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REVIEW

The Role of Cytokines in Early Pregnancy: Fertilization, Implantation, and Maintenance

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Abstract

Purpose of the Review Early pregnancy presents a unique immunological phenomenon, wherein the maternal immune system must tolerate the allogeneic fetus. The complex immunoregulation required to orchestrate this balance is believed to be mediated by cytokine profiles specific to pregnancy. This article examines the responsible cytokines and their roles, and how their interplay predicts continued pregnancy or spontaneous miscarriage. It also explores the conflicting theories on their contribution to pregnancy outcomes.

Recent Findings Recent studies have furthered the hypothesis that the maternal immune response is responsible for outcomes across the pregnancy spectrum, from early pregnancy loss to preeclampsia. They dispute, however, previous notions that successful pregnancy is exclusively a phenomenon of immune suppression. Reproductive failure cannot easily be explained by simple imbalances of the Th1- and Th2-associated cytokines. Furthermore, therapeutics have been suggested for recurrent pregnancy failure based on the importance of cytokines in early pregnancy.

Summary While disruptions in cytokine balance have been associated with poor outcomes, recent research has challenged the paradigm that cytokine levels alone are determinative. Instead, they advance a revised model of cytokines as mediators of a delicate sequence of pro- and anti-inflammatory events that facilitate pregnancy continuation.

Keywords Early pregnancy · Pregnancy immunology · Cytokines · Recurrent pregnancy loss

Introduction

Cytokines play an important role in early pregnancy to mediate the maternal response to the developing embryo. These small cell-signaling proteins facilitate immune reactivity such that there is sufficient maternal protection against infection while also preventing rejection of the pregnancy. Cytokines serve as key regulators of the complex processes of fertilization, implantation, and trophoblast invasion, and their interplay is finely balanced [1]. Dysfunctional maternal immune response has been proposed to play a role across pregnancy, from early pregnancy loss to preeclampsia [2, 3]. While many studies have measured relative quantities of cytokines in early pregnancy, there is little consensus on how the function and interplay of these molecules change in that critical time [4]. Through a stepwise progression through the phases of early pregnancy, this review will summarize the key cytokines involved, the prevailing models of cytokine signaling, and hypotheses of their roles in pregnancy outcomes. It will, in particular, highlight the conflicting evidence in the literature regarding their exact impact on clinical pregnancy rates and miscarriage.

Establishing Maternal-Fetal Immune Tolerance

Pregnancy requires both a robust maternal immunologic response while avoiding rejection of the allogeneic fetus. Early theories assumed that the "fetal allograft" requires a state of maternal immunosuppression. This model is exemplified by autoimmune diseases like systemic lupus erythematous, for which a lapse in tolerance to self-antigens and subsequent increased inflammatory response leads to a high risk of recurrent pregnancy loss. Similarly, antiphospholipid antibodies induce trophoblastic apoptosis, abnormal spiral artery formation, and degrade the vascular endothelium [5].

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Table 1 Summary of the roles of cytokines in early pregnancy

Cytokine	Early pregnancy process	Pro-gestational effects	Anti-gestational effects
Activin	Trophoblast invasion	Increased trophoblast invasion and differentiation	Decreased endothelial cell proliferation for spiral artery remodeling
C-reactive protein	Maintenance		Increased in preeclampsia
Interferon-gamma	Immune tolerance		Decreased tolerance
	Fertilization		Reduced sperm motility
	Implantation		Decreased embryo implantation when elevated relative to IL-4
	Trophoblast invasion		Increased trophoblast apoptosis
	Maintenance		Increased miscarriage rates
Interleukin-1	Fertilization		Reduced sperm motility
	Implantation	Increased embryo implantation	Decreased embryo implantation
	Trophoblast invasion	Increased trophoblast invasion	
	Maintenance	Increased hCG production	Increased in infections that can adversely affect pregnancy
Interleukin-2	Maintenance		Increased miscarriage rates
Interleukin-4	Maintenance	Decreased miscarriage rates	
Interleukin-5	Maintenance	Decreased miscarriage rates	
Interleukin-6	Fertilization	Supports oocyte maturation	Impairs oocyte development Reduced sperm motility
	Trophoblast invasion	Increased trophoblast invasion and differentiation	
	Maintenance	Increased hCG production Decreased miscarriage rates	Increased in infections that can adversely affect pregnancy Increased in preeclampsia
Interleukin-10	Immune tolerance	Increased tolerance	
	Trophoblast invasion		Decreased trophoblast invasion
	Maintenance	Decreased miscarriage rates	
Interleukin-12	Fertilization	Increased ovum fertilization	Impaired ovum fertilization
	Trophoblast invasion		Decreased trophoblast invasion
Interleukin-17A	Fertilization		Reduced sperm motility
Leukemia inhibitor factor	Implantation	Enables embryo implantation	
	Trophoblast invasion	Increased trophoblast differentiation	
Placental growth factor	Trophoblast invasion	Decreased trophoblast apoptosis and increased angiogenesis	
Toll-like receptor 4	Maintenance		Increased in infections that can adversely affect pregnancy
Transforming growth factor-beta	Implantation	Increased embryo implantation	
	Trophoblast invasion		Increased trophoblast apoptosis Decreased endothelial cell proliferation for spiral artery remodeling
Tumor necrosis factor-alpha	Fertilization		Reduced sperm motility
	Implantation	Increased embryo implantation	Decreased embryo implantation when elevated relative to IL-4
	Trophoblast invasion		Increased trophoblast apoptosis
	Maintenance	Increased hCG production	Increased miscarriage rates Increased in infections that can adversely affect pregnancy Increased in preeclampsia
Tumor necrosis factor-beta	Maintenance		Increased miscarriage rates
Vascular endothelial growth factor	Trophoblast invasion	Decreased trophoblast apoptosis and increased angiogenesis	

