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Review

Immunological Response during Pregnancy in Humans and Mares

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Abstract: The immunology of pregnancy deals with the immune responses of a mother and her fetus to each other. More knowledge has been acquired over the last decade to give insight into the complicated immunological processes that help the developing fetus to survive in most circumstances. During this unusual state, the mother's immune system must remain tolerant to paternal major histocompatibility complex (MHC) antigens while retaining normal immunological competence for pathogen defense, which is a difficult act. In the last decade, numerous processes have been revealed that may explain why the mother does not reject the foreign fetus. To understand how these processes work, the need to look at both fetal and maternal aspects, including trophoblast cell characteristics, local maternal factors, and changed MHC class I expression, is required. Horses, because of their unique anatomy and physiology, are a very useful animal model in pregnancy immunology research. In pregnant mares, chorionic girdle cells generate cytotoxic antibodies to paternal MHC class I antigens, enabling a more in-depth study of these invasive trophoblasts and their effect on the mother's immune system. Therefore, this review will concentrate on the immune response during pregnancy in both humans and horses.

Keywords: immunology; pregnancy; horse; mare; human; immunological responses

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1. Introduction

The immunological functions are influenced by a multitude of factors, for example, age or genes, due to the intricacy of the immune processes and their interconnection with other systems [1]. When confronted with pathogens, the immune system has at its disposal the components that produce the processes of specific (acquired) and nonspecific (innate) immunity. The initial line of defense is nonspecific mechanisms which work regardless of past pathogen exposure. This immunity serves as a barrier against infections and illnesses brought on by the environment. These processes of nonspecific immunity mechanisms are less accurate, but they allow for the rapid identification and killing of invading microbes. T lymphocytes, B lymphocytes, antigen-presenting cells, cytokines, and antibodies are key components of specific immunity, which is defined by extreme precision of antigen recognition [2]. Acquired immunity cells can generate an infinite number of receptors. Furthermore, their exposure to the antigen leads to the establishment of immunological memory, whereas re-exposure to the same antigen triggers an immune response [3].

Embryo implantation in the mother's womb generates an immune response which is the animal's evolutionary adaptation. In spite of its ideal settings and protection, the fetus' close proximity to the mother's uterine tissue makes it vulnerable to her immune system. That is why the immune system's function alters during pregnancy [4]. Paternal alloantigens may severely challenge the immune system of the mother during gestation [5]. While pregnant, as long as the mother's MHC antigen tolerance is maintained, her immune system should be able to protect the fetus from pathogens, which is a delicate balancing act [6]. Trophoblast 'split tolerance' is a condition when one component of the immune

system responds to antigens while another tolerates them [7]. This type of response is essential because the trophoblast must be immunologically protected in order to prevent destruction [4].

Pregnancy's decidua serves as a chemokine-producing location that attracts neutrophils, NK cells, and dendritic cells [8]. Studies show that decidual NK cells and antigen-presenting cells (APC) play an important role in modulating trophoblast invasion and decidual vascularization throughout pregnancy. Several immune system elements, including adaptive immune cells, must be engaged in the identification and tolerance of paternal alloantigens through APC presentation throughout the whole gestation period [9]. It has been proved that the adaptive immune system relies on Foxp3+ regulatory T cells that ensure immunological tolerance in connection to the developing fetus [10]. Furthermore, immunological tolerance can be maintained by a different subpopulation of suppressor T cells, CD4+HLA-G+ (CD-cluster of differentation, human leukocyte antigen G-HLA-G), according to new research [11,12]. It was documented that innate immune cell populations seem to dominate during pregnancy [13,14]. Knowing the details of all of this will allow research about reproduction pathology to be performed. However, several of processes are still unknown.

The nonsurgical recovery of early-stage embryos and conceptuses, as well as the isolation of pure trophoblast cell populations, are possible because of the horse conceptus' unique structure and physiology, and such an outcome is not possible in other model organisms. Pregnant mares also produce strong cytotoxic antibody responses to MHC class I antigens produced by chorionic girdle cells, allowing for a more in-depth examination of the antigenicity of these invasive trophoblasts and their impact on the maternal immune system. On the other hand, none of the mare trophoblast populations express MHC class II molecules. These factors have resulted in horses being a particularly helpful animal model in pregnant immunology research [7]. Thus, this review will focus on the immunological response during pregnancy in humans and horses.

2. Cell-Mediated Immune Response during a Healthy Pregnancy

Immunological tolerance in the maternal–fetal interface is critical for a healthy pregnancy outcome. This process is most significant at the decidua, implantation location, and placentation [9]. The placenta is the sole organ that connects two distinct beings, the mother and the fetus, and is referred to as the blood–placental barrier [15]. This barrier controls the exchange of substances between the mother's and fetus' circulations [5]. The chorionic villi are the major functioning components which, in the adjacent intervillous region, separates fetal blood from maternal blood by only three to four cell layers (the placental membrane) [15]. Equine placenta has six tissue layers, and thus the barrier is very firm. It is called the diffuse epitheliochorial placentae type [16], and thus it differs from the human discoid, hemochorial type.

The mother's immune system needs to tolerate the semiallogeneic embryo for 9 months in humans and 11 months in horses [9]. A healthy pregnancy is distinguished by a mild systemic inflammatory state that is well-controlled and maintained. While the adaptive immune response is more active during implantation, delivery, and intrauterine infections, the innate immune response continually examines the maternal–fetal interface for foreign antigens that might jeopardize the pregnancy. During pregnancy, the decidual layer is a critical location for innate immune responses. During pregnancy, there are numerous maternal immune cells close to the trophoblast in the uterus mucosa, with the most common being macrophages and the cluster of differentiation three plus (CD3+) T cells. Other cells seen in the decidua include CD56+ cells, CD38+ cells, CD2+/− cells, CD3+/− cells, and CD16+ NK cells. B cells, on the other hand, are almost nonexistent in the decidua [17].

The composition of the immune cells changes during pregnancy. While circulating leukocytes in the first trimester of healthy human pregnancies are composed primarily of peripheral NK cells (pNK), decidual leukocytes are dominated by decidual NK cells (dNK) [18,19], with the remaining 30% composed of macrophages and T cells [20]. There

are fewer dNK cells in the pregnancy during the second trimester, and their number continuously decreases until there are none left. For successful implantation, endometrial decidualization and leukocyte migration to the endometrial stroma are needed. An important step in the process is the infiltration of this tissue by NK cells [21,22].

Similar findings were obtained in horses. In this species, pNK have been discovered; [23] however, they have not yet been identified in the uterus. It is yet unclear how they work in vivo [7]. According to a study on porcine pregnancy, NK cells may be drawn to a species' uterus that have an epitheliochorial type of placentation [24]. This placentation is seen in both strepsirrhine primates and laurasiatherians, and it is a derived state in both species. Long gestation durations, tiny litters, and precocial pups are all commonly seen in this condition [25]. A distinct fraction of trophoblast cells invade the endometrium during an equine pregnancy, resulting in the formation of endometrial cups, which are unique, separated structures. Shortly after the trophoblasts have penetrated [26], there is a rise in the number of of maternal leukocytes, including CD4+ and CD8+ lymphocytes, as well as plasma cells, macrophages, and eosinophils, that are seen in the stroma at the periphery of the lymph sinuses around every endometrial cup [27]. Thought-provoking is why and how the endometrial cups in mares are eventually destroyed after successfully evading the maternal immune effectors for two months [7]. In the dying cups, there are many visible clusters of CD4+ and CD8+ lymphocytes, as well as inflammatory leukocytes [28]. A lack of MHC class I antigen expression may result in NK cells that serve as cytotoxic cells. However, it is not obvious whether the cups' death is mostly due to invading immune cells or if they just die at the end of their normal lifecycle [7].

