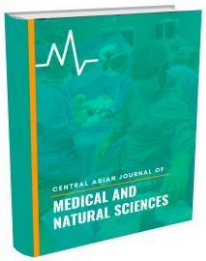

CENTRAL ASIAN JOURNAL OF MEDICAL AND NATURAL SCIENCES
https://cajmns.centralasianstudies.org/index.php/CAJMNS
Volume: 05 Issue: 04 | October 2024 ISSN: 2660-4159

Article

Understanding of the Immunological Tolerance Mechanisms Underlying the Maternal-Fetal

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Abstract: A unique set of communications is needed during a human pregnancy between the mother's uterus and the foetus with extra embryonic or placental membranes. One such communication is the immune system's adaptation to the developing embryo due to a variety of variables and cells. One risk factor that increases the chance of embryo rejection and infertility is the imbalance of immunological responses between the mother and foetus. Maternal immunity is therefore essential for the initiation and continuation of pregnancy. We present a thorough summary of the existing knowledge regarding immunological tolerance mechanisms underlying the maternal-fetal interface in this study.

Keywords: maternal-fetal interface, immune tolerance, embryo, trophoblast, pregnancy

1. Introduction

Physiological and immunological changes occur during pregnancy raising some infections' risk and severity. It's crucial to comprehend how the mother immune system functions during pregnancy in order to demonstrate how it maintains tolerance for the allogeneic. The mother's immune system undergoes numerous adjustments in order to protect herself and her unborn child from infections and prevent negative immune reactions against the allogeneic fetus [1]. In this review, we attempt to summarise the current understanding of the modifications to the peripheral maternal immune system that take place in a typical pregnancy in order to shield the foetus from rejection.

2. Results and Discussion

Some notes on maternal inflammatory system

The body's defense against exogenous stimulants and spasms is provided by the immune system, a complex network of tissues, cells, and organs. The key to a healthy immune system is its remarkable ability to distinguish between the body's own cells and foreign cells. Significant changes in the mother's immune system take place throughout pregnancy in order to shield the allogeneic foetus from harmful immune reactions and to protect the mother and her unborn child from infections.

Although there isn't much evidence to suggest that a mother's immune system is decreased generally during pregnancy, Normally, defenses live in peace with cells that contain unique chemicals known as "self" markers [2]. In order to determine the best vaccination techniques, it may also be necessary to accept the immunological changes that

Citation: Salih, L. A., Al-Azzawi, T. R., Al-Darraji, M. N. Understanding of the Immunological Tolerance Mechanisms Underlying the Maternal-Fetal. Central Asian Journal of Medical and Natural Science 2024, 5(4), 53-63.

Received: 26th Jun 2024
Revised: 3rd Jul 2024
Accepted: 10th Jul 2024
Published: 17th Jul 2024

occur during pregnancy. such as the flu and pertussis, to safeguard the unborn child and the expectant mother. It is important to understand the characteristics of the immune system throughout pregnancy in order to understand how the mother's immune system maintains tolerance towards the allogeneic fetus. Characterizing the maternal immune system during pregnancy maintains tolerance towards the allogeneic fetus. Anatomically, derived cells, including fetal trophoblast and maternal immune cells and stromal cells in this overview, we have discussed the significant changes that the mother immune system goes through. major adaptation during a healthy pregnancy. The immune system of the pregnant mother adapt [3].

Immunological tolerance and physical alterations are characteristic of pregnancy; the immune system's primary goal is to defend the host against infections. Physiological and immunological changes occur during pregnancy, increasing the risk and severity of some infections. The ability of the innate immune system to detect and react to invasive pathogens, as well as to coordinate cell movement for monitoring, is necessary for this function. The human decidua is home to a large population of immune cells during a normal pregnancy. These cells are mostly innate, including macrophages, natural killer (NK) cells, dendritic cells (DCs), and adaptive, which include CD8+ T cells, CD4+ T cells, and regulatory T cells (Treg). These cells interact with the trophoblast, a placenta cell, and do not remain indifferent to the presence of the fetus [4].

