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Cytokine landscapes of pregnancy: mapping gestational immune phases

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ABSTRACT

Background Synchronised physiological adaptations occur during pregnancy to achieve systemic, immune and neuroendocrine equilibrium in the mother's body, allowing semiallogenic fetal growth.

Main text Depending on the cytokine profile alterations occurring through pregnancy, the latter can be divided into three distinct phases. In the first immunological phase of pregnancy, proinflammatory cytokines promote inflammatory reactions needed for implantation. In the second phase, a possible change from proinflammatory to anti-inflammatory cytokines creates a symbiosis between maternal and fetal components, ensuring fetal development. In the third phase, inflammatory and cytolytic cytokines operate again to reinforce an inflammatory environment for parturition. The article offers a detailed account of immune adaptations during pregnancy and highlights the distinctive cytokine profiles that mark each phase.

Conclusion By providing a simplified depiction of pregnancy phases based on cytokine profiles, the article aims to inspire more research in reproductive immunology and improve the management of pregnancy-related inflammation and infection.

INTRODUCTION

Pregnancy presents a complex physiological condition which is meticulously regulated. Inflammatory and anti-inflammatory immune factors have major functions in the instituting, maintenance and completion of pregnancy. Inflammatory reactions aid the process of implantation and parturition, while immunological tolerance is necessary to maintain the semiallogenic fetus healthy and developing. Perinatal depression, preterm birth and pre-eclampsia are just some of the pregnancy-related diseases that have been linked to an abnormal immune profile in women.[1]

Pregnancy may be classified into three distinct immunological stages based on how various sets of cytokines control it.[2 3] The initiation of inflammatory reactions, which are important to implant trophoblast cells into the endometrium, occurs during the first trimester of pregnancy. The second phase is characterised by a requisite anti-inflammatory state which is indispensable for facilitating symbiotic maternal–fetal cohabitation. This anti-inflammatory condition is crucial not only for maintaining a harmonious in utero environment that supports the collaborative existence of mother and fetus but also for ensuring the appropriate growth and developmental progression of the latter entity.

Immune cells that are active during various gestational phases, including B cells, T cells, macrophages and natural killer (NK) cells, among others, coordinate harmoniously. It is believed that pregnancy is accompanied with polarised immune responses, with T cells playing a significant orchestrating role.[4] The two kinds of T helper cells (CD4+) are known as T helper 1 cells (Th1) and T helper 2 cells (Th2), and they differ from one another in terms of their capacity to generate cytokines. Activated Th1 cells secrete proinflammatory cytokines, such as interferon-gamma (IFN-γ) and tumour necrosis factor-alpha (TNF-α). In contrast, activated Th2 cells release anti-inflammatory cytokines, including interleukin-10 (IL-10), IL-4 and IL-13, which facilitate wound healing and immune tolerance.[5] Wegmann and colleagues presented the idea of pregnancy-related cytokine shift from a Th1 cascade to a Th2 cascade in order to promote immune suppression and tolerance towards the semiallogenic fetus, while simultaneously encouraging development of the latter.[6] The fetal blastocyst invades the uterine endometrium, inducing damage to the maternal tissue underlying. This process involves disruption of maternal blood vessels to secure an adequate blood supply essential for fetal development. Consequently, successful embryonic attachment to the uterine wall ensues. To safeguard the healing system of the uterus and to make it easier for damaged maternal cells to be evacuated from the uterus, these invasive physiological processes cause a maternal inflammatory response.[3]

Various endocrinological, physiological and immunological factors play a role in preventing infections during normal pregnancy. Some infections are common in pregnancy and occur more frequently as they have

such serious clinical repercussions for the fetus.[7 8] Understanding the immunological alterations of pregnancy may be crucial for formulating the best plans for administering vaccinations, such as those for pertussis and influenza, which serve as prophylactic measures safeguarding both maternal and fetal health during gestation.[9] This manuscript elucidates the three immunological regulatory phases inherent to pregnancy, delineated by the operative functions of proinflammatory and anti-inflammatory cytokines, in a manner that is both clear and comprehensible. It is important for mothers and clinicians to have a thorough understanding of the immunological adaptations that occur at various gestational phases to alleviate the physiological burden of pregnancy and give the fetus a healthy onset in life.