During implantation and placentation, the embryo also plays a very important role by signaling its presence through producing embryonic signals. Embryo–maternal "information exchange" is thought to be essential for effective embryo implantation in conjunction with hormonal preparation [29]. When it comes to embryos, primates and horses are the only ones that produce the crucial trophoblastic protein known as gonadotropin (CG) [30]. According to studies, human chorionic gonadotropin (hCG) is one of the major indicators of the embryo that enhances the endometrium's responsiveness to the sex steroid hormone [31,32]. The reproduction of mammals seems to have evolved through a number of divergent paths which have resulted in multiple different types of chemical signals being used in the process of implantation [30] There are a number of hormones that are secreted by the conceptus that act on the endometrium to inhibit prostaglandin production, as well as to increase protein synthesis. Ovaries can also be stimulated to secrete more progesterone by these chemical signals [33]. Gonadotropin-releasing hormone (GnRH), which is generated by the early blastocyst, controls the early embryo's production of CG [30]. Embryos may also influence their own movement inside the oviduct and uterus in some mammals. This phenomenon can be seen in horses. The oocytes that have not been fertilized stay in the oviduct and cannot be transferred to the uterus in mares, while fertilized eggs are capable of being moved into the uterus [33]. Focal adhesion molecules (FAMs), which are not suppressed in pregnant mares, may be used by embryo movement to begin communication by chemical signals. The research suggests that FAMs could be relevant in the maintenance of the CL [34].

2.1. NK Cells

Natural killer (NK) cells during early pregnancy are the main leukocyte population in the decidua of humans. In most species, uNK and dNK vary from peripheral cells in their phenotypic and functional characteristics [26]. Different NK cell subtypes are seen in the peripheral blood, including those with low CD56 expression that specialize in cytolysis, and those with high CD56 expression that prefer cytokine secretion. CD56 bright NK cells predominate in the uterine mucosa during the first trimester of pregnancy which are similarly biased toward cytokine production [35]. Their number diminishes during midgestation, and they are missing during the term [20]. The regulatory subset is the CD56 bright CD16-NK subset. These NK cell activities in the uterine mucosa before

and throughout pregnancy, as well as in the endometrial and decidua tissues, are a clear example of its regulating role [36].

Even though they are called "natural killer", these uterine cells are mildly lytic and actually contribute to the development and continuation of pregnancy. When it comes to lymphocyte 'behavior', NK cells frequently defy the guidelines set by their T cell and B cell counterparts. NK cells remained 'armed' but not deadly. It is a fascinating biological contradiction, since they looked to be completely capable of killing target cells while also being plainly self-tolerant [37]. Although they have been connected to vascular remodeling and the encouragement of trophoblast invasion, the precise role of NK cells in pregnancy is still unknown [26]. Numerous reproductive health issues in women, such as preeclampsia, have been connected to altering the number and type of NK cells in the bloodstream [38]. In humans, and also in mice, the connection between uNK activating receptors and the allogeneic paternal MHC I is critical for various processes occurring during pregnancy, such as trophoblast invasion or fetal growth [39,40]. The formation of the placenta requires the collaboration of maternal NK cells and fetal trophoblast cells, which restructure the blood supply [35]. The human endometrium is highly reliant on mature NK cells prior to implantation, although, in mice, fully developed NK cells are not present until implantation [41], which shows that other models for reproductive studies are required.

Moreover, in horses, these cells are of great interest in reproductive studies. Because the horse uterus lacks the spiral artery modification, which has been found in animals with hemochorial placentae, this uNK cell activity can allow trophoblast invasion and endometrial remodeling to occur separately from placentation [26]. Fetal endometrial cup cells invading the uterine stroma and being destroyed by the mare's leukocytes is typical during a healthy developing horse pregnancy. It is possible that NK cells or lymphokine-activated killer cells may be involved in this process; however, the existence of these cell types in the equine uterus has not yet been well verified [42].

2.2. Lymphocytes T

As a result of pregnancy, the endometrium develops a large concentration of leukocytes with distinct regulatory roles. The regulatory T cells (Treg) are one of the two primary regulating populations (decidual macrophages are the second population) [43]. Crucial functions are provided by the subpopulation of CD4+/CD25+ Treg cells, as they help in the establishment of immunological tolerance during pregnancy, preventing autoimmunity and allowing for the growth of a semiallogeneic fetus in the womb [44,45]. Even in the first months of human pregnancy, a systemic increase in the Treg cell population can be noticed [46]. Treg are unique to paternally derived cells, indicating that their aim is to prevent paternally produced cells to be rejected by the mother's immune system [44]. In addition to decreasing autoimmune reactions, maternal Treg prevent an intense allogeneic response targeted at the fetus. As a result of their absence, the immune system rejects the fetus, resulting in a miscarriage. Thus, regulatory T cells are required for the fetal allograft to be accepted by the mother's immune system [47].

CD4+ and CD8+ T lymphocytes predominate in the stratum compactum above the stratum spongiosum in the mare's endometrium. After antigenic stimulation of the endometrial lining, the number of CD4+ and CD8+ cells increases, indicating the beginning of an adaptive immune reaction [48]. In mares, Agrícola et al. found a substantial reduction in the proportion of cells expressing CD2, CD3, and CD19 in the course of the final trimester of pregnancy compared to early postpartum levels ($p < 0.05$). However, the dynamics of CD4, CD8, and NK cell expression did not alter between these two periods of the study [49]. What is more, allograft rejection can be caused by the principal effectors of cell-mediated immune responses, CD8+ cytotoxic T cells, and so may have a negative influence during pregnancy [50], and, as other studies have shown, a rise in the number of CD8+ have been linked to preterm miscarriages in human pregnancies [51,52]. The expression of the FOXP3 gene does not vary between nonpregnant mares in the luteal phase of the estrous cycle

and mares with early pregnancies, but the CD4+FOXP3+ T cell population was increasing dramatically in the peripheral blood mononuclear cells (PBMCs) of pregnant mares. As a result, while Tregs appear to have a role at the horse's maternal–fetal interface, it is uncertain if they have an influence on the T cell populations observed in the periphery [50].

2.3. Macrophages

Cells that are macrophages make up about 30% of decidual cells at the implantation area [53] and their amount stays high during pregnancy, in contrast to NK cells [14]. It has been hypothesized that they play an important role in embryonic evolution, placentation, and fetal growth [54]. These phagocytotic mononuclear cells have a role in both the innate and adaptive immune systems [55]. A one-way mixed lymphocyte response suggests that macrophages play a part in human decidua immunosuppression, leading to fetal tolerance [56].

There are two types of macrophages: typically activated macrophages (M1) and alternatively activated macrophages (M2). When Th1 cytokines are administered to macrophages, they become proinflammatory type 1 macrophages (M1 cells) instead of M2-type ones. This group of cells can help guard against infections in the uterus and placenta, but they are not involved in fetal tolerance [57]. M2-type macrophages, which include M2a, M2b, M2c, and M2d subsets, help to restructure tissues and also have immunosuppressive capabilities. They also induce Th2-type responses, which are characterized by antibody synthesis, plasma cell upkeep, and improved phagocytic activity [58]. In addition, M2 cells express CD163, a mononuclear phagocyte-restricted cell surface glycoprotein antigen, which has been found to have an anti-inflammatory effect [55,59]. Gene expression analysis reveals that M2 cells predominate in the human decidua, contributing to the immunosuppressive condition required to maintain the semiallogeneic fetus [60].

