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The Role of Cytokines, Hormones, and Cellular Regulation in Improving Maternal and Fetal Well-Being

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ABSTRACT

Maternal and fetal well-being is a complex interplay of various factors. A key factor is that women receiving early and adequate pregnancy care are more likely to achieve positive pregnancy outcomes. Several studies have identified internal maternal factors as significant contributors to the well-being of both mother and fetus. However, scientific research and discussions on the role of cytokines, hormones, and cellular regulation in maternal and fetal well-being outcomes still need to be completed. Progesterone, a vital hormone for pregnancy and humans, influences immune function directly and through mediators by promoting the synthesis of T helper cell-type cytokines. The favorable benefits of dydrogesterone on repeated spontaneous miscarriages and impending miscarriages may be attributed to the regulating effects of these cytokines and the hormone's capacities. T helper cell-produced cytokines are linked to allograft rejection. Lastly, our finding of cellular regulatory mechanisms, including apoptosis, autophagy, and cellular senescence, highlights the multifaceted nature of maintaining maternal and fetal health during pregnancy. This review aims to delve deeper into the role of cytokines, hormones, and cellular regulation in enhancing maternal and fetal well-being.

Keywords: Cellular regulation, cytokines, hormones, maternal and fetal well-being.

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INTRODUCTION

Maternal and fetal well-being encompasses a variety of factors, including maternal age, socioeconomic status, race/ethnicity, pre-existing health conditions, and access to prenatal care. Preeclampsia, gestational diabetes, and chromosomal abnormalities are among the pregnancy issues that are more likely to occur in older mothers with low socioeconomic status and limited access to prenatal care.¹⁻³ However, several intrinsic factors, such as cytokines, hormones, and underlying cellular regulations, are also essential in improving maternal well-being and preventing adverse effects on pregnancy.⁴

Cytokines play a crucial role in immune regulation during pregnancy, which maintains immune tolerance to the fetus, preventing rejection by the maternal immune system. Hormones, such as progesterone and estrogen, influence immune and endocrine responses during pregnancy, further modulating the maternal-fetal immune interaction. Numerous immune cells, including

N.K. cells, T cells, and placental tissue help provide a favorable environment for the developing fetus via complex and multifaceted cellular regulations. Together, cytokines, hormones, and cellular regulatory mechanisms contribute to fetal growth and development by influencing several processes such as organogenesis, neurodevelopment, and tissue differentiation.⁵⁻⁸

An imbalance in cytokines during pregnancy can lead to uncontrolled inflammation. This can lead to increasing risk for preeclampsia and restricted fetal growth mediated by elevated levels of pro-inflammatory cytokines such as TNF- α , IFN- γ , IL-2, IL-8, and IL-6. Uncontrolled inflammation can also cause maternal tiredness and disturbed sleep quality. Furthermore, disruptions in hormone levels, such as progesterone, relaxin, oxytocin, thyroid hormones, cortisol, and estrogen, can lead to cytokine imbalances and are pivotal in physiological and psychological adjustments during pregnancy. Imbalance in these hormones may result in discomforts like nausea

and vomiting, increased anxiety and stress, disruptions in the maternal-fetal bond, and more severe complications such as preeclampsia and gestational diabetes.^{1,4,9} Lastly, cellular dysregulation can also cause an increased risk for severe pregnancy complications, such as fetal-maternal HLA-C mismatch that is caused by dysregulation in maternal T cell recognition of the fetus.^{2,4}

Pregnancy presents distinct health risks for both the mother and the fetus due to its semi-allogeneic nature, making the conceptus susceptible to maternal immune response. As a result, each pregnancy is distinct, with outcomes influenced by factors like genetics, environmental exposures, and maternal health history.^{2,4} By comprehending the functions of cytokines, hormones, and cellular regulation, customized medical approaches can be developed for individual patients, enhancing prenatal care efficacy and minimizing complication risks. Furthermore, scant literature presently examines the complex interplay among cytokines, hormones, and cellular

regulation during pregnancies. This review further discusses the role of cytokines, hormones, and cellular regulation in improving maternal and fetal well-being.

