Osovska Zinaida, student of higher medical education**,** Bukovinian State Medical University, Chernivtsi, Ukraine

Pecheriaha Svitlana, Candidate of Medical Sciences, assistant Department of Obstetrics, Gynecology and Perinatology, Bukovinian State Medical University, Chernivtsi, Ukraine, https://orcid.org/0000-0003-3884-9109

FETAL IMMUNOLOGICAL TOLERANCE: MECHANISMS OF FORMATION AND THE ROLE OF THE UTEROPLACENTAL BARRIER

Abstract

Fetal immunological tolerance is one of the key mechanisms underlying a successful pregnancy, ensuring the survival of the genetically semi-allogeneic fetus within the maternal organism. A central role in this process is played by the uteroplacental barrier, which not only serves as a physical interface separating the maternal and fetal circulations but also functions as an active immunoregulatory complex. Its major components include trophoblast cells, decidual tissue, regulatory T lymphocytes (Tregs), uterine natural killer (uNK) cells, placental macrophages, non-classical major histocompatibility complex molecules (HLA-G and HLA-E), cytokines, extracellular vesicles, and hormonal factors.

This review summarizes current evidence regarding the cellular and molecular mechanisms involved in the development of prenatal and postnatal fetal immunological tolerance. Dynamic changes in the immune environment throughout pregnancy are discussed, ranging from the controlled inflammatory response required for embryo implantation to the establishment of a tolerogenic microenvironment and the reactivation of pro-inflammatory signals preceding labor. Particular attention is given to the role of HLA-G in suppressing NK- and

T-cell cytotoxicity, interactions between trophoblasts and decidual immune cells, the vertical transfer of maternal immune cells, fetomaternal microchimerism, and the influence of the maternal microbiota on fetal immune system programming.

Disruption of uteroplacental tolerance mechanisms is considered an important pathogenic factor in the development of preeclampsia, placental dysfunction, recurrent pregnancy loss, preterm birth, and fetal growth restriction. Current evidence on the long-term effects of intrauterine immune programming on postnatal immunity is also reviewed, including responses to infectious agents, dietary antigens, and vaccines. Available data indicate that the uteroplacental barrier represents a highly specialized immunological system that determines not only pregnancy outcomes but also the development of immune competence and long-term health of the child.

Keywords: fetal immunological tolerance, uteroplacental barrier, trophoblast, HLA-G, regulatory T lymphocytes, uterine natural killer cells, placenta, pregnancy.

Problem statement. The development of fetal immunological tolerance is one of the key aspects of reproductive immunology. Despite being genetically semi-allogeneic to the mother, the fetus normally avoids rejection by the maternal immune system. Current scientific evidence indicates that pregnancy is not a state of generalized immune suppression but rather a complex, dynamic, and highly regulated remodeling of immune responses aimed at maintaining tolerance to fetal antigens while preserving the ability to combat infections [1].

A central role in this process is played by the uteroplacental barrier, which is considered not only an anatomical structure separating the maternal and fetal circulations but also an integrated functional immunological system. Its components include trophoblast cells, decidual tissue, maternal immune cells

(regulatory T cells, uterine natural killer cells, and macrophages), placental macrophages (Hofbauer cells), extracellular vesicles, cytokines, major histocompatibility complex molecules (particularly HLA-G), and hormonal signals [2, 4, 6].

Disruption of the interactions among these components has been associated with the development of numerous obstetric complications. According to recent meta-analyses, preeclampsia affects approximately 4.43% (95% CI: 3.73–5.20%) of pregnancies worldwide, with higher rates observed in low-income countries. Hypertensive disorders of pregnancy complicate 5–10% of all pregnancies. Preterm birth remains a major global health challenge: in 2020, an estimated 13.4 million infants were born preterm worldwide, accounting for nearly 10% of all live births. Recurrent pregnancy loss affects 1–2% of women conceiving naturally and up to 10–15% of those undergoing assisted reproductive technologies [3, 16].