Nevertheless, this immune suppression model has been challenged by studies wherein allogeneic embryo trophoblasts do not elicit rejection, and a boost in cytokine production by TGF-B actually prepares the uterus to be tolerant to paternal antigens [6]. One study looking at women who used donor eggs to achieve pregnancies that ultimately resulted in male fetuses found that fetal cells from this completely allogeneic offspring were able to persist in maternal circulation for at least 9 years postpartum, suggesting that some degree of immune tolerance or evasion of immune surveillance occurs in successful pregnancies and does not rely on any genetic similarities between the mother and the fetus [7]. This new "immunotrophic theory" focused attention to the tight equilibrium of immunomodulation at the maternal-fetal interface. This body of research revealed that a balance is required between pro- and anti-inflammatory cytokine pathways. This would occur through suppression of the maternal cell-mediated anti-fetal reactivity of T helper 1 (Th1) type cells involved in cellular immunity that facilitated allograft rejection, and conversely a protective release of anti-inflammatory cytokines from T helper 2 (Th2) type cells [8]. Abnormally elevated levels of Th1-type cytokines have been associated with spontaneous miscarriage in both mice and human studies, whereas successful pregnancy has been proposed to follow from high Th2 activity, leading to the belief that successful pregnancies exhibit Th2-bias [9]. For example, the Th2 cytokine Interleukin-10 (IL-10) is thought to create a tolerant immune environment during the duration of the pregnancy, whereas progesterone-mediated suppression of the Th1 cytokine interferon-gamma (IFN-γ) release contributes to maternal immune tolerance. The effect of progesterone can be demonstrated via its antagonist, mifepristone, which induces the release of IFN-γ and the protease granzyme B by natural killer (NK) cells to reduce immune tolerance to the early pregnancy [10].

This "Th1/Th2 paradigm" revised the initial immunosuppression model, though mice studies have challenged the view of Th1 as harmful and Th2 as supportive of continued pregnancy. The uterus in early pregnancy is replete with Th1-type cytokines, and the absence of NK cells, counterintuitively, was associated with reproductive compromise. Recent evidence has propounded this view of a more complicated balance between the pro- and anti-inflammatory signaling to permit pregnancy progression.

Fertilization

Cytokines, via the follicular fluid microenvironment, have been observed to play a role in pregnancy as early as fertilization. Levels of interleukin-6 (IL-6) and interleukin-12 (IL-12) are believed to play important roles in fertilization, though there is debate as to their function. Interleukin-6 may support oocyte maturation and has been associated with high rates of clinical pregnancy, though it has conversely been implicated in impaired oocyte development and lower pregnancy rates [11]. The same is true for IL-12, a pro-inflammatory cytokine for which high levels have been associated with increased rates of ovum fertilization [12] but also failed fertilization and low rates of clinical pregnancy [13]. It is unclear how levels of these cytokines affect early pregnancy outcomes, as well as their exact mechanisms of action.

Cytokines can also influence fertilization by impacting sperm function. Animal studies from as early as 1979 demonstrated the abortive effect of inducing immunization with paternal cells [14, 15]. For example, IL-6 and tumor necrosis factor-alpha (TNF-A) have been shown to reduce motility of sperm, a finding in common with interferon-gamma (IFN-Y), interleukin-17A (IL-17A), and interleukin-1B (IL-1B) for which exposed sperm have reduced motility and viability [16]. While these findings suggest a potential therapeutic pathway to treat male factor infertility or enhance intrauterine insemination (IUI) pregnancy rates, their clinical utility has not been clearly established.