The role of cytokines in improving maternal and fetal well-being

As the primary immune system signaling molecules, cytokines are crucial for managing the mother's immunological tolerance of the fetus and averting the semi-allogeneic fetus from being rejected. Furthermore, cytokines control several facets of placental growth, vascularization, and operation, guaranteeing a sufficient flow of nourishment and oxygen to the developing embryo. Preterm delivery, intrauterine growth restriction (I.U.G.R.), and preeclampsia are among the pregnancy problems that have been linked to the dysregulation of cytokine signaling pathways.^{5,10,11}

The class of signaling proteins known as interleukin cytokines, generated by immune cells, are crucial for controlling placental development and maternal-fetal immunological tolerance. TGF- β and IL-10 are examples of interleukins that improve immunosuppressive responses, which lower maternal immune reactivity to the fetus and avoid fetal rejection. On the other hand, pro-inflammatory cytokines like IL-6 and TNF- α can upset the immunological balance between the mother and the fetus and lead to pregnancy problems, including premature delivery and preeclampsia.^{9,12,13}

T cells display dynamic phenotypic and functional changes during pregnancy, which are crucial for adaptive immunity. Because they reduce the mother's immune system's reaction to fetal antigens, regulatory T cells, or Tregs, are essential for preserving maternal-fetal tolerance. On the other hand, if dysregulated, effector T cell subsets, including Th1 and Th17 cells, can cause inflammation and tissue damage, which may result in miscarriage or other difficulties.^{5,14}

The role of T-helper (Th) cell subsets and interleukins such as Th1, Th2, IL-17, and IL-22 in promoting maternal and fetal well-being is the subject of extensive research in maternal-fetal immunology. These immune mediators regulate complex interactions at the maternal-fetal interface,

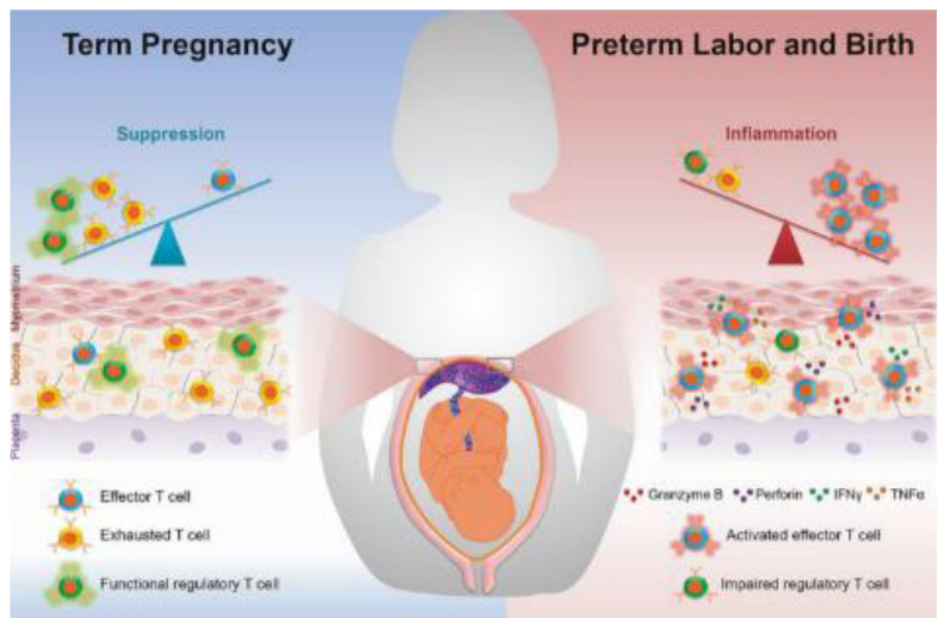


Figure 1. Comparison of the balance of the immune system regarding T cells in pregnancy.¹⁵

influencing pregnancy outcomes and fetal development. A comprehensive review of their roles highlights the balance between maternal immune tolerance and defense against pathogens, which ultimately shapes the pregnancy trajectory.¹¹