Immunological disturbances of uteroplacental tolerance play a pivotal role in the pathogenesis of these conditions and also influence the development of the child's immune system during the postnatal period, thereby determining susceptibility to infectious, allergic, and autoimmune diseases later in life [5, 13, 14].

Analysis of recent research and publications. Contemporary studies on immunological tolerance during pregnancy demonstrate a shift from the traditional concept of immune suppression toward the understanding of pregnancy as a process of dynamic immune adaptation. Wang J. et al. (2024) emphasize that pregnancy represents a complex biological compromise in which the maternal immune system balances protection against pathogens with tolerance toward fetal antigens [1].

The uteroplacental barrier is currently regarded as an integrated immunological system. Menzies F.M. (2025) describes the placenta as an active immunological environment regulating interactions between the maternal and fetal

organisms [2]. Balasundaram P. and Farhana (2025) further highlight the immunology of the maternal–fetal interface [4, 5].

An important mechanism underlying fetal tolerance is the expression of non-classical HLA-G molecules on trophoblast cells. Zhuang B. et al. (2021) and Mao J. et al. (2023) demonstrated that HLA-G suppresses the cytotoxic activity of NK cells and T lymphocytes, promotes angiogenesis, and supports immune tolerance [8, 9].

Regulatory T cells (Tregs) play a critical role in maintaining tolerance and establishing immunological memory. Liu H. et al. (2026) and Thiele K. et al. (2025) demonstrated that pregnancy-induced Tregs may exert long-lasting effects on subsequent pregnancies and maternal postnatal immunity [10, 11].

Uterine natural killer cells and placental macrophages, including Hofbauer cells, contribute to spiral artery remodeling, tissue homeostasis, and protection against infections (Xu L. et al., 2021; Thomas J.R. et al., 2021) [6, 12].

Breakdown of immune tolerance has been linked to various pregnancy-related pathologies. Using single-cell profiling approaches, Luo F. et al. (2023) identified immune dysregulation in preeclampsia, including impaired HLA-F-mediated tolerance mechanisms [15]. Konnikova L. (2025) emphasized the active role of the fetus in shaping placental immunity and highlighted the association between immune dysregulation and preterm birth [17].

The establishment of postnatal tolerance involves the vertical transfer of maternal immune cells (Stelzer I.A. et al., 2021) as well as the influence of the maternal microbiota on immune system development (Cherayil B.J. & Jain N., 2024; Faas M.M., 2025) [5, 14].

Purpose of the article. The aim of this study was to provide a comprehensive analysis of the mechanisms underlying the development of fetal immunological tolerance and to determine the multifunctional role of the

uteroplacental barrier in ensuring successful pregnancy outcomes based on current scientific evidence.

Presentation of the main material of the study. Immunological tolerance during pregnancy represents a complex biological compromise. On the one hand, the maternal immune system must remain capable of recognizing and eliminating infectious threats; on the other hand, it must refrain from mounting an immune response against the fetus, which expresses paternally derived antigens [1]. Contemporary scientific evidence describes this process as a dynamic regulatory equilibrium that changes throughout the course of pregnancy. In particular, the first stage, embryo implantation, is characterized by a controlled inflammatory response, whereas placental development requires the establishment of a tolerogenic decidual microenvironment. Toward the end of gestation, inflammatory signaling increases again, facilitating the initiation of labor [4].

The uteroplacental barrier represents the central anatomical and functional site where this immunological tolerance is maintained. Trophoblast cells not only provide physical separation between maternal blood and fetal tissues but also actively participate in the regulation of immune processes [5]. They generate and transmit immunomodulatory signals, influence immune cell migration, modify the local cytokine profile, and promote remodeling of the uterine vascular network. Consequently, the placenta performs multiple functions, acting simultaneously as a transport, endocrine, and immune organ that plays a crucial role in creating optimal conditions for fetal development in utero [6].