OVERVIEW OF IMMUNE ADAPTATIONS IN PREGNANCY

To safeguard the mother and unborn child from infections while preventing deleterious immune responses towards the allogeneic fetus, significant immunological modifications occur within the maternal immune system throughout gestation. Despite insufficient evidence supporting a global immunosuppressive effect during pregnancy, heightened susceptibility to specific infections indicates noteworthy qualitative changes in immune function.[10]

The interplay between systemic immune adaptations and localised alterations within the female reproductive tract is complex. Specifically, as systemic immune responses in the peripheral blood undergo modifications to safeguard both the mother and fetus, there is a concurrent transformation in the local environment of reproductive tract. This transformation facilitates fetal implantation and growth. These adaptive changes, evident at varying pregnancy stages, collectively establish an environment optimised for fetal development and the maintenance of maternal health. It is noteworthy that the three distinct phases of pregnancy, elaborated upon in the Cytokine profile demarcating the phases of pregnancy section, manifest unique immune signatures that impact both the systemic circulation and the reproductive tract.

Neutrophils constitute a crucial component of the innate immune system, using mechanisms such as phagocytosis, inflammatory mediator secretion, neutrophil extracellular trap deployment and reactive oxygen species (ROS) generation for effective pathogen neutralisation.[11] From the first trimester, neutrophils rise steadily.[12 13] Pregnancy also increases bone marrow neutrophil-producing cytokines granulocyte colony-stimulating factor (G-CSF) and granulocyte-macrophage colony-stimulating factor (GM-CSF).[12] As the pregnancy progresses, the neutrophil functions get altered. Neutrophils' activity requires high energy and thereby needs high production of ATP through glycolysis and conserves oxygen for mitochondrial ROS and nitrogen species synthesis. The hexose monophosphate shunt facilitates the transformation of glucose into nicotinamide adenine dinucleotide phosphate, serving the metabolic demands associated with oxidative bursts. In the presence of metabolic stimuli, neutrophils instigate the activation of respective enzymes, engendering the formation of enzyme conglomerates along the cellular membrane, thereby enhancing anabolic processes. Notably, throughout gestation, there is observed retrograde transport of metabolic enzymes towards centrosomes within neutrophils, indicative of a potential suppression of metabolic augmentation.[14 15] Neutrophils express less CD10 and more CD15 in pregnancy, most prominently in the third trimester.[16] Enhanced populations of myeloid-derived suppressor cells (MDSCs)—a heterogeneous assembly of cells, encompassing both mature and immature monocytic or granulocytic phenotypes possessing immunosuppressive functions—are observed concomitantly. These augmentations in MDSC levels are speculated to play a pivotal role in sustaining the immunosuppressive milieu imperative for maternal–fetal tolerance. Notably, diminished concentrations of MDSCs during gestation are associated with an elevated risk of miscarriage.[17]

During gestation, there is a noted augmentation in complement system activity, as evidenced by elevated plasma levels of C3a, C4a, C5a, C4d, C3, C9 and SC5b.[18 19] Concurrently, a surge in regulatory proteins such as factor H, an inhibitor of alternative C3 convertase, occurs, serving as a counterbalancing mechanism.[20] Furthermore, gestation induces an increment in the concentration of decay-accelerating factor within peripheral blood mononuclear cells.[21] This particular complement inhibitor impedes the activation of downstream complements through the inhibition of C3 convertases. There is also a significant increase in the levels of pregnancy-associated plasma protein A, another inhibitor of C3, during the second and third trimesters of pregnancy.[22] Both pre-eclampsia and premature delivery have been associated with heightened complement activity,[23] underscoring the imperative of maintaining complement activation equilibrium for the assurance of favourable pregnancy outcomes.[24]