Th1 cells are crucial for host defense against intracellular infections because they produce pro-inflammatory cytokines, including tumor necrosis factor- α (TNF- α) and interferon- γ (IFN- γ). The Th1 response needs to be carefully controlled throughout pregnancy in order to keep the fetus from rejecting the mother while yet being able to combat illness. Recurrent miscarriages and unsuccessful implantations have been linked to overly active Th1 activation during pregnancy, underscoring the significance of immunological balance in the mother-fetal bond.^{16,17}

On the other hand, Th2 cells secrete anti-inflammatory cytokines that support tissue healing and immunological tolerance, such as interleukin-13 (IL-13), interleukin-5 (IL-5), and interleukin-4 (IL-4). At the mother-fetal interface, Th2 responses prevail, which promotes placental growth and the mother's ability to tolerate the immune system of the semi-allogeneic fetus. Preeclampsia and fetal growth restriction are two pregnancy illnesses linked to dysregulation of Th2 responses, indicating a potential function

for these immune systems in preserving maternal-fetal health.^{5,18,19}

Th17 cells are the primary producers of IL-17, a key mediator of inflammation and tissue remodeling. Preterm delivery and preeclampsia are two pregnancy problems that have been linked to dysregulated production of IL-17, even though IL-17 protects the body against external infections. In the placenta and decidua, IL-17 has pleiotropic effects on many cell types, affecting barrier function, angiogenesis, and immune cell recruitment.²⁰⁻²²

IL-22, produced by Th22 cells and other immune cells, plays a dual role in inflammation and tissue repair. In the context of pregnancy, IL-22 is involved in regulating trophoblast invasion, placental development, and maternal-fetal tolerance. Dysregulation of IL-22 signaling has been associated with adverse pregnancy outcomes, including preterm birth and intrauterine inflammation.²⁰⁻²²

The role of hormones in improving maternal and fetal well-being

Hormones, including but not limited to progesterone, estrogen, and human chorionic gonadotropin (hCG), exert profound effects on maternal physiology and fetal development during pregnancy. These hormones regulate various processes such as implantation, placental growth,

and maintenance of uterine quiescence, ensuring optimal conditions for fetal growth and development. Imbalanced hormonal levels or aberrant hormonal signaling can lead to poor pregnancy outcomes, highlighting the importance of hormonal regulation in maternal and fetal well-being.^{23,24}

Hormonal regulation is also one of the main determinants of pregnancy outcomes because hormones significantly influence maternal physiology, placental function, and fetal development. Progesterone, estrogen, and human chorionic gonadotropin (hCG) are some of the essential hormones involved in the establishment and maintenance of pregnancy.^{12,13} These hormones modulate uterine receptivity, promote placental growth and vascularization, and regulate immune responses at the maternal-fetal interface. Dysregulation of hormonal signaling pathways can disrupt this process, thereby contributing to conditions such as recurrent miscarriage and fetal growth restriction.^{12,25}

Downregulation of cellular immunity and an increase in humoral immunity are linked to a healthy pregnancy. The increase of Th2 reactivity cytokines and the downregulation of Th1 reactivity cytokines are most likely to blame for this. Since Th1-type cytokines harm the conceptus, shifting away from Th1 reactivity and Th1 cytokines is favorable for a healthy pregnancy. Abortion was the result of giving pregnant mice modest dosages of the inflammatory Th1 cytokines TNF- α and IFN- γ . Simultaneously, in an immunologically driven mouse abortion model, anti-TNF- α antibody infusion decreased abortion rates. Human trophoblast cells are inhibited in vitro from growing and undergo apoptosis by TNF- α and IFN- γ .^{1,3,26}

Recurrent spontaneous miscarriage (R.S.M.) is the term used to describe two or more miscarriages that occur before the 20th week of pregnancy. Spontaneous miscarriage is defined as a miscarriage that occurs during the first 20 weeks of pregnancy.²⁷ Researchers have examined immunological variables that could induce R.S.M. without a genetic, viral, or endocrinological background because about 60% of R.S.M. cases are unexplained. Research has been done on how maternal