During early pregnancy, successful implantation depends on the ability of trophoblast cells to invade the uterine wall and induce remodeling of maternal blood vessels. This process involves direct interaction between fetal cells and the maternal immune system but normally does not trigger an aggressive immune response. Instead, specialized maternal immune cells, including uterine natural killer (uNK) cells, macrophages, and regulatory T cells (Tregs), actively cooperate

to support vascular development, tissue remodeling, and the establishment of immune tolerance toward the genetically distinct fetus [7].

An important mechanism underlying this tolerance is the expression of non-classical major histocompatibility complex molecules, particularly HLA-G. Trophoblast cells exhibit a unique pattern of HLA molecule expression that distinguishes them from most other cell types. This enables them to evade attack by the maternal immune system while simultaneously establishing regulatory interactions with maternal immune cells. Studies by Zhuang B. et al. (2021) confirmed that HLA-G is a key mediator of maternal tolerance toward the fetus [8], whereas Mao J. et al. (2023) elucidated its role in suppressing excessive activity of T lymphocytes and natural killer cells, thereby preventing fetal rejection. HLA-G has also been shown to interact with microRNAs, suppress NK-cell cytotoxicity, and stimulate the secretion of growth factors that support fetal growth and development [9].

Regulatory T cells (Tregs) play a pivotal role in maintaining the physiological course of pregnancy. They suppress excessive immune responses directed against fetal antigens, thereby promoting the establishment of an anti-inflammatory environment and contributing to the development of immunological memory associated with pregnancy. Recent studies by Liu H. et al. (2026) and Thiele K. et al. (2025) suggest that regulatory T cells are not merely transiently activated during pregnancy but may also generate long-lasting immunological memory that influences both subsequent pregnancies and the maternal postnatal immune status [10, 11].

Uterine natural killer (uNK) cells are actively involved in the formation of the placental bed, vascular remodeling, cytokine secretion, and interactions with trophoblast cells. Their activity must remain tightly balanced, as both insufficient and excessive uNK-cell function may impair embryo implantation, placental

development, or the harmonious immunological dialogue between the maternal organism and the fetus [1].

Macrophages of the placenta and decidual tissue are responsible for the clearance of cellular debris, tissue remodeling, and protection against infections. However, their activity must be strictly regulated to prevent excessive inflammation. In particular, placental macrophages known as Hofbauer cells constitute an important component of the fetal innate immune system. These cells are capable of adapting their phenotype in response to infections, hypoxia, metabolic disturbances, and environmental influences. Their remarkable plasticity explains the ability of the placenta to simultaneously protect the fetus and convey signals reflecting adverse intrauterine conditions [12].

The establishment of prenatal and postnatal fetal tolerance involves not only mechanisms that protect the fetus from maternal immune aggression but also the programming of the developing immune system of the future child. During intrauterine life, the fetus is exposed to maternal antigens and immune cells that contribute to the development of regulatory immune mechanisms. Stelzer I.A. et al. (2021) reported that the vertical transfer of maternal immune cells may stimulate fetal immune system development [13]. Furthermore, recent reviews by Cherayil B.J. and Jain N. (2024), as well as Faas M.M. and Smink A.M. (2025), have emphasized the importance of interactions among the intrauterine environment, maternal microbiota, and early immune adaptation in newborns [5, 14].

Following birth, postnatal immunological tolerance continues to develop under the influence of breastfeeding, microbial colonization, exposure to environmental antigens, and the long-term effects of intrauterine programming. Prenatal immune signals have a substantial impact on the newborn’s ability to respond appropriately to microorganisms, dietary antigens, and vaccine

components, thereby ensuring the balanced regulation of these immune responses [15].

