELO, Goddijn M, van der Hoorn MLP. Comparison and appraisal of (inter)national recurrent pregnancy loss guidelines. *Reprod Biomed Online.* 2019; 39(3): 497-503. doi: 10.1016/j.rbmo.2019.04.008.

[2] Quenby S, Gallos ID, Dhillon-Smith RK, Podesek M, Stephenson MD, Fisher J, et al. Miscarriage matters: the epidemiological, physical, psychological, and economic costs of early pregnancy loss. *Lancet.* 2021; 397(10285): 1658-1667. doi: 10.1016/S0140-6736(21)00682-6.

[3] Gudnadottir U, Du J, Hugerth LW, Engstrand L, Schuppe-Koistinen I, Wiberg Itzel E, et al. Pre-pregnancy complications - associated factors and wellbeing in early pregnancy: a Swedish cohort study. *BMC Pregnancy Childbirth.* 2023 Mar 8; 23(1): 153. doi: 10.1186/s12884-023-05479-8.

[4] Iordăchescu DA, Paica CI, Boca AE, Gică C, Panaitescu AM, Peltecu G, et al. Anxiety, Difficulties, and Coping of Infertile Women. *Healthcare (Basel).* 2021; 9(4): 466. doi: 10.3390/healthcare9040466.

[5] Chen SL, Chang SM, Kuo PL, Chen CH. Stress, anxiety and depression perceived by couples with recurrent miscarriage. *Int J Nurs Pract.* 2020; 26(2): e12796. doi: 10.1111/ijn.12796.

[6] Bagkou Dimakou D, Lissauer D, Tamblyn J, Coomarasamy A, Richter A. Understanding human immunity in idiopathic recurrent pregnancy loss. *Eur J Obstet Gynecol Reprod Biol.* 2022; 270: 17-29. doi: 10.1016/j.ejogrb.2021.12.024.

[7] Turesheva A, Aimagambetova G, Ukybassova T, Marat A, Kanabekova P, Kaldygulova L, et al. Recurrent Pregnancy Loss Etiology, Risk Factors, Diagnosis, and Management. Fresh Look into a Full Box. *J Clin Med.* 2023; 12(12): 4074. doi: 10.3390/jcm12124074.

[8] Ewington LJ, Tewary S, Brosens JJ. New insights into the mechanisms underlying recurrent pregnancy loss. *J Obstet Gynaecol Res.* 2019; 45(2): 258-265. doi: 10.1111/jog.13837.

[9] Garmendia JV, De Sanctis CV, Hajdúch M, De Sanctis JB. Exploring the Immunological Aspects and Treatments of Recurrent Pregnancy Loss and Recurrent Implantation Failure. *Int J Mol Sci.* 2025; 26(3): 1295. doi: 10.3390/ijms26031295.

[10] Lanier LL. Five decades of natural killer cell discovery. *J Exp Med.* 2024; 221(8): e20231222. doi: 10.1084/jem.20231222.

[11] Cavalcante MB, da Silva PHA, Carvalho TR, Sampaio OGM, Câmara FEA, Cavalcante CTMB, Barini R, Kwak-Kim J. Peripheral blood natural killer cell cytotoxicity in recurrent miscarriage: a systematic review and meta-analysis. *J Reprod Immunol.* 2023; 158: 103956. doi: 10.1016/j.jri.2023.103956.

[12] Rao VA, Kurian NK, Rao KA. Cytokines, NK cells and regulatory T cell functions in normal pregnancy and reproductive failures. *Am J Reprod Immunol.* 2023; 89(2): e13667. doi: 10.1111/aji.13667.

[13] Tao Y, Li YH, Zhang D, Xu L, Chen JJ, Sang YF, et al. Decidual CXCR4^{+} CD56^{bright} NK cells as a novel NK subset in maternal-foetal immune tolerance to alleviate early pregnancy failure. *Clin Transl Med.* 2021 Oct; 11(10): e540. doi: 10.1002/ctm2.540.

[14] Choudhury RH, Dunk CE, Lye SJ, Harris LK, Aplin JD, Jones RL. Decidual leucocytes infiltrating human spiral arterioles are rich source of matrix metalloproteinases and degrade extracellular matrix in vitro and in situ. *Am J Reprod Immunol.* 2019; 81(1): e13054. doi: 10.1111/aji.13054.