Approximately 80% of all monocytes in peripheral blood of healthy people are classic monocytes ($CD14^{high}$ CD16–), which perform phagocytic activities. Adults with chronic or acute inflammatory conditions have been found to have high numbers of non-classic monocytes ($CD14^{low}$ $CD16^{high}$), which are proinflammatory.[25] Intermediate monocytes ($CD14^{high}$ $CD16^{intermediate}$) may be a stage in transition since they have the ability to both inflame and phagocytose.[25] Pregnancy causes an increase in monocytes, starting in the first trimester.[26 27] While classic monocytes decline and the fraction of non-classic monocytes remains the same, this rise is mostly caused by greater levels of 'intermediate' monocytes.[28 29] Elevated production of IL-12 and TNF-α in response to stimulation in monocytes derived from pregnant women throughout gestation, along with observed phagocytic dysfunction,[30 31] may be attributable to an augmentation in intermediate monocytes.[32]

During the initial trimester of gestation, the placental decidua harbours distinctive NK cells that are indispensable for the development of the spiral artery and the process of fetal implantation.[33] Conversely, limited knowledge exists pertaining to the influence of pregnancy on the prevalence of circulating NK cells. Although a diminution in NK cell counts has been observed,[34 35] preponderance of studies yields no substantial disparities in NK cell subsets, invariant NK T cells and type II non-classic NK T cells within peripheral blood between pregnant and non-pregnant females.[36 37]

In a typical human pregnancy, there are several different approaches of coping with the semiallogenic fetus, which include changes in the adaptive immune responses as well.[38] B cell lymphocytopenia and decreased reactivity to infectious pathogens are characteristics of pregnancy.[39] Beyond this notion of old age, a number of studies support the notion that B cells execute pivotal functions during gestation, undergoing a series of modifications influencing their proliferation dynamics. These alterations encompass transitions among distinct subtypes, fluctuations in antibody secretory profiles, cytokine balance modulation and the orchestration of the activity of additional immune cellular components.[40–43] By creating shielding antibodies in response to the foreign paternal antigens, B cells create a tolerant environment throughout pregnancy.[44–46] To support a normal pregnancy, regulatory B cells have taken on anti-inflammatory traits. Additionally, synchronous changes in the interactions between pregnancy hormones and B cells are one of the immense physiological changes that occur throughout pregnancy.[40]

A lot of research supports the idea that pregnancy is characterised by a predominant Th2 cell immunological profile, which is anti-inflammatory in nature, as opposed to a Th1 cell proinflammatory milieu,[6 47 48] but contradiction exists.[49] Anti-inflammatory cytokines are present at higher levels during pregnancy, which is consistent with research demonstrating that during gestation, Th1 and Th17-associated autoimmune conditions exhibit amelioration, while autoimmune disorders related to Th2 experience exacerbation.[50] Early stages of pregnancy are characterised by a progressive shift from cellular-mediated, proinflammatory Th1 responses to humoral, anti-inflammatory Th2 cell responses.[51 52] By 4 weeks after delivery, this pregnancy-related Th2 phenotype disappears.[53] In a recent study, there was no observed alteration in CD4+ T cells producing IL-4. However, there was a reduction in the proportion of CD4+ cells producing IFN during the third trimester.[54] A steady percentage of CD3+ CD8IFN−+ cells throughout gestation and no alterations in Th1/Th2 cells throughout pregnancy have been seen in other investigations.[55] However, a recent study found that compared with other trimesters, the postpartum phase had decreased plasma IL-2 levels, which are suggestive of Th1 cells.[56]

CYTOKINE PROFILE DEMARCATING THE PHASES OF PREGNANCY

Proinflammatory cytokines regulating the implantation phase

Proinflammatory refers to substances or processes that promote inflammation. Proinflammatory cytokines serve a crucial function in the immune response by safeguarding the body against microbial invasion and tissue damage. Ensuring the protection of the developing fetus from infection has significant importance. During the course of pregnancy, it is important to participate in tissue remodelling of the uterus and placenta to facilitate the accommodation of the developing fetus. It facilitates the degradation of the endometrium and stimulates angiogenesis.[57 58] Seminal plasma serves a critical immunoregulatory role and triggers an inflammatory response in the endometrium during the post-coitus stage of pregnancy. Due to this, a range of immune effector cells are drawn to the implantation site. It is now recognised that cytokines, prostaglandins and other steroid-binding proteins all play a role in this inflammatory response, even if the exact mediators are still unclear.[59] The key regulator in the inflammatory state is transforming growth factor-beta 1 (TGF-β1), which is found in seminal plasma. The human semen contains a wide range of cytokines that include TNF-α, IFN-γ, vascular endothelial growth factor (VEGF), IL-1a/b, IL-2, 4, 6, 8, 11 and 12, monocyte chemotactic and activating factor. These are secreted and regulated on activation and expression of T cells.[59] Various other mediators may also bear immunoregulatory functions in the post-coital uterus, like the macrophage inflammatory proteins, eotaxin, keratinocyte-derived chemokine, monocyte chemotactic protein-1 and IL-9.[60] Primary cytokines exert regulatory control over uterine immune mechanisms, encompassing the trafficking, recruitment and activation of granulocytes, alongside processing and presentation of paternal antigens. Such regulatory mechanisms facilitate immunosurveillance, thereby fostering conditions conducive to embryonic implantation and pregnancy establishment, while simultaneously promoting sperm survival and subsequent expulsion from the female reproductive tract[59 61] (figure 1).