To enable appropriate maternal decidua tissue restructuring and embryo invasion, apoptosis is critical during implantation [61]. Macrophages engulfing apoptotic cells, on the other hand, may inhibit the release of possibly proinflammatory and proimmunogenic intracellular substances that might occur during secondary necrosis, according to some studies [62]. Allogenicity of the placenta may make this procedure crucial for the fetus' well-being [14]. When a typical placental bed is examined histologically, it is shown to have a considerable number of macrophages that are primarily found in the proximity of apoptotic cells. Macrophages are abundant in the decidua and the tissues near the placenta during the first weeks of implantation in humans [63]. It has also been seen that macrophages accumulate near the implantation site in rodents [64].

In horses, studies about uterine macrophages during pregnancy are unique [65]. After ovulation, macrophages and other cells, such as dendritic cells, mast cells, and neutrophils, are found in the endometrium of mares [66,67]. In addition, the quantity of macrophage-like cells in the endometrial lamina propria of the mare is unaffected by the stage of the estrous cycle [68].

2.4. Other Antigen-Presenting Cells

As a result of their ability to play a variety of roles, antigen-presenting cells (APC) are interesting prospects for regulating the essential immunological balance between pathogen protection and tolerance of the fetal allograft. Through phagocytosis, as a result of which MHC class II antigens are presented, by secreting cytokines such as interleukin-10 (IL-10) or by expressing inhibitory receptors, they can enhance immunity as well as mediate tolerance [69]. The challenges to being recognized by the mother's immune system are mostly overcome through fetus trophoblasts. It has been found that trophoblast cells do not exhibit MHC class I or class II molecules, but extravillous cytotrophoblast cells produce the nonclassic MHC gene that synthesizes HLA-G, which may limit NK cell activity [6]. To ensure pregnancy success and to prevent the activation of abortogenic cells of the NK lineage, paternal peptides that attach to the class I MHC groove appear to be crucial [70].

An extensive and diverse population of APCs can be found in the early pregnancy decidua in humans. APCs are designed to trigger and sustain immune responses. Bone marrow-derived dendritic cells (DC) are the most effective presenters through these APCs. Research suggests that DCs have a function in the development of tolerance [69]. As a result of the difficulty of isolating and identifying DCs in decidual tissues, there has been little research on decidual cells in humans. This is due to the fact that there is no single marker that can be used to identify DCs in decidual tissues [9]. Dendritic cells convert antigens into peptides, which are then presented as ligands for antigen-specific T cell receptors in the context of MHC class I and class II molecules [71]. By presenting specific antigens on MHC molecules, mature DCs are the only APCs that can excite naive T lymphocytes [72]. The maturation phase of the DC may have a role in spontaneous pregnancy failure. For example, murine models (CBA/J $\times$ DBA/2J) with high abortion rates develop DCs that have a more matured phenotype compared to mice with low abortion rates [73]. It has been demonstrated that women with a history of recurrent loss during the eighth week of pregnancy have significantly more CD83+ DCs in their deciduas than normal controls of the same gestational age [74]. Uterine complexity suggests that the success or failure of the pregnancy is not entirely dependent on immunological factors. Both innate and adaptive processes appear to be involved when it comes to DCs, which appear to be crucial modulators of pregnancy [75].

In horses, when the chorionic girdle trophoblasts infiltrate the pregnant mare's uterus early in the pregnancy, they produce endometrial cups, unique tissue formations in the surface of the endometrium. The maternal immune system recognizes the MHC class I antigens that are expressed on the surface of these trophoblasts during pregnancy and develops a strong humoral immune response [26]. Due to the MHC comparability between the foal and mare, the nonsuccess of the maternal immune system to identify fetal antigens and oppositely may result in a deficiency of the placental partition in mares [76]. The chorionic girdle trophoblast populates the horse placenta. Especially high quantities of maternal and paternal polymorphic MHC class I antigens are present in these cells of fetal descent [26].

3. Cytokine Response during Pregnancy

Cytokines are tiny polypeptides that are capable of influencing a wide range of biological processes in living beings, which include pregnancy and the development of the embryo. In the present state of knowledge, the function of cytokines in embryology is poorly understood [77] and research into the role of cytokines in the body of a pregnant woman and mare is limited. These proteins play a function in the regulation of immune response, inflammatory responses, healing, and hematopoiesis on a local and systemic level. Since cytokines may have such a large impact on cell activity, migration, cell-to-cell contact, proliferation, and gene expression levels, cytokines and interferons (IFNs) are essential regulators of a successful pregnancy [78].

Maternal immune responses work to regulate inflammation via regulatory and anti-inflammatory mediators, whereas placental formation and implantation are both proinflammatory activities [79]. Due to the presence of paternal MHC antigens, the conceptus may be seen as an allograft, presuming that alterations in the pattern of the cytokines produced by the T cells have a substantial influence on immune tolerance or rejection. This may indicate that Th1-type cytokines that encourage allograft rejection may jeopardize pregnancy, while on the contrary, Th2-type cytokines that suppress Th1 reactions increase the allograft tolerance and therefore enhance the fetus' chances to survive [80].

3.1. Systemic Cytokine Response

The "transition" from Th1 to Th2 cytokine production throughout a successfuly developing pregnancy, relative to women that were not pregnant, was found by utilizing isolated PBMCs from pregnant women in the first and last trimesters [81,82]. The hypothesized Th1/Th2 cytokine switch during pregnancy was shown to be associated with an increase

in anti-inflammatory Th2 cytokine synthesis in the second trimester [83,84]. A significant reduction in serum proinflammatory cytokines was observed in the third trimester, such as TNF-α, INF-γ IL-1-α IL-1-β IL-2, and IL-12p70, comparable to those seen in healthy women during the first trimester of pregnancy [85]. In another study, the increase of TNFα occurred among the first, second, and third trimesters of a successful pregnancy (108.00 pg/mL, 153.01 pg/mL, and 172.89 pg/mL, respectively) [86]. Thus, there are opposite data about changes of TNFα during pregnancy, which is essential for the survival of the placenta trophoblast cells during normal pregnancy and to the apoptosis process to be controlled [87]. However, the differences may be induced by environmental factors such as stress or a proinflammatory diet [88]. Another cytokine that changes during pregnancy is IFN-γ, which influences maternal vascular remodeling and angiogenesis [89]. Once again, the results are in contrast. There are studies confirming the decrease of IFN-γ following the pregnancy [85]. Whereas, in another study, there was an increase between the first and last trimesters of pregnancy [90]. However, the study participants were overweight and the subclinical viral infection was not excluded. Other proinflammatory cytokines, of which concentrations decrease during pregnancy, are IL-1β, IL-2, and IL-8. During a healthy pregnancy, maternal blood levels of each of these cytokines stayed at low levels [85,90]. Once again, the data are misleading, which perhaps is connected with the reported concentrations below the lower limit of detection, or its short half-life in circulation.

One of the most important cytokines during pregnancy are anti-inflammatory cytokines, such as IL-10 or IL-4, because they activate the Treg [91,92]. It was documented that both of them rise in the third trimester of a healthy pregnancy or continue to be constant during pregnancy [85,90,93]. In addition, the lower concentration of anti-inflammatory cytokines during the second trimester was proposed as an early indicator of preeclampsia [81], which, in the future, may be the early biomarkers of pregnancy health.