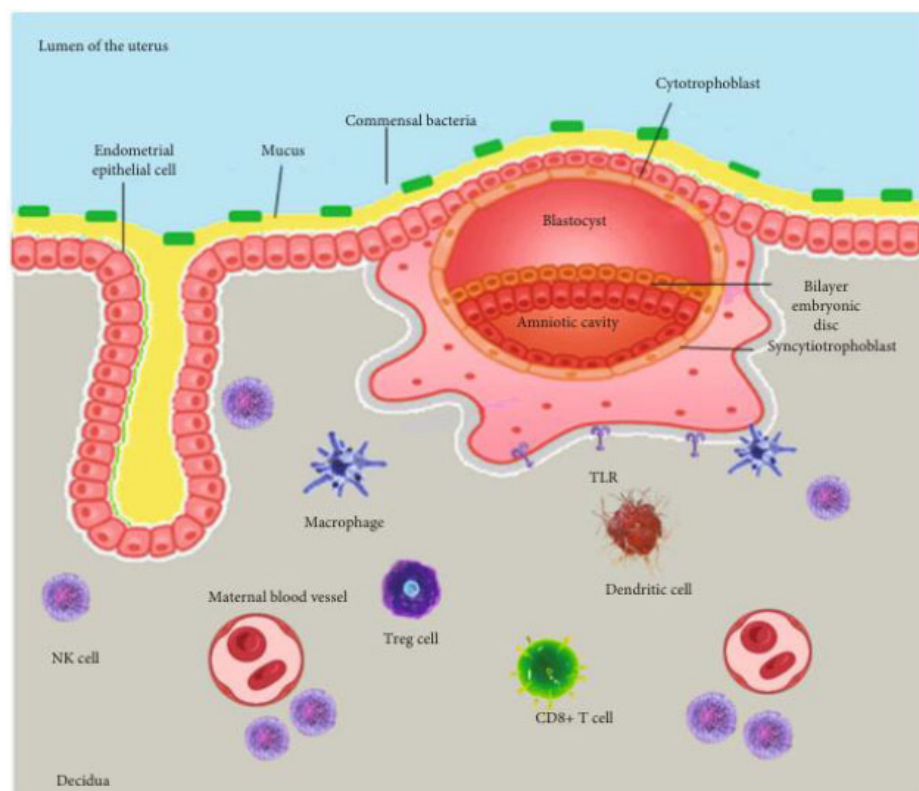


Figure 2. Illustration of the cellular immune system in pregnancy.³⁸

and cell-mediated immunity variables affect the development of R.S.M. A distinct set of R.S.M. instances is associated with antiphospholipid antibodies, which seem to protect the fetoplacental unit against humoral immunological stimuli.^{28,29}

Maternal cell-mediated immune effectors, including natural killer (N.K.) cells, macrophages, and T lymphocytes, have been investigated in maternal peripheral blood and uteroplacental tissue. In this regard, cytokines, in particular, have drawn much interest. Not surprisingly, given that cytokines mediate an astounding range of immunological responses, such as rejection of allografts, immunity to infection, autoimmune disorders, and hypersensitivity, they also impact the bond between the mother and daughter. Peripheral lymphocytes from women with a history of R.S.M. released substantially more Th1 cytokines with embryotoxic activity when activated with human trophoblast antigen.⁸ The Th2 anti-inflammatory cytokines IL-4, IL-5, and IL-10 were considerably elevated in blood lymphocytes activated with a mitogen or co-cultured with placental cells from healthy pregnant women, whereas those with R.S.M. of

unknown etiology showed remarkable improvement. Amounts of TNF- α , IFN- γ , and IL-2, three pro-inflammatory cytokines. The notion that Th1 or pro-inflammatory cytokines predominate in R.S.M. and that Th2 bias is stronger in healthy pregnancies is supported by the larger ratio of inflammatory/anti-inflammatory cytokines in R.S.M. patients. Comparable findings were also observed in peripheral blood. In the decidua of women with R.S.M. of unknown etiology, there were reportedly fewer T cell clones releasing anti-inflammatory cytokines than in the decidua of women with normal pregnancies at the maternal-fetal interface.^{30,31}