Every stage of embryonic development requires a distinct immune milieu to support and shield the developing embryo. Among the earliest immune-modulating elements involved in placenta action that alters the characteristics of the signals at the uterus is embryo-derived human chorionic gonadotropin (hCG), which is necessary for anti-inflammatory signals because implantation and early placentation require inflammatory mechanisms. However, as fetal growth is associated with greater tolerance, anti-inflammatory cues are necessary [5]. Given that the placenta expresses father's proteins as an allograft, in healthy immunological conditions, ought to be turned down. The mother immune system has developed and reached a cooperative state, even if a highly precise and active mechanism exists to prevent a maternal immune response to paternal antigens supporting one another to make the pregnancy happen. The placenta determines uterine maternal immune cells by secreting hormones and cytokines from trophoblast cells. and the maternal systemic immune system, as well as the immunological environment at the mother/fetal environment [6]. Even if a very specific and effective mechanism is in place to stop the mother's immune system from reacting to the antigens on the father. Maternal immune suppression is similar to that which is induced in recipients of organ transplants. All prior research, however, points to tumor-induced tolerance as the more similar process to immunological tolerance during pregnancy than graft-induced tolerance [7].

Pregnancy-related immune suppression may resemble the process behind malignancy

Immune suppression patterns seen in tumours can resemble those seen in foetal development. immunosuppressive cell prevalence, has been noted in pathological circumstances, including cancer, however, they also play a crucial role in the regular immunological suppression patterns that are seen during fetal development [8]. Many tumours also show an altered balance between the phenotypes of T lymphocytes, Th1 and Th2 cells, favouring a more favourable Th2-polarized milieu; this has been reported in numerous malignancies. These cells include leukemic cutaneous T cell lymphoma, melanoma, and glioma. Blastocyst implantation typically occurs in a Th1-dominant environment. which quickly starts to lean toward the Th2 phenotype in order to facilitate the immunological tolerance required for the continuation of pregnancy [9]. Decline a few weeks after delivery and remain high while tumours grow, much like the Th1/Th2 balance. indicating that immune suppression in tumours may begin in a manner akin to foetal development that never ends, in contrast to angiogenesis, which begins in a manner akin to normal wound healing that never ends [10].

The development of the fetal-maternal immune system

The development of the foetal immune system in utero and how it interacts with the immune system of the mother to determine the outcome of pregnancy are still partially understood. In addition to actively responding to external stimuli, trophoblast cells are also responsible for secreting the majority of cytokines. When it comes to foetal acceptance or rejection, these cells are crucial. The placenta protects the developing embryo from invasive pathogens by acting as an immunological barrier. How is the mother going to be able to bear the foetus for nine months? Medawar [11] suggested three options that have been thoroughly investigated:

1) Foetal isolation (mechanical barrier) from the mother's immune system.
2) Immunological suppression of the mother's defense mechanism.
3) The foetus may be immunologically immature, meaning it is undetectable to the mother.