Implantation

Cytokines have been studied in endometrial tissue in order to elucidate whether they alter tissue receptivity for implantation. The human endometrium typically achieves maximal receptivity 7–10 days after ovulation [17] as a result of a series of complex interactions between various growth factors, transcription factors, hormones, and cytokines [4]. The implantation period requires an initial acute pro-inflammatory phase followed by a profound anti-inflammatory phase, and this pathway enables the endometrium to respond to the embryo [18]. Early rejection involves alterations in cytokines in decidual cells like leukemia inhibitor factor (LIF), interleukin 6 (IL-6), vascular endothelial growth factor A (VEGF-A), and stromal cell-derived factor 1. Uterine natural killer (uNK) cells then secrete cytokines (predominantly GM-CSF, LIF, IL-1, IL-6, and IL-11) that form networks that engage in creating tolerance at the maternal-fetal interface through a local injury inducing a mild inflammatory-like response. Counterintuitively, it is postulated that this inflammatory microenvironment supports uterine receptivity for blastocyst attachment [19].

Leukemia inhibitory factor (LIF), a member of the IL-6 family of cytokines, is produced by the human fetal membranes and expressed in amnion and chorion cells in response to infectious stimuli. It is thought to play a key role in mediating interactions between leukocytes in maternal decidual tissue and embryonic cytotrophoblasts to induce conditions necessary for embryo implantation [4]. Several mouse studies have examined the role of LIF in reproduction; inactivation of the homozygous LIF gene inhibits

murine fertility [20, 21], and exposure to recombinant LIF corrected implantation failure in LIF-deficient mice [6]. Such animal studies established LIF as an initial cytokine necessary for embryo implantation. Although human studies show LIF production is significantly higher in fertile women compared to infertile women at the time of expected implantation [20], screening for LIF mutations in unexplained infertility or recurrent implantation failure has not been found to have clinical utility [4]. A clinical trial of recombinant LIF administration for female infertility showed no significant improvement in the treatment group [21], though the results must be interpreted cautiously as study participants were not selected based on demonstrated LIF deficiency [6]. Integration of cytokines including LIF into human embryo culture media has been observed to have improved ongoing pregnancy rates, though the effects on live birth rates or on newborn outcomes are unclear [22].

Interleukin-1 (IL-1) is another proinflammatory cytokine involved in embryo implantation. Produced by trophoblastic cells and decidual cells at the maternal-fetal interface, IL-1's receptors can be found in endometrial epithelial cells and trophoblastic cells [4]. In vitro studies of human cells indicate that IL-1 regulates matrix-degrading metalloproteinases (MMP), which are requisite for cytotrophoblast invasion [23]. Mice studies, however, show equivocal results regarding its effect on pregnancy: treatment with an IL-1 receptor antagonist during early pregnancy led to decreased rates of embryo implantation [24], whereas mice lacking type 1 IL-1 receptors had no significant reproductive issues apart from slightly decreased litter size [25]. A similar discrepancy is observed among patients undergoing IVF or ICSI; while IL-1 concentrations in endometrial secretions are not significantly associated with clinical pregnancy [26••], serum IL-1 levels can be predictive of IVF cycle outcomes [27].

Transforming growth factor-beta (TGF-B) has also been studied in implantation. This family of growth factors is thought to contribute to endometrial implantation by increasing oncofetal fibronectin levels in the extracellular matrix (ECM) and promoting trophoblast adhesion to the ECM [4, 28]. TNF-alpha (TNF-a) regulates MMP activity during embryo implantation to exert control over trophoblast invasion in the receptive endometrium [29]. As MMPs permit degradation of the uterine epithelium and invasion of the uterine stroma [30•], careful regulation of MMP activity by cytokines and other signaling molecules may facilitate successful implantation and development of viable intrauterine pregnancies.

These cytokines have been extensively studied in recurrent implantation failure (RIF). Women with RIF have been found to have higher ratio of IFN-y:IL-4 and TNF-a:IL-4, as well as high levels of IL-1B in their uterine fluid as well as increased expression of pro-inflammatory cytokines compared to fertile controls [3]. Based on these observations, it is suggested that patients with RIF may benefit from immune-suppressive medications like tacrolimus, which suppresses production of T cell-derived cytokines. Treatment appears to decrease cytokine levels but without clear benefit to livebirth rates [31, 32].