Few studies have been done on the functions of cytokines during pregnancy in livestock, although it has been discussed in connection to acute-phase proteins during the canine peri- and postimplantation period [94]. It is now proved that equine abortions are caused by both infectious and noninfectious conditions. According to Fedorka et al., late-gestation mares with healthy cytokine profiles did not seem to vary with time, whereas mares with placenta inflammations had an enhanced cytokine response. Serum concentrations of IL-2, IL-5, IL-6, IL-10, IFN, and TNF were shown to be elevated in mares with placentitis [95]. Recent research on horses using an experimental paradigm to induce ascending placentitis examined the cytokine response to placental infection. It revealed a rise in blood concentrations of proinflammatory IL-2 and IFN, anti-inflammatory IL5 and IL-10, as well as pleiotropic IL-6 and TNF [96]. These cytokines, which are potent cell-signaling chemicals, and the development of several lymphocyte populations associated with the fetus' adaptive immunological-mediated tolerance, are linked to both a rapid and temporary innate immune reaction when pathogens are detected [95].

In conclusion, in most studies, it was postulated that TNF-α rose during gestation, IL-8 was shown to be decreased in the second trimester, and IL-4 levels stayed consistent throughout the whole pregnancy [81]. In addition, the increased Th1 proinflammatory cytokines, such as TNF-α, IFN-γ, IL-2, IL-8, and IL-6, all have been associated with serious pregnancy outcomes such as preeclampsia or preterm labor [97,98]. The researchers concluded that a mismatch between maternal proinflammatory cytokines and immunological regulatory factors (such as Tregs and IL-10) caused reproductive issues. However, the investigation of the link between proinflammatory and anti-inflammatory cytokine levels revealed significant inconsistencies, but did not reveal the preponderance of a specific immune response. Thus, understanding the changes in the maternal cytokine profile in detail may assist to differentiate between a healthy pregnancy and one marred by pregnancy problems, and could also allow scientists to better understand the immune response during pregnancy [81].

3.2. Local Cytokine and Hormonal Response

The embryo binds to the layer of the endometrium after fertilization, and semiallogeneic fetal extravillous trophoblasts (EVTs) start to penetrate the uterine mucosa but are not eliminated by the host's (i.e., the mother's) immune system [99]. The development and maintenance of a normal pregnancy are impossible without trophoblast invasion, the careful cooperation of immune cells and cytokines, and the interaction between EVTs and immune cells. As cytokines are secreted by these cells, they work together to keep the immune system in balance [100]. During the midsecretory phase, hormones from the ovaries cause the uterus to generate proinflammatory mediators, including IL-8, IL-15, IL-6, CXCL10, and CXCL11 [84,101].

TGF-β1 is a cytokine that acts as a negative regulator in the endometrium. A TGF-β route redirected native T cells away from the Treg cell pathway and toward the Th17 cell pathway when the pathogens that promote IL-6 or IL-1 production activated DCs [102]. High TGF-β concentrations stop human Th17 cell development, although IL-1 and IL-6 are required [103,104]. In addition, TGF-β1 activation is required for the synthesis of CD4+FOXP3+ Tregs, which can then release TGF-β1 and engage in immune control. Low cytotoxic dNK cells can regulate vascular reorganization at the maternal–fetal contact by producing vascular endothelial growth factor, angiopoietin, and TGF-β1 [105]. There is also a correlation between TGF-β1 and NK cells because the decidual stromal cells secrete TGF-β1 that converts CD56dimCD16+ NK cells into CD56brightCD16- NK cells [106].

Early pregnancy spiral artery remodeling is linked to the production of angiogenic growth factors by the dNK cells during 8–10 weeks of gestation [107]. The dNK cells release cytokines (IL-8 and INF- inducible protein, IP10) that enhance EVT invasion by boosting MMP-9 production and lowering EVT apoptosis between 12 and 14 weeks. TNF-α, TGF-β, as well as IFN-γ can also be secreted by dNK to limit EVT invasion in later stages [108]. The inflammatory process of parturition is well known. Maternal leukocytes (innate and adaptive) are selectively drawn to the reproductive organs in late pregnancy by a number of chemotactic factors secreted by these tissues (e.g., CXCL8, CXCL10, CCL2, and CCL3) [109,110]. Pregnancy is induced by the release of proinflammatory mediators such as cytokines (IL-1, IL-6, IL-8, and TNF), MMPs, and prostaglandins, which cause the cervical effacement/dilation and the rupture of the membranes, resulting in the birth of the child [105]. If this proinflammatory route is prematurely activated and the maternal–fetal interaction is compromised, it may lead to premature delivery [111].

In a study by Lennard et al., all endometrial samples from pregnant mares, and a significant level of TGF-β1 expression, was identified at the junction of the fetal endometrial cups and the maternal endometrium. As this is further examined, the lymphocytes and glandular epithelium can be shown to be the primary contributors to this signal [112,113]. In situ hybridization of fetal and endometrial tissues revealed diverse and fascinating patterns of IGF-2, TGF-β1, and EGF gene expression, suggesting that peptide growth factors are also important regulators of fetal and placental development in the horse. For example, the unique and localized patterns of TGF-β1 gene expression among fetal and endometrial tissues in the horse pregnancy imply a function for TGF-β1 in the chorionic girdle invasion and differentiation of the noninvasive trophoblast of allantochorion, as was observed in rodents [11].

4. Conclusions

The survival of a species depends on safeguarding the growing fetus. The immune system was developed to defend the host against infections that were able to infiltrate the organism. Whenever a fetus is being protected by its mother's immune system, the mother's health must be maintained as much as possible. While protecting the fetus from pathogens, females carrying an allogeneic fetus must tolerate and avoid immune-mediated harm to the fetus. Thus, many processes influence the pregnancy in humans and, similarly, in mares.

The unique anatomy and physiology of the horse seems to be a good model for further reproduction studies. For example, the isolation of a pure trophoblast cell population, and the antigenicity of its invasiveness, seems to be easier to examinate in this species. Equine placenta allows for a better separation between the maternal and trophoblas-dependent processes, and thus in-depth examination is possible. However, there is lack of studies, especially connected with the cell-mediated reaction. The lack of species-specific monoclonal antibodies seems to limit the research. However, technologies are improving, and thus there is hope that our knowledge will expand.