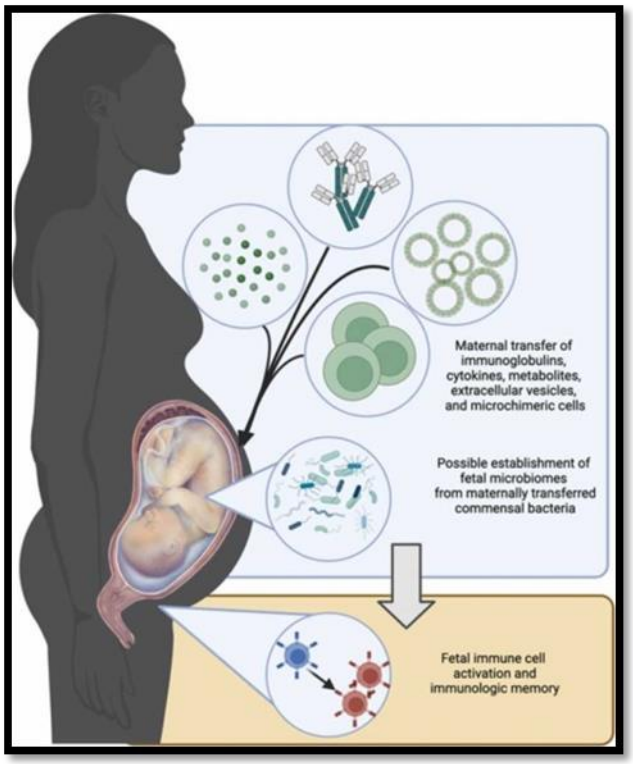

Figure 1. Fetal-maternal immune activation [12]

Role of Placenta in immunity during pregnancy

The placenta plays a crucial role as a mediator between the foetus and the mother by supplying signals that control the immune system's activity in the mother and act as barriers to shield the foetus from harmful signals. It has been demonstrated that the placenta performs a variety of tasks during pregnancy, such as transferring hormones, metabolites, gases, and nutrients between the mother and the foetus as well as acting as an impervious barrier [13]. The placenta serves as an immunological barrier to keep infections out of the foetus. A weak immunological barrier that separates the mother and the foetus is the placenta. Syncytiotrophoblast (SYN) cells serve as a barrier between the blood of the mother and the foetus. The placenta plays a crucial role in the fetus's development by transmitting maternal IgG and removing potentially hazardous cytotoxic antibodies. Nonetheless, in certain rare cases, autoantibodies may result from a foetal autoimmune illness that was passively acquired the survival of the —immunogenic foetus has been explained by a number of theories relating to placental protection of the foetus, such as expression (or lack

thereof) of histocompatibility antigens on foetal tissues, maternal immune tolerance to foetal antigens, and inhibition and/or regulation of maternal anti-fetal immune responses. However, the workings of the systems are still not entirely clear [14].

How does the placenta impede the body's immunological reaction?

The placenta is an active organ that is essential for erecting a barrier that prevents infections. The intricate interactions between the placenta's physiological circuits, It is worthwhile to look into its complex role in preventing the mother's immune system from rejecting the foetus as well as shielding it from infection. Maternal immune responses are dynamic; implantation and parturition cannot occur throughout the first and third trimesters without a pro-inflammatory state [15]. Placental trophoblast cells send out signals that closely control these responses.

The trophectoderm layer of the blastocyst gives rise to three different types of trophoblast cells: syncytiotrophoblasts (SYNs), cytotrophoblasts (CTBs), and extravillous trophoblasts (EVTs). cause the placenta to mount a specific immune response during pregnancy, and type I interferon is one of the most important signalling channels in the trophoblast cells. Type I interferon-β basal expression and downstream ISGs have physiological roles in preserving pregnancy's homeostasis, but more significantly, they give the placenta the necessary awareness to react to infections. IgG molecules' capacity to bind to Fc receptors on the trophoblast's outer membrane, which shields them from lysosomal enzyme degradation during pinocytosis, is linked to IgG penetration into the placenta (trophoblast) [16].

Class G immunoglobulins are members of the primary immunoglobulin class that confers humoral protection against microorganisms. One aspect the humoral immune system of the mother defence during pregnancy is the transition from the synthesis of cytotoxic immunoglobulins of subclass G2 to immunoglobulins of subclass G1 that are non-cytotoxic. A process of adaptation like this stops the emergence of cytotoxic reactions that are dependent on antibodies and aim to cause foetal rejection. Simultaneously, there is proof that during pregnancy, fetoplacental tissues release cytokines on their own that suppress the immunological response of cells and promote the humoral immune response to be activated by raising the levels of interleukins 4, 5, 10, and transforming expansion factor (βF). This activation is especially noticeable during the third and second trimesters of pregnancy, when there is a significant increase in the mother's blood count of lymphocytes, which respond to interaction with paternal leukocytes carrying foreign antigens inherited by the fetus by secreting interleukin 4.