Disruptions in immune regulation and placental function contribute significantly to adverse pregnancy outcomes. According to the World Health Organization, approximately 13.4 million infants were born preterm worldwide in 2020, representing more than one in ten live births. Preeclampsia is currently estimated to affect 2–8% of pregnancies globally. Recurrent pregnancy loss occurs in approximately 1–2% of women attempting natural conception, although some reviews report a prevalence ranging from 3% to 5%, depending on the diagnostic criteria applied. Although these pathological conditions are multifactorial in origin and cannot be attributed solely to immunological mechanisms, impaired immune regulation at the uteroplacental interface remains a key contributor to their pathogenesis [3, 16].

One of the most extensively studied manifestations of disrupted uteroplacental tolerance is preeclampsia. Using single-cell profiling approaches, Luo F. et al. (2023) provided a detailed characterization of immune dysregulation at the maternal–fetal interface associated with this condition. Among their findings were disturbances in HLA-F-related signaling pathways and abnormalities in immunological communication between trophoblast cells and maternal immune cells [15].

Immune dysregulation has also been increasingly implicated in the pathogenesis of preterm birth. Konnikova L. (2025) demonstrated that the fetus actively participates in shaping the placental immune environment and that disruption of this bidirectional interaction may trigger premature initiation of labor [17].

Overall, the uteroplacental barrier should be regarded not merely as an anatomical structure but as a highly specialized immunological system that coordinates maternal–fetal interactions throughout pregnancy. A deeper

understanding of the mechanisms underlying fetal immune tolerance may contribute to the development of novel approaches for the prevention and treatment of pregnancy-related complications.

Conclusion. The development of prenatal and postnatal fetal immunological tolerance represents a complex, dynamic, and multilayered process in which the uteroplacental barrier plays a central integrative role. This unique structure not only provides physical separation between the maternal and fetal circulations but also actively regulates immunological communication between the mother and the fetus through the coordinated actions of trophoblast cells, decidual immune cells, HLA-G molecules, regulatory T cells, uterine natural killer cells, and placental macrophages.

Analysis of current evidence indicates that successful immunological tolerance depends on a delicate balance between pro-inflammatory and anti-inflammatory signals, which varies throughout different stages of pregnancy. Disruption of this balance constitutes an important pathogenic factor in the development of major obstetric complications, including recurrent pregnancy loss, preeclampsia, fetal growth restriction, and preterm birth. Furthermore, proper functioning of the uteroplacental barrier has long-term implications, influencing the programming and maturation of the child's immune system after birth.

These findings highlight the importance of further research into the mechanisms of maternal–fetal tolerance as a basis for developing novel preventive and therapeutic strategies in modern obstetrics and perinatology.

References

1. Wang, J., Han, T., & Zhu, X. (2024). Role of maternal-fetal immune tolerance in the establishment and maintenance of pregnancy. Chinese medical journal, 137(12), 1399–1406. https://doi.org/10.1097/CM9.0000000000003114

2. Menzies F. M. (2025). The Placenta as an Immunological Environment. British journal of biomedical science, 82, 14910. https://doi.org/10.3389/bjbs.2025.14910

3. Vera-Ponce, V. J., Loayza-Castro, J. A., Ballena-Caicedo, J., Valladolid-Sandoval, L. A. M., Zuzunaga-Montoya, F. E., & Gutierrez De Carrillo, C. I. (2025). Global prevalence of preeclampsia, eclampsia, and HELLP syndrome: a systematic review and meta-analysis. Frontiers in reproductive health, 7, 1706009. https://doi.org/10.3389/frph.2025.1706009

4. Balasundaram, P., & Farhana, A. (2025). Immunology at the Maternal-Fetal Interface. In *StatPearls*. StatPearls Publishing. https://pubmed.ncbi.nlm.nih.gov/34662056/

5. Cherayil, B. J., & Jain, N. (2024). From Womb to World: Exploring the Immunological Connections between Mother and Child. ImmunoHorizons, 8(8), 552–562. https://doi.org/10.4049/immunohorizons.2400032