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References

1. Stokes, D.M.; Male, P.V. *Immunolog*; Elsevier Health Sciences: Amsterdam, The Netherlands, 2020.
2. Dymarska, E. The factors modulating the human immune system. *Zesz. Nauk. Państwowej Wyższej Szkoły Zawodowej Witelona W Legn.* **2016**, *19*, 21–27.
3. Trzeciak-Ryczek, A.; Tokarz-Deptuła, B.; Niedźwiedzka-Rystwej, P.; Deptuła, W. Adipose tissue—Component of the immune system. *Cent.-Eur. J. Immunol.* **2011**, *36*, 95–99.
4. Trowsdale, J.; Betz, A.G. Mother's little helpers: Mechanisms of maternal-fetal tolerance. *Nat. Immunol.* **2006**, *7*, 241–246. [CrossRef]
5. Aluvihare, V.R.; Kallikourdis, M.; Betz, A.G. Regulatory T cells mediate maternal tolerance to the fetus. *Nat. Immunol.* **2004**, *5*, 266–271. [CrossRef] [PubMed]
6. Weetman, A.P. The Immunology of Pregnancy. *Thyroid* **1999**, *9*, 643–646. [CrossRef]
7. Noronha, L.E.; Antczak, D.F. Maternal Immune Responses to Trophoblast: The Contribution of the Horse to Pregnancy Immunology. *Am. J. Reprod. Immunol.* **2010**, *64*, 231–244. [CrossRef]
8. Olmos-Ortiz, A.; Flores-Espinosa, P.; Mancilla-Herrera, I.; Vega-Sánchez, R.; Díaz, L.; Zaga-Clavellina, V. Innate Immune Cells and Toll-like Receptor–Dependent Responses at the Maternal–Fetal Interface. *Int. J. Mol. Sci.* **2019**, *20*, 3654. [CrossRef]
9. Ehsu, P.; Nanan, R.K.H. Innate and Adaptive Immune Interactions at the Fetalâ€"Maternal Interface in Healthy Human Pregnancy and Pre-Eclampsia. *Front. Immunol.* **2014**, *5*, 125. [CrossRef]
10. Bilate, A.M.; Lafaille, J.J. Induced CD4+Foxp3+ Regulatory T Cells in Immune Tolerance. *Annu. Rev. Immunol.* **2012**, *30*, 733–758. [CrossRef]
11. Fan, D.-X.; Duan, J.; Li, M.-Q.; Xu, B.; Li, D.-J.; Jin, L.-P. The decidual gamma-delta T cells up-regulate the biological functions of trophoblasts via IL-10 secretion in early human pregnancy. *Clin. Immunol.* **2011**, *141*, 284–292. [CrossRef]
12. Tilburgs, T.; Schonkeren, D.; Eikmans, M.; Nagtzaam, N.M.; Datema, G.; Swings, G.M.; Prins, F.; Van Lith, J.M.; Van Der Mast, B.J.; Roelen, D.L.; et al. Human Decidual Tissue Contains Differentiated CD8+Effector-Memory T Cells with Unique Properties. *J. Immunol.* **2010**, *185*, 4470–4477. [CrossRef] [PubMed]
13. Mincheva-Nilsson, L.; Baranov, V.; Yeung, M.; Hammarstrom, S.; Hammarstrom, M.L. Immunomorphologica studies in human decidua-associated lymphoid cells in normal early pregnancy. *J. Immuno.* **1994**, *152*, 2020–2032.
14. Mor, G.; Abrahams, V.M. Potential role of macrophages as immunoregulators of pregnancy. *Reprod. Biol. Endocrinol.* **2003**, *1*, 119. [CrossRef] [PubMed]
15. Liu, L.; Liu, X. Contributions of Drug Transporters to Blood-Placental Barrier. *Drug Transp. Drug Dispos. Eff. Toxic.* **2019**, *1141*, 505–548. [CrossRef]
16. Pozor, M. Equine placenta—A clinician's perspective. Part 1: Normal placenta—Physiology and evaluation. *Equine Veter.-Educ.* **2015**, *28*, 327–334. [CrossRef]
17. Wood, K.J.; Sakaguchi, S. Regulatory T cells in transplantation tolerance. *Nat. Rev. Immunol.* **2003**, *3*, 199–210. [CrossRef]
18. Cristiani, C.M.; Palella, E.; Sottile, R.; Tallerico, R.; Garofalo, C.; Carbone, E. Human NK Cell Subsets in Pregnancy and Disease: Toward a New Biological Complexity. *Front. Immunol.* **2016**, *7*, 656. [CrossRef]
19. Gaynor, L.M.; Colucci, F. Uterine Natural Killer Cells: Functional Distinctions and Influence on Pregnancy in Humans and Mice. *Front. Immunol.* **2017**, *8*, 467. [CrossRef]
20. Moffett-King, A. Natural killer cells and pregnancy. *Nat. Rev. Immunol.* **2002**, *2*, 656–663. [CrossRef]

21. Fernekorn, U.; Kruse, A. Regulation of Leukocyte Recruitment to the Murine Maternal/Fetal Interface. *Immunol. Pregnancy* **2005**, *89*, 105–117. [CrossRef]
22. Williams, P.; Searle, R.; Robson, S.; Innes, B.; Bulmer, J. Decidual leucocyte populations in early to late gestation normal human pregnancy. *J. Reprod. Immunol.* **2009**, *82*, 24–31. [CrossRef] [PubMed]
23. Viveiros, M.; Antczak, D. Characterization of equine natural killer and IL-2 stimulated lymphokine activated killer cell populations. *Dev. Comp. Immunol.* **1999**, *23*, 521–532. [CrossRef]
24. Croy, B.; Waterfield, A.; Wood, W.; King, G.J. Normal murine and porcine embryos recruit NK cells to the uterus. *Cell. Immunol.* **1988**, *115*, 471–480. [CrossRef]
25. Carter, A.M.; Enders, A.C. The Evolution of Epitheliochorial Placentation. *Annu. Rev. Anim. Biosci.* **2013**, *1*, 443–467. [CrossRef] [PubMed]
26. Noronha, L.; Huggler, K.; de Mestre, A.; Miller, D.; Antczak, D. Molecular evidence for natural killer-like cells in equine endometrial cups. *Placenta* **2012**, *33*, 379–386. [CrossRef]
27. Allen, W.R. The physiology of early pregnancy in the mare. *AAEP Proc.* **2000**, *46*, 338–354.
28. Grünig, G.; Triplett, L.; Canady, L.; Allen, W.; Antczak, D. The maternal leucocyte response to the endometrial cups in horses is correlated with the developmental stages of the invasive trophoblast cells. *Placenta* **1995**, *16*, 539–559. [CrossRef]
29. Fujiwara, H.; Ono, M.; Sato, Y.; Imakawa, K.; Iizuka, T.; Kagami, K.; Fujiwara, T.; Horie, A.; Tani, H.; Hattori, A.; et al. Promoting Roles of Embryonic Signals in Embryo Implantation and Placentation in Cooperation with Endocrine and Immune Systems. *Int. J. Mol. Sci.* **2020**, *21*, 1885. [CrossRef]
30. Herrler, A.; von Rango, U.; Beier, H.M. Embryo-maternal signalling: How the embryo starts talking to its mother to accomplish implantation. *Reprod. Biomed. Online* **2003**, *6*, 244–256. [CrossRef]
31. Rao, C.; Lei, Z. The past, present and future of nongonadal LH/hCG actions in reproductive biology and medicine. *Mol. Cell. Endocrinol.* **2007**, *269*, 2–8. [CrossRef]
32. Fazleabas, A.; Kim, J.; Strakova, Z. Implantation: Embryonic Signals and the Modulation of the Uterine Environment—A Review. *Placenta* **2004**, *25*, S26–S31. [CrossRef] [PubMed]
33. Goff, A.K. Embryonic Signals and Survival. *Reprod. Domest. Anim.* **2002**, *37*, 133–139. [CrossRef]
34. Klohonatz, K.M.; Cameron, A.D.; Hergenreder, J.R.; Da Silveira, J.C.; Belk, A.D.; Veeramachaneni, D.N.R.; Bouma, G.J.; Bruemmer, J.E. Circulating miRNAs as Potential Alternative Cell Signaling Associated with Maternal Recognition of Pregnancy in the Mare. *Biol. Reprod.* **2016**, *95*, 124. [CrossRef] [PubMed]
35. Parham, P. NK Cells and Trophoblasts. *J. Exp. Med.* **2004**, *200*, 951–955. [CrossRef] [PubMed]
36. Manaster, I.; Mandelboim, O. The Unique Properties of Uterine NK Cells. *Am. J. Reprod. Immunol.* **2010**, *63*, 434–444. [CrossRef] [PubMed]
37. Di Santo, J.P. Natural killer cells: Diversity in search of a niche. *Nat. Immunol.* **2008**, *9*, 473–475. [CrossRef] [PubMed]
38. Lash, G.E.; Bulmer, J.N. Do uterine natural killer (uNK) cells contribute to female reproductive disorders? *J. Reprod. Immunol.* **2011**, *88*, 156–164. [CrossRef] [PubMed]
39. Madeja, Z.; Yadi, H.; Apps, R.; Boulenouar, S.; Roper, S.J.; Gardner, L.; Moffett, A.; Colucci, F.; Hemberger, M. Paternal MHC expression on mouse trophoblast affects uterine vascularization and fetal growth. *Proc. Natl. Acad. Sci. USA* **2011**, *108*, 4012–4017. [CrossRef]
40. Hiby, S.E.; Apps, R.; Sharkey, A.; Farrell, L.E.; Gardner, L.; Mulder, A.; Claas, F.H.; Walker, J.; Redman, C.C.; Morgan, L.; et al. Maternal activating KIRs protect against human reproductive failure mediated by fetal HLA-C2. *J. Clin. Investig.* **2010**, *120*, 4102–4110. [CrossRef]
41. King, A. Uterine leukocytes and decidualization. *Hum. Reprod. Updat.* **2000**, *6*, 28–36. [CrossRef]
42. Engelhardt, H.; King, G.J. Uterine natural killer cells in species with epitheliochorial placentation. *Nat. Immun.* **1996**, *15*, 53–69. [PubMed]
43. Svensson-Arvelund, J.; Mehta, R.B.; Lindau, R.; Mirrasekhian, E.; Rodriguez-Martinez, H.; Berg, G.; Lash, G.E.; Jenmalm, M.C.; Ernerudh, J. The Human Fetal Placenta Promotes Tolerance against the Semiallogeneic Fetus by Inducing Regulatory T Cells and Homeostatic M2 Macrophages. *J. Immunol.* **2015**, *194*, 1534–1544. [CrossRef] [PubMed]
44. Zenclussen, A.C. Regulatory T cells in pregnancy. *Springer Semin. Immunopathol.* **2006**, *28*, 31–39. [CrossRef] [PubMed]
45. Piccinni, M.-P. T cells in normal pregnancy and recurrent pregnancy loss. *Reprod. Biomed. Online* **2006**, *13*, 840–844. [CrossRef]
46. Mjösberg, J.; Svensson-Arvelund, J.; Johansson, E.; Hellström, L.; Casas, R.; Jenmalm, M.; Boij, R.; Matthiesen, L.; Jönsson, J.-I.; Berg, G.; et al. Systemic Reduction of Functionally Suppressive CD4dimCD25highFoxp3+Tregs in Human Second Trimester Pregnancy Is Induced by Progesterone and 17β-Estradiol. *J. Immunol.* **2009**, *183*, 759–769. [CrossRef]
47. Leber, A.; Teles, A.; Zenclussen, A.C. Regulatory T Cells and Their Role in Pregnancy. *Am. J. Reprod. Immunol.* **2010**, *63*, 445–459. [CrossRef]
48. Christoffersen, M.; Troedsson, M. Inflammation and fertility in the mare. *Reprod. Domest. Anim.* **2017**, *52* (Suppl S3), 14–20. [CrossRef]
49. Agrícola, R.; Carvalho, H.; Barbosa, M.; Pereira, M.; Medeiros, J.; Ferreira-Dias, G. Blood Lymphocyte Subpopulations, Neutrophil Phagocytosis and Proteinogram During Late Pregnancy and Postpartum in Mares. *Reprod. Domest. Anim.* **2008**, *43*, 212–217. [CrossRef]