[15] Saito S, Nakashima A, Shima T, Tsuda S. Pregnancy depends on a delicate balance of immune activation and regulation. *Explor Immunol.* 2021; 1: 461-78. doi: 10.37349/ei.2021.00031.

[16] Ning F, Liu H, Lash GE. The Role of Decidual Macrophages During Normal and Pathological Pregnancy. *Am J Reprod Immunol.* 2016; 75(3): 298-309. doi: 10.1111/aji.12477.

[17] Shimada S, Ebina Y, Iijima N, Deguchi M, Yamada H. Decidual CD68^{+} HLA-DR^{+} CD163^{-} M1 macrophages increase in miscarriages with normal fetal chromosome. *Am J Reprod Immunol.* 2018; 79(2). doi: 10.1111/aji.12791.

[18] Blazkova J, Gupta S, Liu Y, Gaudilliere B, Ganio EA, Bolen CR, et al. Multicenter Systems Analysis of Human Blood Reveals Immature Neutrophils in Males and During Pregnancy. *J Immunol.* 2017; 198(6): 2479-2488. doi: 10.4049/jimmunol.1601855.

[19] Nair RR, Sinha P, Khanna A, Singh K. Reduced Myeloid-derived Suppressor Cells in the Blood and Endometrium is Associated with Early Miscarriage. *Am J Reprod Immunol.* 2015; 73(6): 479-86. doi: 10.1111/aji.12351.

[20] Yang X, Tian Y, Zheng L, Luu T, Kwak-Kim J. The Update Immune-Regulatory Role of Pro- and Anti-Inflammatory Cytokines in Recurrent Pregnancy Losses. *Int J Mol Sci.* 2022; 24(1): 132. doi: 10.3390/ijms24010132.

[21] Zhu L, Chen H, Liu M, Yuan Y, Wang Z, Chen Y, et al. Treg/Th17 Cell Imbalance and IL-6 Profile in Patients With Unexplained Recurrent Spontaneous Abortion. *Reprod Sci.* 2017; 24(6): 882-890. doi: 10.1177/1933719116670517.

[22] Tang C, Hu W. The role of Th17 and Treg cells in normal pregnancy and unexplained recurrent spontaneous abortion (URSA): New insights into immune mechanisms. *Placenta.* 2023; 142: 18-26. doi: 10.1016/j.placenta.2023.08.065.

[23] Farshchi M, Abdollahi E, Saghafi N, Hosseini A, Fallahi S, Rostami S, et al. Evaluation of Th17 and Treg cytokines in patients with unexplained recurrent pregnancy loss. *J Clin Transl Res*. 2022; 8(3): 256-265.

[24] Dutta S, Sengupta P, Liew FF. Cytokine landscapes of pregnancy: mapping gestational immune phases. *Gynecology and Obstetrics Clinical Medicine*. 2024; 4: e000011. doi:10.1136/gocm-2024-000011.

[25] Shah NM, Lai PF, Imami N, Johnson MR. Progesterone-Related Immune Modulation of Pregnancy and Labor. *Front Endocrinol (Lausanne).* 2019; 10: 198. doi: 10.3389/fendo.2019.00198.

[26] Thaker R, Oza H, Verma V, Gor M, Kumar S. The Association of Circulatory Cytokines (IL-6 and IL-10) Level with Spontaneous Abortion-a Preliminary Observation. *Reprod Sci*. 2021; 28(3): 857-864. doi: 10.1007/s43032-020-00292-6.

[27] You Y, Stelzl P, Joseph DN, Aldo PB, Maxwell AJ, Dekel N, et al. TNF-α Regulated Endometrial Stroma Secretome Promotes Trophoblast Invasion. Front Immunol. 2021; 12: 737401. doi: 10.3389/fimmu.2021.737401.

[28] Zhou J, Wang Y, Chen M, Kayashima Y, Townley-Tilson D, Sadig MM, et al. TNF-α-Induced Downregulation of ID2 in Human First Trimester Trophoblast Cells. *Asian Journal of Biological Sciences*. 2025; 18(2): 323-332. doi: 10.3923/ajbs.2025.323.332.