The ability of blood mononuclears to manufacture interleukins two is normally diminished in the third trimester. This shows that a particular immune response is formed in the pregnant body in response to foreign foetal antigens, and that the humoral type of the response is more prevalent than the cellular one [17]. It is also crucial to note that pregnant women's bodies produce more anti-inflammatory cytokines from their monocytes than do non-pregnant women, suggesting that pregnant women's immune systems have evolved in another way [18]. Since the trophoblast is encircled by a coating of mucopolysaccharide-derived amorphous fibrinoid material, it is consistently shielded from immune aggressiveness of the mother's body [19]. The trophoblast divides into the cytotrophoblast and syncytiotrophoblast cell layers during the last six to seven days of development. During the eighth or ninth day of conception, a protrusion known as the trophoblast produces primary villi that face the decidual uterine membrane.

The decidual sheath is a modified tissue of the functional layer of the endometrium, as is widely known, containing everything needed to support the growing embryo throughout its first few weeks of life, including glycogen, lipids, and vitamins [20]. About three to four days later (12 to 13 days following fertilization), From the side of the chorion, connective tissue begins to form into the principal villi. Secondary villi then form, and blood vessels start to form in the villi at the start of week 3. The formation of tertiary villi.

The placentation phase is thus finished [21]. Additionally, the trophoblast is an immunosorbent type that deactivates the immunoaggression of maternal antigens in a variety of ways. Thus, trophoblasts start producing two unique proteins right away: glycodelin and trophoblastic β1-globulin (TBG) at the time of development. Currently, it is established that TBG has an immunosuppressive effect. that the trophoblast starts to produce in little amounts and progressively increases towards the end of pregnancy, Alternatively, to be more precise, up to 35–36 weeks, or until the placenta begins to physiologically age [22].

How a blastocyst defends itself against rejection by its mother

In humans, trophoblast cells develop four days after fertilization and are derived from a blastocyst. In women, trophoblast invasion of the maternal spiral arteries results in a significant increase in uterine blood flow and direct contact between maternal blood and foetal trophoblast cells, which give nutrients to the developing embryo and go on to form an important component of the placenta [10]. Most frequent cytokines, such as chemokine ligand 2 (CCL2), transforming growth factor (TGF), and chemokine ligand (CXCL12 and CXCL8), are secreted by trophoblast cells. The generation of cytokines by trophoblasts promotes the recruitment and development of immune cellsmoreover, these cells help draw in peripheral monocytes, neutrophils, and natural killer cells (NKs), and other cells to the location of binding of implantation, providing them with a phenotype for a successful pregnancy [11].

Differentiated from peripheral natural killer cells (pNKs), decidual natural killer cells (dNKs) produce transforming growth factor-beta-12 (TGFβ12) and interleukin-15 (IL-15) (trophoblast cells). Placental function and decidual vascular remodelling depend on these specific NKs [9]. Chemokine and cytokine expressions that have the potential to draw in and instruct immune cells are actively reacted to by trophoblast cells. Innate immune sensors trigger a response from two types of receptors are Toll-like (TLRs) and Nod-like (NLRs) which offer prompt defense against microbial invasion or tissue damage caused by bacteria, viruses, and other microorganisms [13]. In a unique fashion, trophoblast cells provide signalling responses and teach immune cells, which aid in the execution of many foetal growth and development activities [14].

The trophoblast invades a vast area, including the inner third of the myometrium, the endometrium, and multiple uterine cellular compartments ready for implantation. It also establishes and supports the complex differentiation process of pregnancy, which involves the endometrium's multiple cellular compartments ready for embryo implantation [8]. Mononuclear macrophages, lymphocytes, and epithelial cells all have toll-like receptors. The placenta consistently expresses these receptors. Placental villi and trophoblasts have TLR2 and TLR4 receptors [17]. Early pregnancy is characterised by a major reduction in TLR2, TLR3, and TLR4 expression. It demonstrates that TLR stimulation in the placenta may have a variety of purposes, including immune cell recruitment, the synthesis of cytokines, and infection defence [18]. Successful pregnancy is regulated by a delicate and intricate immune system throughout a normal pregnancy. The placenta, immune cells, and trophoblasts comprise the fetus's natural defence mechanism, shielding it from both internal and external threats.