6. Xu, L., Li, Y., Sang, Y., Li, D. J., & Du, M. (2021). Crosstalk Between Trophoblasts and Decidual Immune Cells: The Cornerstone of Maternal-Fetal Immunotolerance. Frontiers in immunology, 12, 642392. https://doi.org/10.3389/fimmu.2021.642392

7. Wu, S., Xie, H., Su, Y., Jia, X., Mi, Y., Jia, Y., & Ying, H. (2023). The landscape of implantation and placentation: deciphering the function of dynamic RNA methylation at the maternal-fetal interface. Frontiers in endocrinology, 14, 1205408. https://doi.org/10.3389/fendo.2023.1205408

8. Zhuang, B., Shang, J., & Yao, Y. (2021). HLA-G: An Important Mediator of Maternal-Fetal Immune-Tolerance. Frontiers in immunology, 12, 744324. https://doi.org/10.3389/fimmu.2021.744324

9. Mao, J., Feng, Y., Zhu, X., & Ma, F. (2023). The Molecular Mechanisms of HLA-G Regulatory Function on Immune Cells during Early Pregnancy. Biomolecules, 13(8), 1213. https://doi.org/10.3390/biom13081213

10. Liu, H., Huang, W., Hu, Z., Han, J., Gao, R., & Qin, L. (2026). Regulatory T cells in human pregnancy: mechanisms, dysregulation, and therapeutic perspectives. *Frontiers in immunology*, *17*, 1815957. https://doi.org/10.3389/fimmu.2026.1815957

11. Thiele, K., Urbschat, C., Riquelme, J. I. A., Ahrendt, L. S., Wöhrle, R., Schepanski, S., Eckert, J. J., Becht, E., Qi, M., Alawi, M., Becker, M., Gagliani, N., Mittrücker, H. W., Diemert, A., & Arck, P. C. (2025). Pregnancy-acquired memory CD4+ regulatory T cells improve pregnancy outcome in mice. Nature communications, 16(1), 6522. https://doi.org/10.1038/s41467-025-61572-w

12. Thomas, J. R., Naidu, P., Appios, A., & McGovern, N. (2021). The Ontogeny and Function of Placental Macrophages. Frontiers in immunology, 12, 771054. https://doi.org/10.3389/fimmu.2021.771054

13. Stelzer, I. A., Urbschat, C., Schepanski, S., Thiele, K., Triviai, I., Wieczorek, A., Alawi, M., Ohnezeit, D., Kottlau, J., Huang, J., Fischer, N., Mittrücker, H. W., Solano, M. E., Fehse, B., Diemert, A., Stahl, F. R., & Arck, P. C. (2021). Vertically transferred maternal immune cells promote neonatal immunity against early life infections. Nature communications, 12(1), 4706. https://doi.org/10.1038/s41467-021-24719-z

14. Faas, M. M., & Smink, A. M. (2025). Shaping immunity: the influence of the maternal gut bacteria on fetal immune development. Seminars in immunopathology, 47(1), 13. https://doi.org/10.1007/s00281-025-01039-8

15. Luo, F., Liu, F., Guo, Y., Xu, W., Li, Y., Yi, J., Fournier, T., Degrelle, S., Zitouni, H., Hernandez, I., Liu, X., Huang, Y., & Yue, J. (2023). Single-cell profiling reveals immune disturbances landscape and HLA-F-mediated immune tolerance at the maternal-fetal interface in preeclampsia. Frontiers in immunology, 14, 1234577. https://doi.org/10.3389/fimmu.2023.1234577

16. World Health Organization. (2025). Preterm birth. https://www.who.int/news-room/fact-sheets/detail/preterm-birth

17. Konnikova L. (2025). Reframing the paradigm-rethinking placental and fetal immunity. Placenta, S0143-4004(25)00164-X. Advance online publication. https://doi.org/10.1016/j.placenta.2025.05.011