[29] Zargar M, Ghafourian M, Behrahi F, Nikbakht R, Salehi AM. Association of recurrent implantation failure and recurrent pregnancy loss with peripheral blood natural killer cells and interferon-gamma level. *Obstet Gynecol Sci.* 2024; 67(1): 112-119. doi: 10.5468/ogs.23120.

[30] Yoo I, Kim D, Han J, Lee S, Hong M, Jeon BY, et al. Transcriptomic analysis of interferon-γ-regulated genes in endometrial explants and their possible role in regulating maternal endometrial immunity during the implantation period in pigs, a true epitheliochorial placentation species. *Theriogenology.* 2020; 155: 114-124. doi: 10.1016/j.theriogenology.2020.05.045.

[31] Freis A, Schlegel J, Daniel V, Jauckus J, Strowitzki T, Germeyer A. Cytokines in relation to hCG are significantly altered in asymptomatic women with miscarriage - a pilot study. *Reprod Biol Endocrinol.* 2018; 16(1): 93. doi: 10.1186/s12958-018-0411-5.

[32] Dirisipam K, Madduru D, Jahan P, Gujrati D. Can circulating levels of transforming growth factor-β1 in early pregnancy serve as a predictive marker of unfavourable outcome? *Placenta.* 2023; 137: 65-69. doi: 10.1016/j.placenta.2023.04.004.

[33] Haider S, Lackner AI, Dietrich B, Kunihs V, Haslinger P, Meinhardt G, et al. Transforming growth factor-β signaling governs the differentiation program of extravillous trophoblasts in the developing human placenta. *Proc Natl Acad Sci USA.* 2022; 119(28): e2120667119. doi: 10.1073/pnas.2120667119.

[34] Fang L, Yan Y, Gao Y, Wu Z, Wang Z, Yang S, et al. TGF-β1 inhibits human trophoblast cell invasion by upregulating kisspeptin expression through ERK1/2 but not SMAD signaling pathway. *Reprod Biol Endocrinol.* 2022; 20(1): 22. doi: 10.1186/s12958-022-00902-9.

[35] Pantos K, Grigoriadis S, Maziotis E, Pistola K, Xystra P, Pantou A, et al. The Role of Interleukins in Recurrent Implantation Failure: A Comprehensive Review of the Literature. *Int J Mol Sci*. 2022; 23(4): 2198. doi: 10.3390/ijms23042198.

[36] Gao R, Kong L, Qing P, Cheng K, Chen H, Zhang S, et al. Interleukin-1β as clinically predictive risk marker for recurrent pregnancy loss in women positive for antinuclear antibody. *Int J Clin Pract.* 2021; 75(12): e14887. doi: 10.1111/ijcp.14887.

[37] Löb S, Amann N, Kuhn C, Schmoeckel E, Wöckel A, Zati Zehni A, et al. Interleukin-1 beta is significantly upregulated in the decidua of spontaneous and recurrent miscarriage placentas. *J Reprod Immunol.* 2021; 144: 103283. doi: 10.1016/j.jri.2021.103283.

[38] Rose-John S. Interleukin-6 Family Cytokines. *Cold Spring Harb Perspect Biol.* 2018; 10(2): a028415. doi: 10.1101/cshperspect.a028415.

[39] Ticconi C, Pietropolli A, Di Simone N, Piccione E, Fazleabas A. Endometrial Immune Dysfunction in Recurrent Pregnancy Loss. *Int J Mol Sci.* 2019; 20(21): 5332. doi: 10.3390/ijms20215332.

[40] Lebedeva OP, Ivaschevici AN. IL-2, IL-10, IL-12 and IL-23 mRNA expression in the decidual tissue in patients with missed and spontaneous abortions in early pregnancy. *Research Results in Biomedicine.* 2019; 5(3): 71-81. (In Russian) doi: 10.18413/2658-6533-2019-5-3-0-8.

[41] Peng Y, Yin S, Wang M. Significance of the ratio interferon-γ /interleukin-4 in early diagnosis and immune mechanism of unexplained recurrent spontaneous abortion. *Int J Gynaecol Obstet.* 2021; 154(1): 39-43. doi: 10.1002/ijgo.13494.