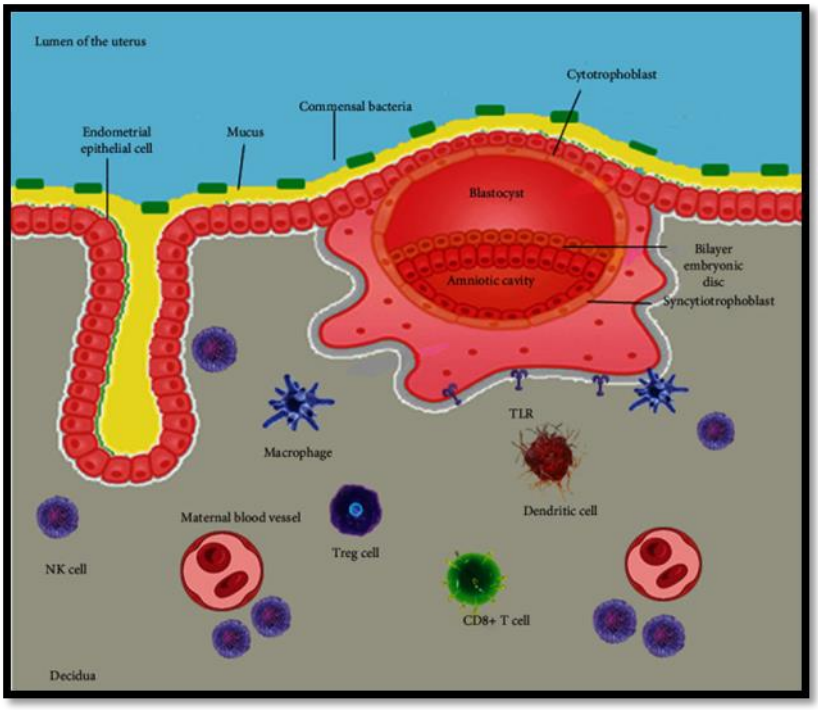

Figure 2. Immune cells during placentation [23]

The placenta's trophoblasts are crucial in preventing the mother's immune system from rejecting the foetus. Delicate crosstalk is developed among trophoblasts produced from foetuses, to guarantee maternal-fetal tolerance and effective placentation, During a typical pregnancy, decidual stromal cells (DSCs) and maternal immune cells Various immune cells, including natural killer (NK) cells and macrophages (M~\s), are present at the maternal–fetal interface, Although the exact mechanisms are yet unknown The trophoblast works in concert with T cells, B cells, myeloid-derived suppressor cells (MDSCs), dendritic cells (DCs), and, NKT mobiles in the immune response throughout a typical pregnancy [24].

The functions of chemokines and cytokines

Research has demonstrated that IL-34 binds to the same receptor as colony-stimulating factor of macrophages, it functions as an immunomodulatory mediator at the mother-foetus contact. Placental cytotrophoblasts, syncytiotrophoblasts, and other human primary trophoblasts from the first trimester and a trophoblast cell line both express IL-35. In an IL-35-dependent manner, trophoblasts stop human naive conventional T cells from proliferating and transform them become regulatory T (iTR35) cells that are induced by IL-35. At the mother-fetal interface, spontaneously aborting mice have comparatively low amounts of IL-35 and iTR35 cells; Exogenous IL-35 suppresses immune-induced abortion and supports iTR35 cells [25].