The inflammatory stage is required to cleanse the wound of debris and dead tissue and to prepare the location for healing. It happens immediately after an injury and is characterised by the production of proinflammatory cytokines and chemokines. These signalling molecules attract immune cells to the site of damage and stimulate the creation of more inflammatory mediators. The inflammatory stage is required to cleanse the wound of debris and dead tissue and to prepare the location for healing.[62] Comparable inflammatory responses to open wounds are seen during implantation, placentation, and the first and early second pregnancy trimesters. The endometrial tissue is damaged when the blastocyst first penetrates the epithelial lining of the uterus and implants itself. For optimal haematological sustenance, the trophoblast of the blastocyst supplants the uterine endothelium and maternal vascular smooth muscle arteries during

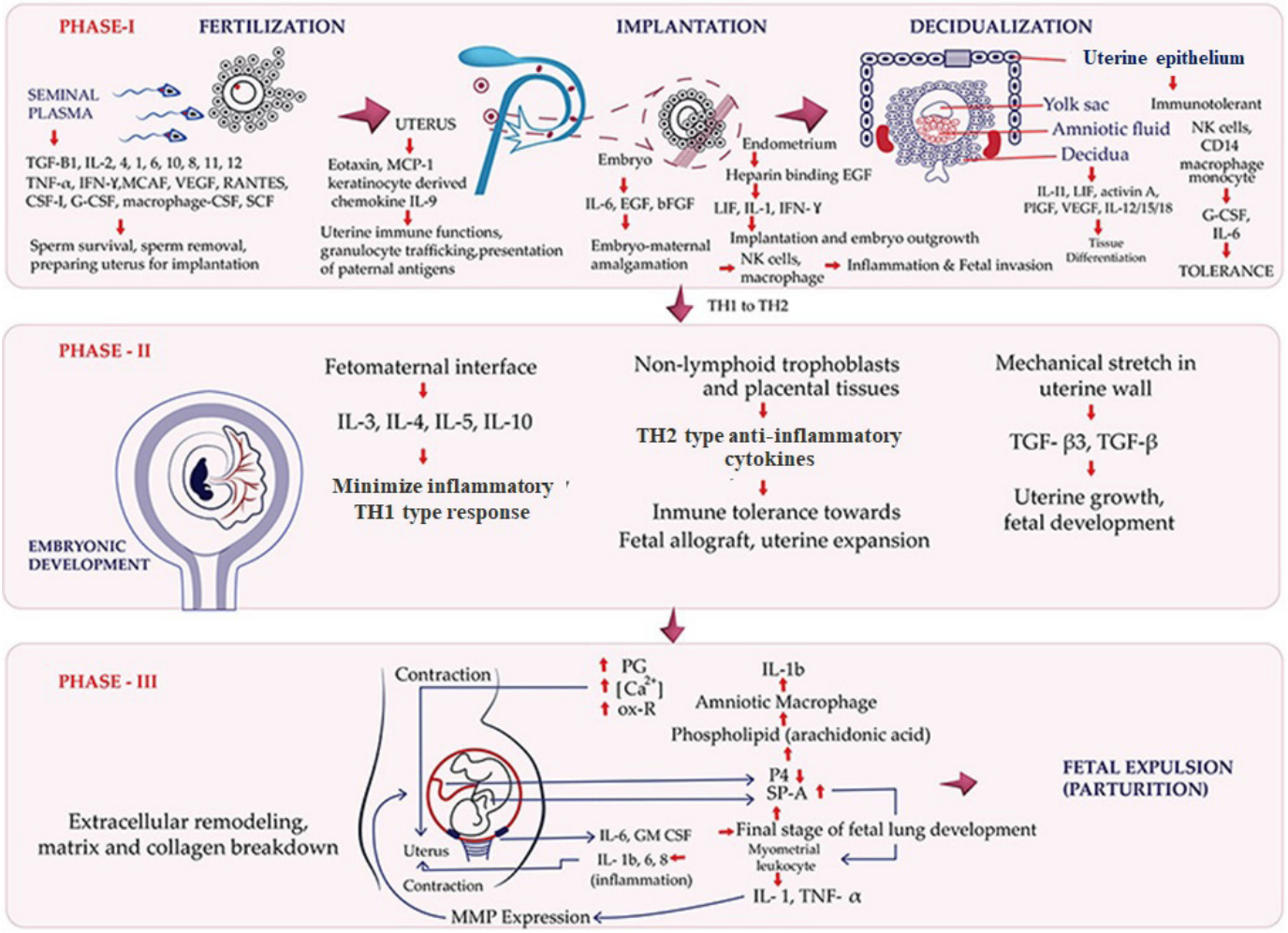

Figure 1 Phases of pregnancy marked by regulatory cytokine profile. This figure depicts the phases of pregnancy, delineated by unique cytokine regulations and immune states. Phase I: covers fertilisation, implantation and decidualisation. Driven by cytokines, prostaglandins (PG) and steroid-binding proteins, this inflammatory phase recruits immune cells to the implantation site, facilitating embryo and placenta integration. A balanced proinflammatory response is pivotal for implantation and placental growth. Phase II: centres on embryonic development, establishing a mother–fetus symbiosis via the placenta, promoting an anti-inflammatory state essential for pregnancy. The placenta manages hormone, immune cell and cytokine exchanges, ensuring immunological tolerance, uterine growth and fetal development. Phase III: marked by renewed inflammation preceding childbirth. Uterine and cervical inflammations intensify, impacting labour onset. Rising PG levels and a balance of cytokines play key roles. Fetal cortisol spurs organ maturation and initiates labour, with cytokines and PG influencing fetal development and childbirth. bFGF, basic fibroblast growth factor; CSF, colony-stimulating factor; EGF, epidermal growth factor; G-CSF, granulocyte colony-stimulating factor; GM-CSF, granulocyte-macrophage colony-stimulating factor; IFN, interferon; IL, interleukin; LIF, leukaemia inhibitory