Comparing women with recurrent miscarriages of unclear etiology to healthy controls, pro-inflammatory cytokine expression was elevated in the endometrium, while anti-inflammatory cytokine expression was downregulated. Thus, it is possible to conclude that an increased predisposition towards Th1 or pro-inflammatory cytokines is linked to inexplicable RSM. Therefore, there is strong evidence linking unexplained recurrent miscarriages to an elevated bias in pro-inflammatory cytokines.^{30,31}

The role of cellular regulatory mechanisms in improving maternal and fetal well-being

Cellular regulatory mechanisms, including apoptosis, autophagy, and cellular senescence, are essential in maintaining maternal and fetal health during pregnancy. These processes ensure proper tissue remodeling, nutrient transport, and immune tolerance at the maternal-fetal interface.^{11,32–34} Dysregulation of cellular homeostasis can disrupt placental function, leading to pregnancy complications such as placental insufficiency and fetal distress.

The complex interplay between Th1, Th2, IL-17, and IL-22 responses is critical for maintaining maternal-fetal immune tolerance and promoting optimal pregnancy outcomes.^{17,33} Imbalances in these immune mediators can disrupt the balance between mother and fetus, thereby contributing to pregnancy complications and poor fetal outcomes. Previous study shown that during the period around implantation, a well-coordinated cellular interaction among immune cells, hormones, and cytokines is crucial. During fertilization, innate immune cells in the uterus play a key role in initiating tissue remodeling for implantation and supporting maternal artery adaptation. Regulatory T cells from the adaptive immune system are indispensable for early pregnancy, as their absence can lead to inflammation and fibrosis, impeding implantation. Disturbances in the uterus, such as the removal of specific cell populations in mouse models, significantly affect pregnancy establishment, reflecting observations in infertile patients.³⁵

Another study also stated that a successful pregnancy hinges on maintaining a delicate molecular equilibrium between these contrasting immunological dynamics: the semi-allogeneic fetus learns to accept both self- and maternal antigens while also developing immunity in readiness for birth. This period of immune maturation links prenatal tolerance with the need for postnatal defense, creating a vulnerable neonatal phase with heightened infection susceptibility.³⁵ A study also investigates the involvement of placental hormones and the fetal protein alpha-fetoprotein (AFP)

in B cell modulation. Human chorionic gonadotropin (hCG), not progesterone, estrogen, or their combination, induces changes in B cell phenotype and enhances IL-10 production, blocking this effect upon hCG inhibition. Interestingly, this cellular regulation, which involved hCG-induced B cell changes, is not associated with altered glycosylation of IgG subclasses.³⁵ A comprehensive understanding of the role of Th cell subsets and interleukins in pregnancy immunology is critical for developing targeted interventions to improve maternal and fetal well-being, ultimately advancing the field of prenatal care and management.^{16,36,37}

CONCLUSION

Since sustaining a pregnancy is one of the most critical aspects of an animal's existence, the reproductive systems are overinsured. Several concurrent processes work together to shield the semi-allogeneic fetus from detrimental immunological responses from the mother. Understanding the complex interactions between cytokines, hormones, and cellular regulation is critical to improving maternal and fetal well-being during pregnancy. By elucidating the molecular mechanisms underlying pregnancy-related pathology, researchers and clinicians can develop targeted interventions to reduce risk, optimize prenatal care, and improve outcomes for mother and child. This review explores the diverse roles of cytokines, hormones, and cellular regulation in improving maternal and fetal health, providing insights that pave the way for advances in prenatal care and management strategies.

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CONFLICT OF INTEREST

The authors declare that there are no conflicts of interest related to the publication of this manuscript.

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All authors contributed and were responsible for preparing this publication manuscript, from searching for ideas to preparing the manuscript.

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