50. Noronha, L.E.; Antczak, D.F. Modulation of T-cell Reactivity During Equine Pregnancy is Antigen Independent. *Am. J. Reprod. Immunol.* **2012**, *68*, 107–115. [CrossRef]
51. Yamada, K. Analysis on the CTL-p frequency before and after immunotherapy for patients with unexplained habitual abortion. *Nihon Sanka Fujinka Gakkai Zasshi* **1993**, *45*, 527–532.
52. Kotlan, B.; Fülöp, V.; Padányi, Á.; Szigetvári, I.; Réti, M.; Gyódi, É.; Fehér, É.; Petrányi, G. High anti-paternal cytotoxic T-lymphocyte precursor frequencies in women with unexplained recurrent spontaneous abortions. *Hum. Reprod.* **2001**, *16*, 1278–1285. [CrossRef] [PubMed]
53. Uckan, D.; Steele, A.; Cherry; Wang, B.Y.; Chamizo, W.; Koutsonikolis, A.; Gilbert-Barness, E.; Good, R.A. Trophoblasts express Fas ligand: A proposed mechanism for immune privilege in placenta and maternal invasion. *Mol. Hum. Reprod.* **1997**, *3*, 655–662. [CrossRef]
54. Care, A.S.; Diener, K.; Jasper, M.J.; Brown, H.M.; Ingman, W.V.; Robertson, S.A. Macrophages regulate corpus luteum development during embryo implantation in mice. *J. Clin. Investig.* **2013**, *123*, 3472–3487. [CrossRef] [PubMed]
55. Schonkeren, D.; van der Hoorn, M.-L.; Khedoe, P.; Swings, G.; van Beelen, E.; Claas, F.; van Kooten, C.; de Heer, E.; Scherjon, S. Differential Distribution and Phenotype of Decidual Macrophages in Preeclamptic versus Control Pregnancies. *Am. J. Pathol.* **2011**, *178*, 709–717. [CrossRef] [PubMed]
56. Mizuno, M.; Aoki, K.; Kimbara, T. Functions of Macrophages in Human Decidual Tissue in Early Pregnancy. *Am. J. Reprod. Immunol.* **1994**, *31*, 180–188. [CrossRef]
57. Gordon, S. Alternative activation of macrophages. *Nat. Rev. Immunol.* **2003**, *3*, 23–35. [CrossRef]
58. Ning, F.; Liu, H.; Lash, G.E. The Role of Decidual Macrophages During Normal and Pathological Pregnancy. *Am. J. Reprod. Immunol.* **2016**, *75*, 298–309. [CrossRef]
59. Böckle, B.; Sölder, E.; Kind, S.; Romani, N.; Sepp, N. DC-SIGN+ CD163+ Macrophages Expressing Hyaluronan Receptor LYVE-1 Are Located within Chorion Villi of the Placenta. *Placenta* **2008**, *29*, 187–192. [CrossRef]
60. Gustafsson, C.; Mjösberg, J.; Matussek, A.; Geffers, R.; Matthiesen, L.; Berg, G.; Sharma, S.; Buer, J.; Ernerudh, J. Gene Expression Profiling of Human Decidual Macrophages: Evidence for Immunosuppressive Phenotype. *PLoS ONE* **2008**, *3*, e2078. [CrossRef]
61. De, M.; Wood, G.W. Influence of Oestrogen and Progesterone on Macrophage Distribution in the Mouse Uterus. *J. Endocrinol.* **1990**, *126*, 417–424. [CrossRef]
62. Piacentini, M.; Autuori, F. Immunohistochemical localization of tissue transglutaminase and Bcl-2 in rat uterine tissues during embryo implantation and post-partum involution. *Differentiation* **1994**, *57*, 51–61. [CrossRef] [PubMed]
63. Miller, L.; Hunt, J.S. Sex steroid hormones and macrophage function. *Life Sci.* **1996**, *59*, 1–14. [CrossRef]
64. Tachi, C.; Tachi, S. Macrophages and Implantation. *Ann. N. Y. Acad. Sci.* **1986**, *476*, 158–182. [CrossRef] [PubMed]
65. Skarzynski, D.J.; Szóstek-Mioduchowska, A.Z.; Rebordão, M.R.; Jalali, B.M.; Piotrowska-Tomala, K.K.; Leciejewska, N.; Ferreira-Dias, G.M. Neutrophils, monocytes and other immune components in the equine endometrium: Friends or foes? *Theriogenology* **2020**, *150*, 150–157. [CrossRef]
66. Watson, E.D.; Dixon, C.E. An immunohistological study of MHC Class II expression and T lymphocytes in the endometrium of the mare. *Equine Veter-J.* **1993**, *25*, 120–124. [CrossRef]
67. Frayne, J.; Stokes, C. MHC Class II positive cells and T cells in the equine endometrium throughout the oestrous cycle. *Veter-Immunol. Immunopathol.* **1994**, *41*, 55–72. [CrossRef]
68. Summerfield, N.J.; Watson, E.D. Endometrial macrophage populations in genitally normal mares at oestrus and dioestrus and in mares susceptible to endometritis. *Equine Veter-J.* **1998**, *30*, 79–81. [CrossRef]
69. Rieger, L.; Honig, A.; Sütterlin, M.; Kapp, M.; Dietl, J.; Ruck, P.; Kämmerer, U. Antigen-Presenting Cells in Human Endometrium During the Menstrual Cycle Compared to Early Pregnancy. *J. Soc. Gynecol. Investig.* **2004**, *11*, 488–493. [CrossRef]
70. Clark, D.A.; Chaouat, G.; Wong, K.; Gorczynski, R.M.; Kinsky, R. REVIEW ARTICLE: Tolerance Mechanisms in Pregnancy: A Reappraisal of the Role of Class I Paternal MHC Antigens*. *Am. J. Reprod. Immunol.* **2009**, *63*, 93–103. [CrossRef]
71. Hart, D.N. Dendritic Cells: Unique Leukocyte Populations Which Control the Primary Immune Response. *Blood* **1997**, *90*, 3245–3287. [CrossRef]
72. Bachy, V.; Williams, D.J.; Ibrahim, M.A.A. Altered dendritic cell function in normal pregnancy. *J. Reprod. Immunol.* **2008**, *78*, 11–21. [CrossRef] [PubMed]
73. Blois, S.; Tometten, M.; Kandil, J.; Hagen, E.; Klapp, B.F.; Margni, R.A.; Arck, P.C. Intercellular Adhesion Molecule-1/LFA-1 Cross Talk Is a Proximate Mediator Capable of Disrupting Immune Integration and Tolerance Mechanism at the Feto-Maternal Interface in Murine Pregnancies. *J. Immunol.* **2005**, *174*, 1820–1829. [CrossRef]
74. Askelund, K.; Liddell, H.; Zanderigo, A.; Fernando, N.; Khong, T.; Stone, P.; Chamley, L. CD83+Dendritic Cells in the Decidua of Women with Recurrent Miscarriage and Normal Pregnancy. *Placenta* **2004**, *25*, 140–145. [CrossRef]
75. Blois, S.M.; Kammerer, U.; Soto, C.A.; Tometten, M.C.; Shaikly, V.; Barrientos, G.; Jurd, R.; Rukavina, D.; Thomson, A.W.; Klapp, B.F.; et al. Dendritic Cells: Key to Fetal Tolerance? *Biol. Reprod.* **2007**, *77*, 590–598. [CrossRef] [PubMed]
76. Jaworska, J.; Tobolski, D.; Janowski, T. Is similarity in Major Histocompatibility Complex (MHC) associated with the incidence of retained fetal membranes in draft mares? A cross-sectional study. *PLoS ONE* **2020**, *15*, e0237765. [CrossRef]
77. Dinarello, C.A. Historical insights into cytokines. *Eur. J. Immunol.* **2007**, *37* (Suppl S1), S34–S45. [CrossRef]
78. Saini, V.; Arora, S.; Yadav, A.; Bhattacharjee, J. Cytokines in recurrent pregnancy loss. *Clin. Chim. Acta* **2011**, *412*, 702–708. [CrossRef]