NK cells, or natural killer cells

The majority of NK cells, known as decidual natural killer (dNK) cells, are specialised cells found in endometrial decidual tissue. Compared to peripheral NK cells, dNK cells have several distinct phenotypic and functional traits, The mechanisms behind the NK's crucial role in pregnancy have only recently come to light [26]. The leukocytes that are most common during pregnancy, NK are stimulated by ovarian hormones and are not very good at cytolysis. Instead, the most prevalent leukocytes during pregnancy, The leukocytes that are most common during pregnancy, About 70% of immune cells in the first trimester of decidua are dNK cells [27]. According to some research, uNK cells greatly

cluster in the mid-secretory phase endometrium and early pregnancy decidua around spiral arterioles in response to rising ovarian-derived progesterone and oestrogen levels [28]. In the human endometrium, oestrogen and progesterone stimulate the production of the chemokines CXCL11, CXCL10, and CXCL12 with the C-X-C motif, which function as chemoattractants. The increase in NK cells in the uterus throughout the menstrual cycle may also be explained by this phenomenon [12].

Human leukocyte antigen functions

Binding peptide antigens and displaying them so that antigen-specific T cells can recognise them is the function of HLA-encoded class I and class II molecules. HLA molecules modulate immunological responses of the mother to the semi-allogeneic fetus, spiral artery remodelling, and pathogen detection in the interactions between foetal trophoblasts and mother's immune cells [20]. At the interaction between the mother and the fetus, HLA molecules' capacity to control immune cell function is influenced by their limited and possibly dynamic expression [27].

Hormones' role in preventing foetal rejection by the immune system

The master hormone that regulates the body's stress response also functions as the primary immune system soother for mothers, according to endocrinologists. Some cases of infertility and recurrent miscarriages may be explained by the findings. They discovered that corticotropin-releasing hormone (CRH), which is released by the hypothalamus to cause the pituitary and adrenal glands to release stress hormones, also manifested itself around adult inflammatory areas. [5]. It has been suggested that alterations in the endocrine system comprise at least some of the mechanisms involved in the development of immunological tolerance during pregnancy. Hormones: progesterone, estrogen, and human chorionic gonadotropin linked to pregnancy—have been shown to give both innate and adaptive immune cells the ability to inhibit the immune system [18].

A systemic increase in Because of corpora lutea (CL), progesterone (P4) and estradiol (E2) levels in the ovary are observed early in pregnancy, shortly after conception. The uterine epithelium is modified by these hormones. Following the embryo's implantation, Human chorionic gonadotropin (hCG) is produced and secreted in increasing amounts by trophoblast cells. HCG stimulates the production of progesterone, ethrone (E1) and estradiol (E2) by the CLs and also encourages angiogenesis in the uterine endothelium and migration and invasion of the uterine wall by trophoblasts [19]. Through immunological tolerance, the mother's immune system must accept a semi-allogeneic foetus expressing foreign antigens. In addition, the mother and the foetus need to be well shielded from any diseases. Evidence has been gathered indicating that hCG hormone can modulate T cells' immune systems [20].

Numerous investigations have demonstrated the significance of progesterone in regulating the function of diverse immune cell types, including the capability to suppress dendritic cells (DCs), monocytes, and macrophages' ability to present Additionally, progesterone affects galectin-1 levels, which encourage the growth and recruitment of uterine DCs that inhibit [21]. Our knowledge of progesterone's inhibitory effects on immunological responses—particularly inflammatory responses—has improved as a result of recent research. Natural killer (NK) cells [24], macrophages [23], and murine dendritic cells [21] are all inhibited by progesterone Progesterone-induced blocking factor (PIBF), a downstream mediator, is responsible for many of the immunological effects of progesterone According to a recent study, PIBF is crucial for immunoregulation during pregnancy since it increases decidual and peripheral NK function in mice lacking in PIBF. Progesterone is a crucial component of this communication, according to Fujiwara, who proposed that the mother immune system and endocrine system work together [25].

Role of semen in inducing maternal immunity

Insemination triggers the induction of the mother's immune response to paternal antigens. Research indicates that this response may also occur before conception and potentially during insemination. Since semen and the conceptus share many antigens, this theory also leaves open the possibility that semen contributes to the initiation of immune responses. Necessary in order to allow for pregnancy. There is ample evidence of the female reproductive tract's (FRT) infiltration of lymphocytes, macrophages, and neutrophils as a result of substances activating the immune system in semen. As a result of this inflammation, the mother's innate and adaptive immune systems have to adjust to the possibility of pregnancy [26]. The female reproductive system is a potentially dangerous place for sperm since it is home to chemicals and cells that shield the female against illness. Reactive oxygen species and a low pH are two of these defencesa wealth of scavenging macrophages, antimicrobial peptidesas well as the antibodies made by the acquired immune system in vertebrates. These chemical and cellular defences may have the unintended effect of protecting the immune system, but they also possess the capacity to lower sperm viability or function, or sperm success.