[42] Hakeem LA, Bello YO, Obajimi GO, Onifade AFA, Ahmed B, Arowojolu AO, et al. Inflammatory cytokines in maternal serum between women with threatened miscarriage and normal pregnancy. *Int J Gynaecol Obstet.* 2024; 164(1): 255-261. doi: 10.1002/ijgo.15009.

[43] Andreescu M, Tanase A, Andreescu B, Moldovan C. A Review of Immunological Evaluation of Patients with Recurrent Spontaneous Abortion (RSA). *Int J Mol Sci.* 2025; 26(2): 785. doi: 10.3390/ijms26020785.

[44] Luu T, Alsubki L, Deutsch G, Riehl V, Mayers M, Guo L, et al. Implantation Failures and Recurrent miscarriages-diagnosis POSTER 8T regulatory and Th17 cells in pregnant women with recurrent pregnancy losses. *J Reprod Immunol.* 2023; 158: 103591. doi: 10.1016/j.jri.2022.103591.

[45] Braga A, Neves E, Guimarães J, Braga J, Vasconcelos C. Th17/Regulatory T cells ratio evolution: A prospective study in a group of healthy pregnant women. *J Reprod Immunol.* 2022;149:103468. doi: 10.1016/j.jri.2021.103468.

[46] Vilsmaier T, Amann N, Löb S, Schmoeckel E, Kuhn C, Zati Zehni A, et al. The decidual expression of Interleukin-7 is upregulated in early pregnancy loss. *Am J Reprod Immunol.* 2021; 86(3): e13437. doi: 10.1111/aji.13437.

[47] Wu L, Li J, Xu HL, Xu B, Tong XH, Kwak-Kim J, et al. IL-7/IL-7R signaling pathway might play a role in recurrent pregnancy losses by increasing inflammatory Th17 cells and decreasing Treg cells. *Am J Reprod Immunol.* 2016; 76(6): 454-464. doi: 10.1111/aji.12588.

[48] Raghupathy R, Szekeres-Bartho J. Progesterone: A Unique Hormone with Immunomodulatory Roles in Pregnancy. *Int J Mol Sci.* 2022; 23(3): 1333. doi: 10.3390/ijms23031333.

[49] AbdulHussain G, Azizieh F, Makhseed M, Raghupathy R. Effects of Progesterone, Dydrogesterone and Estrogen on the Production of Th1/Th2/Th17 Cytokines by Lymphocytes from Women with Recurrent Spontaneous Miscarriage. *J Reprod Immunol.* 2020; 140: 103132. doi: 10.1016/j.jri.2020.103132.

[50] Lombardelli L, Logiodice F, Aguerre-Girr M, Kullolli O, Haller H, Casart Y, et al. Interleukin-17-producing decidual CD4+ T cells are not deleterious for human pregnancy when they also produce interleukin-4. *Clin Mol Allergy.* 2016; 14: 1. doi: 10.1186/s12948-016-0039-y.

[51] Logiodice F, Lombardelli L, Kullolli O, Haller H, Maggi E, Rukavina D, et al. Decidual Interleukin-22-Producing CD4+ T Cells (Th17/Th0/IL-22+ and Th17/Th2/IL-22+, Th2/IL-22+, Th0/IL-22+), Which Also Produce IL-4, Are Involved in the Success of Pregnancy. *Int J Mol Sci.* 2019; 20(2): 428. doi: 10.3390/ijms20020428.

[52] Vota D, Aguero M, Grasso E, Hauk V, Gallino L, Soczewski E, Pérez Leirós C, Ramhorst R. Progesterone and VIP cross-talk enhances phagocytosis and anti-inflammatory profile in trophoblast-derived cells. *Mol Cell Endocrinol.* 2017; 443: 146-154. doi: 10.1016/j.mce.2017.01.022.

[53] Verma P, Verma R, Nair RR, Budhwar S, Khanna A, Agrawal NR, et al. Altered crosstalk of estradiol and progesterone with Myeloid-derived suppressor cells and Th1/Th2 cytokines in early miscarriage is associated with early breakdown of maternal-fetal tolerance. *Am J Reprod Immunol.* 2019; 81(2): e13081. doi: 10.1111/aji.13081.