79. Robertson, S.A.; Care, A.S.; Moldenhauer, L.M. Regulatory T cells in embryo implantation and the immune response to pregnancy. *J. Clin. Investig.* **2018**, *128*, 4224–4235. [CrossRef]
80. Chaouat, G.; Menu, E.; Delage, G.; Moreau, J.F.; Khrishnan, L.; Hui, L.; Meliani, A.A.; Martal, J.; Raghupathy, R.; Lelaidier, C.; et al. Immuno-endocrine interactions in early pregnancy. *Hum. Reprod.* **1995**, *10* (Suppl S2), 55–58. [CrossRef]
81. Spence, T.; Allsopp, P.J.; Yeates, A.J.; Mulhern, M.S.; Strain, J.J.; McSorley, E.M. Maternal Serum Cytokine Concentrations in Healthy Pregnancy and Preeclampsia. *J. Pregnancy* **2021**, *2021*, 6649608. [CrossRef]
82. Reinhard, G.; Noll, A.; Schlebusch, H.; Mallmann, P.; Ruecker, A.V. Shifts in the TH1/TH2 Balance during Human Pregnancy Correlate with Apoptotic Changes. *Biochem. Biophys. Res. Commun.* **1998**, *245*, 933–938. [CrossRef] [PubMed]
83. Mor, G.; Cardenas, I. The Immune System in Pregnancy: A Unique Complexity. *Am. J. Reprod. Immunol.* **2010**, *63*, 425–433. [CrossRef]
84. Mor, G.; Cardenas, I.; Abrahams, V.; Guller, S. Inflammation and pregnancy: The role of the immune system at the implantation site. *Ann. N. Y. Acad. Sci.* **2011**, *1221*, 80–87. [CrossRef]
85. Doria, A.; Cutolo, M.; Ghirardello, A.; Zen, M.; Villalta, D.; Tincani, A.; Punzi, L.; Iaccarino, L.; Petri, M. Effect of pregnancy on serum cytokines in SLE patients. *Arthritis Res. Ther.* **2012**, *14*, R66. [CrossRef] [PubMed]
86. Subha, M.; Pal, P.; Pal, G.K.; Habeebullah, S.; Adithan, C.; Sridhar, M.G. Decreased baroreflex sensitivity is linked to sympathovagal imbalance, low-grade inflammation, and oxidative stress in pregnancy-induced hypertension. *Clin. Exp. Hypertens.* **2016**, *38*, 666–672. [CrossRef] [PubMed]
87. Straszewski-Chavez, S.L.; Abrahams, V.M.; Mor, G. The Role of Apoptosis in the Regulation of Trophoblast Survival and Differentiation during Pregnancy. *Endocr. Rev.* **2005**, *26*, 877–897. [CrossRef] [PubMed]
88. Lindsay, K.L.; Buss, C.; Wadhwa, P.D.; Entringer, S. Maternal Stress Potentiates the Effect of an Inflammatory Diet in Pregnancy on Maternal Concentrations of Tumor Necrosis Factor Alpha. *Nutrients* **2018**, *10*, 1252. [CrossRef]
89. Murphy, S.P.; Tayade, C.; Ashkar, A.A.; Hatta, K.; Zhang, J.; Croy, B.A. Interferon Gamma in Successful Pregnancies1. *Biol. Reprod.* **2009**, *80*, 848–859. [CrossRef]
90. Nayak, M.; Eekhoff, E.; Peinhaupt, M.; Heinemann, A.; Desoye, G.; van Poppel, M.N. Cytokines and their association with insulin resistance in obese pregnant women with different levels of physical activity. *Cytokine* **2016**, *77*, 72–78. [CrossRef]
91. Chatterjee, P.; Chiasson, V.L.; Bounds, K.R.; Mitchell, B.M. Regulation of the Anti-Inflammatory Cytokines Interleukin-4 and Interleukin-10 during Pregnancy. *Front. Immunol.* **2014**, *5*, 253. [CrossRef]
92. Witkowska-Piłaszewicz, O.; Pingwara, R.; Winnicka, A. The Effect of Physical Training on Peripheral Blood Mononuclear Cell Ex Vivo Proliferation, Differentiation, Activity, and Reactive Oxygen Species Production in Racehorses. *Antioxidants* **2020**, *9*, 1155. [CrossRef] [PubMed]
93. Sipak-Szmigiel, O.; Podolska, M.; Płonka, T.; Włodarski, P.; Ronin-Walknowska, E. Changes in the concentration of sHLA-I and selected cytokines in pregnancy complicated by antiphospholipid syndrome. *Ginekol. Pol.* **2011**, *82*, 354–358.
94. Schäfer-Somi, S. Cytokines during early pregnancy of mammals: A review. *Anim. Reprod. Sci.* **2002**, *75*, 73–94. [CrossRef]
95. Fedorka, C.; Ball, B.; Walker, O.; McCormick, M.; Scoggin, K.; Kennedy, L.; Squires, E.; Troedsson, M. Alterations of Circulating Biomarkers During Late Term Pregnancy Complications in the Horse Part I: Cytokines. *J. Equine Veter-Sci.* **2021**, *99*, 103425. [CrossRef]
96. Fedorka, C.E.; Scoggin, K.E.; Ali, H.E.; Loux, S.C.; Dini, P.; Troedsson, M.H.T.; Ball, B.A. Interleukin-6 pathobiology in equine placental infection. *Am. J. Reprod. Immunol.* **2020**, *85*, e13363. [CrossRef]
97. Arikan, D.C.; Aral, M.; Coskun, A.; Ozer, A. Plasma IL-4, IL-8, IL-12, interferon-γ and CRP levels in pregnant women with preeclampsia, and their relation with severity of disease and fetal birth weight. *J. Matern. Neonatal Med.* **2012**, *25*, 1569–1573. [CrossRef]
98. Pinheiro, M.B.; Martins-Filho, O.A.; Mota, A.P.L.; Alpoim, P.N.; Godoi, L.C.; Silveira, A.C.; Teixeira-Carvalho, A.; Gomes, K.B.; Dusse, L.M. Severe preeclampsia goes along with a cytokine network disturbance towards a systemic inflammatory state. *Cytokine* **2013**, *62*, 165–173. [CrossRef]
99. Ferreira, L.M.; Meissner, T.B.; Tilburgs, T.; Strominger, J.L. HLA-G: At the Interface of Maternal–Fetal Tolerance. *Trends Immunol.* **2017**, *38*, 272–286. [CrossRef]
100. Yockey, L.J.; Iwasaki, A. Interferons and Proinflammatory Cytokines in Pregnancy and Fetal Development. *Immunity* **2018**, *49*, 397–412. [CrossRef]
101. Sentman, C.L.; Meadows, S.K.; Wira, C.R.; Eriksson, M. Recruitment of Uterine NK Cells: Induction of CXC Chemokine Ligands 10 and 11 in Human Endometrium by Estradiol and Progesterone. *J. Immunol.* **2004**, *173*, 6760–6766. [CrossRef]
102. Saito, S.; Nakashima, A.; Shima, T.; Ito, M. Th1/Th2/Th17 and Regulatory T-Cell Paradigm in Pregnancy. *Am. J. Reprod. Immunol.* **2010**, *63*, 601–610. [CrossRef] [PubMed]
103. Peck, A.; Mellins, E.D. Plasticity of T-cell phenotype and function: The T helper type 17 example. *Immunology* **2010**, *129*, 147–153. [CrossRef]
104. Crome, S.Q.; Wang, A.Y.; Levings, M.K. Translational Mini-Review Series on Th17 Cells: Function and regulation of human T helper 17 cells in health and disease. *Clin. Exp. Immunol.* **2009**, *159*, 109–119. [CrossRef] [PubMed]
105. Yang, D.; Dai, F.; Yuan, M.; Zheng, Y.; Liu, S.; Deng, Z.; Tan, W.; Chen, L.; Zhang, Q.; Zhao, X.; et al. Role of Transforming Growth Factor-β1 in Regulating Fetal-Maternal Immune Tolerance in Normal and Pathological Pregnancy. *Front. Immunol.* **2021**, *12*, 689181. [CrossRef] [PubMed]