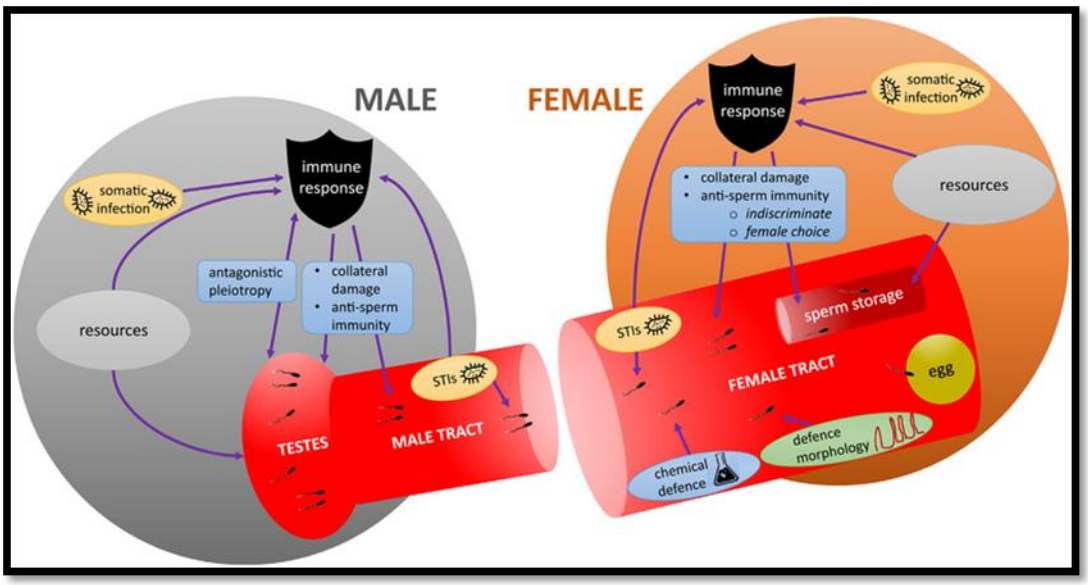

Figure 3. The interplay between immunity and sperm success in males and females [2]

Semen presents a consistent and significant challenge to the cervical and uterine mucosa because it contains a large number of male gamete-specific antigens as well as paternal major histocompatibility complex (MHC) antigens. In the context of active immunity, during insemination, pregnancy-protective alloantibodies against the paternal antigen may be produced and they grow during pregnancy due to the mother's blood containing more fetal antigens inherited from the father. Any disturbance of Antigenicity of spermatozoa or semen may ensue in aberrant alloantibody formation and pregnancy issues since semen-related components are recognized to start an inflammatory cascade in the mucosa of the endometrium. One of the pregnancy-protective alloantibodies that can be made against the paternal antigens is the anti-paternal cytotoxic antibody (APCA). It cytotoxic effects on paternal leucocytes and targets paternal human leucocyte antigens (HLAs) [27].

Simultaneously, semen exposure is now known to be protective against pre-eclampsia and other pregnancy-related diseases and advantageous in IVF pregnancies19. During insemination, lymphocyte populations are activated and expand. which have a causal connection to those that subsequently facilitate the implantation of embryos, is one possible mechanism for understanding the advantages of semen during pregnancy [28]. The enhanced cellularity and cytokine production that result from the presence of seminal vesicle

fluid demonstrate that certain components in the ejaculate's plasma portion are necessary for lymphocyte activation [29].