factor; MCAF, monocyte chemotactic and activating factor; MCP, monocyte chemoattractant protein; MMP, matrix metalloproteinases; NK, natural killer cells; ox-R, oxytocin receptor; P4, progesterone; PlGF, placenta growth factor; RANTES, regulated upon activation, normal T cell expressed and secreted; SCF, stem cell factor; SP-A, surfactant proteins A; TGF, transforming growth factor; TH, T helper; TNF, tumour necrosis factor; VEGF, vascular endothelial growth factor.

the secondary phase of embryonic development.[63] A protracted inflammatory response is required to ensure the healing of the damaged uterine epithelium as well as to remove the debris left behind by these activities. During this period, the mother's body is trying to immunologically adapt to the fetus and the body experiences numerous other physiological changes including endocrine modulation.[64–66] A variety of cytokines (IL-6, epidermal growth factor (EGF), basic fibroblast growth factor) are produced by pre-implanted embryos, which aid in the integration of the embryo and the mother at the implantation sites. The uterine epithelium, which is also important for blastocyst growth, is said to secrete heparin-binding EGF at the time of blastocyst attachment to the uterine wall. Key cytokines, such as leukaemia inhibitory factor (LIF)-like cytokines and components of the IL-1 system, mediate the implantation process and are implicated in the immunological response.[67] The process of tissue differentiation is aided by various cytokines to promote cellular differentiation, like activin A, LIF,

IL-11 and monoclonal non-specific suppressor factor-b.[68] Precise modulation of cytokine secretion within the endometrial tissue is imperative for the recruitment of maternal uterine NK cells and macrophages. This recruitment is mediated through chemotactic signals and L-selectin expression, facilitating an orchestrated inflammatory response. Such inflammation is crucial for the invasive process of fetal trophoblasts into the decidua and uterine vasculature. Throughout gestation, these trophoblasts undergo differentiation, culminating in a structure that mimics endothelial tissue. This pseudoendothelial layer plays a pivotal role in the reconstitution of maternal spiral arteries, thereby ensuring efficient nutrient and oxygen delivery to the developing fetus[69] (figure 1).