106. Keskin, D.B.; Allan, D.S.J.; Rybalov, B.; Andzelm, M.M.; Stern, J.N.H.; Kopcow, H.D.; Koopman, L.A.; Strominger, J.L. TGFβ promotes conversion of CD16 $^{+}$ peripheral blood NK cells into CD16 NK cells with similarities to decidual NK cells. *Proc. Natl. Acad. Sci. USA* **2007**, *104*, 3378–3383. [CrossRef] [PubMed]
107. Lash, G.E.; Schiessl, B.; Kirkley, M.; Innes, B.A.; Cooper, A.; Searle, R.F.; Robson, S.C.; Bulmer, J.N. Expression of angiogenic growth factors by uterine natural killer cells during early pregnancy. *J. Leukoc. Biol.* **2006**, *80*, 572–580. [CrossRef]
108. Zhang, X.; Wei, H. Role of Decidual Natural Killer Cells in Human Pregnancy and Related Pregnancy Complications. *Front. Immunol.* **2021**, *12*, 728291. [CrossRef]
109. Gomez-Lopez, N.; Estrada-Gutierrez, G.; Jimenez-Zamudio, L.A.; Vega-Sanchez, R.; Vadillo-Ortega, F. Fetal membranes exhibit selective leukocyte chemotaxic activity during human labor. *J. Reprod. Immunol.* **2009**, *80*, 122–131. [CrossRef]
110. Gomez-Lopez, N.; Tanaka, S.; Zaeem, Z.; Metz, G.A.; Olson, D.M. Maternal circulating leukocytes display early chemotactic responsiveness during late gestation. *BMC Pregnancy Childbirth* **2013**, *13*, S8. [CrossRef]
111. King, A.; Allan, D.S.; Bowen, M.; Powis, S.J.; Joseph, S.; Verma, S.; Braud, V.M. HLA-E is expressed on trophoblast and interacts with CD94/NKG2 receptors on decidual NK cells. *Eur. J. Immunol.* **2000**, *30*, 1623–1631. [CrossRef]
112. Lennard, S.N.; Stewart, F.; Allen, W.R. Transforming growth factor ?1 expression in the endometrium of the mare during placentation. *Mol. Reprod. Dev.* **1995**, *42*, 131–140. [CrossRef] [PubMed]
113. Lennard, S.; Stewart, F.; Allen, W.; Heap, R. Growth Factor Production in the Pregnant Equine Uterus1. *Biol. Reprod.* **1995**, *52*, 161–170. [CrossRef]