The biological role of sperms extends beyond oocyte fertilization, since they modulate immunological processes involved in female management of reproductive investment, although there is little evidence to support the idea that seminal plasma has a direct impact on the female reproductive tissues after implantation. Immune responses can have a direct detrimental effect on sperm, especially in vertebrates where anti-sperm antibodies can develop in both male and female organisms as an auto-immune reaction. The immunological responses of females can either be an adaptive feature of female choice, or they might damage sperm without discrimination, which could lead to infertility. Sperm are undoubtedly at risk from the immune systems of both the male and female, especially in species where immunity is developed. It is maybe astonishing that both males and females keep the sperm from being completely destroyed and continue to be viable. Differentiating between the consequences of different male sperm for evolution are enormous. In order to directly visualize the fate of individual male sperm or haploid subsets of sperm within the female immune environment, it may be necessary to employ novel approaches to advance the identification of the female immune system's ability to distinguish between distinct sperm morphologies and genotypes [29].

3. Conclusion

A healthy pregnancy must be established, maintained, and completed with the support of the immunological system of the mother. Numerous resistant system cells and chemicals are essential to the development and function of the fetus and placenta, but the precise processes by which these objectives are met are not fully understood. The immune system's effector cells both inhibit and encourage placental growth. It is generally known that during pregnancy, there are immunological changes between T helper 1 (Th1) and T helper 2 (Th2). Proinflammatory and anti-inflammatory effects must be carefully balanced.

In this review, we examine the data pertaining to humoral (hormones and cytokines) and cell-mediated immunological systems that underlie maternal tolerance of fetal tissues. We also point out how many questions remain in our comprehension of these mechanisms. Furthermore, we provide a summary of the clinical signs of a compromised mother's immune system during pregnancy that are associated with increased vulnerability to autoimmune illnesses, common bacterial, viral, and parasite infections. Consequently, it is anticipated that additional investigation into the dynamic dialogue between trophoblasts and DICs will clarify the pregnancy tolerance mechanism. More significantly, it will provide a new scientific basis for the recognition and treatment of illnesses linked to anomalies in pregnancy tolerance. In addition, the discovery research on tumor immune evasion and transplant immunity will be prompted and advanced by understanding of maternal-fetal immunological tolerance.

The immune change that takes place during pregnancy is regulated by hormones. Hormones, such as estriol and estradiol, throughout pregnancy, progesterone and glucocorticoids rise and have an impact on transcriptional signaling of inflammatory immune responses both systemically and at the maternal-fetal interface The inflammatory response to semen is stimulated by substances found in seminal plasma, most likely TGF-β, which has been shown to be necessary for this reaction in the past. The hypothesis that these cells support the mother's immune system's initial reaction to the implanting conceptus is supported by the reaction's kinetics, features of lymphocytes that have been stimulated, and the ability of the stimulated cells to migrate into uterine tissues. It would offer a scientific justification for the growing body of research showing that being in contact with semen promotes successful pregnancy via methods aside from encouraging conception.

Thus, comprehending the immunology of pregnancy has several implications: preserving the mother's and the baby's future health; protecting the mother and fetus; and

successfully completing the pregnancy (overcoming infertility). Immunological issues that arise during pregnancy have the potential to influence not only the unborn child but also subsequent generations.

4. Future directions

Nevertheless, in spite of all of this information, we are still unsure of how these immune system alterations affect the way immunological diseases progress and the chance of infection during pregnancy. Pregnancy continues to be one of the most vulnerable periods for the mother and the fetus in terms of morbidity and death. These hazards are obviously modulated by significant simultaneous endocrinological and physiological (e.g., circulatory changes, elevated abdomen pressure) changes. More careful methods will be needed to identify the precise role that immunological alterations play in pregnancy outcomes, though. Systems immunology is capable of impartially integrating a lot of data. These investigations have shown great value when combined with comprehensive clinical outcomes where conventional experimental methods are impractical for obvious ethical concerns in human health research. Ultimately, there is great potential for these objective approaches to human immunology to direct therapeutic measures during pregnancy; however, doctors' coordinated efforts Molecular immunologists, epidemiologists, and biostatisticians will be required.

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