Furthermore, development of the placenta is mostly cytokine dependent, regulated by the IL-12/IL-15/IL-18 system, VEGF and placental growth factor, which play a role in tissue remodelling and angiogenesis among other regulatory functions.[70 71] It is critical to strictly regulate the activity of uterine NK cells, because the IFN-γ produced by these cells aids in trophoblast invasion by inducing apoptosis. Activated leucocytes recruited to the decidua generate a spectrum of regulatory cytokines, further enriching the pre-existing inflammatory microenvironment therein.[68] Consequently, the procedures of implantation and placentation inherently embody proinflammatory processes, orchestrated by an array of growth factors and proinflammatory cytokines.

The proinflammatory response is required for tissue remodelling and angiogenesis, but it must be strictly managed to avoid embryo and placental rejection. It is linked to hormone regulation, cell regulation and cytokine control. Progesterone suppresses the proinflammatory response and promotes the anti-inflammatory response during implantation. NK cells aid in the remodelling of the endometrium and the promotion of angiogenesis. Macrophages aid in the recruitment of other immune cells to the site of implantation and promote tissue remodelling. During placentation, progesterone and oestrogen continue to play an essential function in regulating the immune response. Progesterone inhibits the proinflammatory response while promoting the anti-inflammatory response. Oestrogen aids in the recruitment and activation of regulatory T cells (Tregs), which are essential for maintaining immune tolerance. NK cells aid in the protection of the placenta from infection and the maintenance of immune tolerance. Macrophages aid in placental remodelling and promote angiogenesis. Tregs assist in suppressing the activity of other T cells and preventing placental rejection. The same cytokines that play a role in modulating the immunological balance during implantation also play a role in placentation.[72–74]

The differentiation between immunological alterations in the peripheral blood and those within the female reproductive tract becomes increasingly pronounced upon analysis of the cytokine profiles throughout various stages of gestation. For example, while systemic modifications are pivotal for safeguarding maternal health and thwarting infections, the predominant role of the reproductive tract is to enable successful implantation and nurture an environment conducive to fetal development. These immunological adaptations are intricately aligned with the sequential phases of gestation, ranging from implantation to placentation, culminating in parturition. The synergistic coordination of these systemic and localised immunological shifts is fundamental to ensuring a successful gestation.

Concurrently, a regulatory mechanism operates within the maternal decidua inflammatory response, where select leucocytes activate immunotolerant NK cells, CD14+ monocytes and additional cell types. These cells subsequently produce anti-inflammatory mediators, including G-CSF and IL-6, among others[75] (figure 1).

Phase of symbiosis between mother and fetus

The second gestational immune phase is regarded to be a calming period. This is the time of pregnancy when the fetus grows rapidly and establishes a symbiotic relationship with the mother components. As a result, the mother, placenta and fetus become acclimated to one another, and the major immune processes work to create an anti-inflammatory state in the mother and child. The placenta regulates the exchange of hormones, immune cells and cytokines between the mother and the fetus. The placenta also generates hormones and cytokines that aid in the maintenance of the symbiotic relationship. The regulation of exosomes produced from placental cells has been seen to be influenced by variations in oxygen tension and glucose content. In addition, it has been shown that maternal exosomes had the capacity to induce the secretion of cytokines from endothelial cells.[76] The presence of maternal decidual stromal cells, invasive placental trophoblast cells and maternal immune cells is essential for the effective establishment and maintenance of pregnancy. Nevertheless, there are still several unresolved issues that need to be addressed. Once maternal immune cells have reached the maternal–fetal interface, cues from the placenta cause their specialisation[77] (figure 1).

A prolong anti-inflammatory milieu is associated with the preservation of early pregnancy, while a dramatic proinflammatory change was found as early as day ET+16 in women who later miscarried.[78] Conventionally, the described anti-inflammatory condition is characterised by a transition in cytokine profile from proinflammatory Th1 cytokines to anti-inflammatory Th2 cytokines. This shift is consequent to the modulation of NK cells and lymphokine-activated killer cells.[51] Modulatory cytokines (IL-3, IL-4, IL-5 and IL-10) are found at the fetomaternal interface, which help to reduce Th1-type responses[79] and increase Th2-type responses. The non-lymphoid trophoblast and placental/decidual tissues are responsible for the majority of the Th2-type cytokines produced in this gestational second phase.[80]

Additionally, cytokines released during this phase aid in the establishment of immunological tolerance to the fetal allograft and the promotion of uterine growth. Due to the

mechanical stretch caused by the developing gestational sac, cytokines (such as TGF-β3) may be produced, which in turn may speed up uterine growth and development.[81 82] IL-1a, IL-1b, IL-6 and IL-8 are also produced by the endometrium during this expanding phase, which is necessary for the maintenance of an anti-inflammatory condition as well as the growth of uterine and fetal tissue.[82] A considerable assortment of cytokines, including but not limited to TGF-β, have been implicated in the regulation of embryonic and fetal development through mechanisms such as the epithelial–mesenchymal transition. These cytokines play a pivotal role in various developmental processes, including erythropoiesis, cardiovascular formation, skeletal development, craniofacial morphogenesis and axial patterning[83–85] (figure 1).

Phase renewed inflammation and onset of parturition

Inflammation must be carefully managed throughout the remainder of the pregnancy in order to forestall the onset of labour too soon. There is a rise in inflammation in the uterus and cervix in the weeks coming up to parturition. It is believed that this inflammation contributes to the commencement of labour. In the weeks before parturition, prostaglandin levels rise in the uterus and cervix. This rise in prostaglandin levels is considered to contribute to the start of labour. It is critical to maintain a balance of proinflammatory and anti-inflammatory cytokines during parturition.[86] The fetus also regulates the commencement of parturition. Cortisol, a hormone produced by the fetal adrenal glands, aids in the maturation of the lungs and other organs of the fetus. Cortisol also contributes to the commencement of labour.[87]

Completion of fetal development and pregnancy is marked by the last immunological phase of pregnancy. This means that the mother must undergo parturition, a process characterised by intermittent inflammatory episodes, for the delivery of the offspring. Concurrently, the initiation of labour and delivery precipitates a reversal of the anti-inflammatory immunological state previously present.[51] Although the particular immunological mechanisms that regulate labour are not totally understood, it has been established that the presence of an inflammatory sequence caused by the coordinated synthesis of cytokines and prostaglandins is a common occurrence.[88] First and foremost, the use of IL-6 and GM-CSF in late pregnancy may be beneficial in the latter stages of fetal lung maturation.[82] Increased levels of phospholipid and surfactant protein-A (SP-A) are associated with a decrease in maternal levels of progesterone and fetal lung maturation. SP-A may cause IL-1b production by stimulating fetal amniotic macrophages that migrate to the uterine wall. This causes the release of inflammatory and prostaglandin molecules, which triggers uterine contractility.[89] Invasion and migration of myometrial leucocytes lead to the generation of the inflammatory and chemotactic cytokines IL-1, IL-6 and IL-8.[82] In human myometrial cells in vitro, cytokines have been shown to raise intracellular phospholipase activity and calcium concentration, and induce the production of oxytocin and prostaglandin receptors, and thus it is clear that cytokines play a role in increasing uterine smooth muscle contraction during the process of parturition.[82] Furthermore, cytokines (IL-1 and TNF-α) promote arachidonic acid release, which lead to an elevated prostaglandin production.[90] The chorioamniotic membranes are also affected by the inflammatory process that has begun at this stage.[91] Cytokine synthesis augmentation within gestational membranes elevates matrix metalloproteinase (MMP) expression levels, a critical agent facilitating extracellular matrix remodelling and destabilisation through the activation of collagen decomposition processes.[92] This cascade precipitates the ensuing rupture and detachment of fetal membranes. Within the cervical epithelium, a plethora of cytokines—encompassing M-CSF, TGF-b1, IL-1a/b, IL-6, IL-7, IL-8 and RANTES (regulated upon activation, normal T cell expressed and secreted)—are secreted, maintaining susceptibility to exogenous IFN-γ and TNF-α.[82] Concurrently, during this pivotal phase, fibroblasts instigate cervical remodelling through a cytokine-mediated inflammatory cascade, predominantly characterised by the overexpression of IL-6 and IL-8, MMP-1 and MMP-3, concomitantly with the inhibition of tissue inhibitors of metalloproteinases.[92] This coordinated response culminates in the immune cell infiltration within the myometrium, inducing an inflammatory reaction that subsequently triggers uterine contractions, fetal expulsion and placental rejection, collectively facilitating the parturition process[64 88] (figure 1).

During pregnancy, alterations in the immune system can profoundly influence the course and outcome of concomitant diseases. Pre-eclampsia, a notable pregnancy-associated complication, is characterised by elevated blood pressure and the presence of proteinuria. Its aetiology is believed to result from a combination of factors, with inflammation playing a pivotal role. Women with pre-eclampsia demonstrate elevated concentrations of proinflammatory cytokines coupled with a decrease in anti-inflammatory cytokines.[93] Similarly, a miscarriage is defined as the spontaneous termination of a pregnancy before 20 weeks of gestation. Women who undergo a miscarriage exhibit elevated levels of proinflammatory cytokines and reduced levels of anti-inflammatory cytokines.[94] Gestational diabetes, which emerges during pregnancy, is postulated to be caused by a combination of genetic predisposition, weight gain and hormonal changes. Women diagnosed with gestational diabetes demonstrate an upregulation of proinflammatory cytokines and a downregulation of anti-inflammatory cytokines.[94]

During gestation, females exhibit increased vulnerability to particular infections, such as urinary tract infections and influenza. This heightened susceptibility is attributed to the natural immunosuppression that occurs during pregnancy, which serves to prevent fetal rejection. Nonetheless, an oversuppressed immune response can elevate the risk of acquiring infections. Intriguingly, this

immunosuppressive state can lead to the alleviation of certain autoimmune disorders, including lupus and rheumatoid arthritis. In contrast, conditions such as multiple sclerosis and type 1 diabetes may exhibit exacerbation during pregnancy.[95] Emerging evidence increasingly suggests a potential association between intrauterine adhesions and the immunological mechanisms of pregnancy.[96]

CONCLUSION

Gestation is characterised by a dynamic interplay between proinflammatory and anti-inflammatory immunological responses, with the predominance of each contingent upon the specific gestational phase under consideration. Throughout the gestational period, a myriad of immunomodulatory cytokines is synthesised. These bioactive proteins play pivotal roles in orchestrating a spectrum of physiological processes including, but not limited to, gametogenesis, the acquisition of uterine receptivity, the inception and unfolding of implantation reactions, embryonic development, fetal maturation and the initiation of parturition.

Cytokines exert their influence either by establishing a state of immune tolerance, which is indispensable for fostering a favourable gestational milieu, or by instigating inflammatory cascades that are instrumental during various stages of pregnancy. The gestational continuum can be stratified into three cardinal phases, each demarcated by distinctive immunological adjustments and corresponding cytokine profiles that oversee these modulations.

It is imperative to underscore the significance of cytokines in meticulously regulating the immune equilibrium during gestation. These cytokines are crucial during the incipient phase of pregnancy where there is an inceptive inflammatory response facilitating the infiltration of semiallogenic fetal cells into the endometrial cellular matrix. Subsequently, as gestation progresses, cytokines are integral in engendering a harmonious symbiotic relationship between the fetus and the mother. This is achieved by promoting tolerance to the fetal allograft. In the terminal stages of pregnancy, cytokines once again spearhead inflammatory processes, crucially contributing to the separation and expulsion of fetal tissues from the maternal counterpart.

In an endeavour to facilitate a more coherent understanding of the intricate network of cytokines, which seamlessly coordinate to regulate physiological activities inherent to each gestational phase, the present discourse offers a simplified, yet comprehensive, conceptual framework.

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