Trophoblast Invasion

During early pregnancy, trophoblasts—the cells of the developing placenta—must invade the maternal uterine tissue to establish a proper connection and ensure nutrient exchange. The invasion of the trophoblasts into the decidualized endometrial stroma is controlled tightly spatially and temporally [19]. Virtually all known cytokines are expressed in the chorion and amnion during the process of normal gestation, serving as key regulators of invasion, trophoblast behavior, and tissue remodeling [33]. Given experimental limitations, the role of individual molecules has been discerned almost exclusively from in vitro assays [33].

Both the placenta itself and decidualized endometrial cells produce cytokines and are themselves targets of their signaling [2, 34]. Trophoblastic invasion requires stepwise balancing actions of pro-inflammatory and anti-inflammatory cytokines. Pro-inflammatory factors including IL-1β and IL-6 regulate integrin expression and protease pathways to promote the invasion of the trophoblasts into the stroma [19]. IL-6 and LIF facilitate trophoblast cell growth, and these trophoblasts undergo differentiation to a more invasive type under the influence of IL-1, LIF, and activin. This process gives rise to trophoblasts that can penetrate the endometrium and establish placental structures [34, 35].

This process is counterbalanced by anti-invasive cytokines. Placental-TGF-beta, TNF-alpha, and IFN-gamma induce trophoblast apoptosis [34]. TGF-beta exerts inhibitory functions in the placenta by limiting trophoblast invasion, proliferation, and differentiation [34]. IL-10 and IL-12 antagonize and mobilize inhibitors of MMPs so as to neutralize invasion-promoting factors [19]. Other cytokines involved include vascular endothelial growth factor (VEGF) and placental growth factor (PlGF), which modulate extravillous trophoblast proliferation and exhibit anti-apoptotic properties [34, 36].

Cytokines also play a key role in angiogenesis and spiral artery remodeling. VEGF and PIGF are crucial to facilitating angiogenesis for the developing placenta [34]. These molecules also promote endothelial cell proliferation, particularly of decidual microvascular endothelial cells [33]. TGF-beta and activin A inhibit VEGF-stimulated proliferation of endothelial cells as well as their basal proliferation [33]. This network of cytokine promotion and inhibition coordinates the proliferation of vascular endothelial cells that brings about the remodeling of the spiral arteries [33].

Maintenance of Pregnancy

After implantation has occurred and maternal-fetal immune tolerance has been established, cytokines continue to play an important role in maintenance of the pregnancy until the time of delivery. From promoting hCG production to regulating the maternal-fetal interface at the cellular level, cytokines have significant influence over pregnancy outcomes.

Several cytokines are involved in inducing hCG production, which helps with maintenance of the corpus luteum and subsequent progesterone release in early pregnancy. For example, IL-1 is produced by placental macrophages and stimulates hCG production from trophoblast cells in the first trimester [37]. Similarly, IL-6 has been implicated in the production of hCG through mechanisms mediated by TNF-A [38], suggesting that a complex interplay of cytokine-mediated events is required for the support of early gestation. The clinical utility of identifying cytokines involved in hCG production is illustrated by studies of hyperemesis gravidarum (HG), a disorder classically associated with significant elevations in hCG levels. Patients with HG have been shown to have elevated levels of TNF-A [39], which could be contributing to elevated hCG levels and may represent an opportunity for therapeutic intervention with relative immunosuppression in the future.

Cytokine levels have also been shown to play a role in several obstetric complications that can affect the duration and safety of pregnancy. Recurrent miscarriages (though without controlling for aneuploidy) have been found to be associated with elevated levels of IL-2, TNF-A, tumor necrosis factor-beta (TNF-B), interferon gamma (IFN-Y), and lower levels of IL-4, IL-5, IL-6, and IL-10 compared to women with a prior history of normal pregnancies [1]. Spontaneous preterm labor, preterm premature rupture of membranes, and preterm birth are often associated with underlying infections, which can lead to the release of pro-inflammatory cytokines such as toll-like receptor 4 (TLR4), TNF-A, IL-1, and IL-6 [40]. Preeclampsia is also associated with higher levels of pro-inflammatory cytokines, including TNF-A, IL-6, and C-reactive protein (CRP) [41]. These studies underscore both the important role of cytokines throughout the pregnancy spectrum, but also the changing cytokine milieu in each phase of pregnancy.

Conclusion

Alterations in cytokine levels have consistently been demonstrated in failed pregnancy and recurrent pregnancy loss. While disruptions in cytokine balance have been associated with poor outcomes, recent research has challenged the paradigm that cytokine levels alone are determinative. Indeed, reproductive failure cannot easily be explained by simple imbalances of the Th1- and Th2-associated cytokines. What has emerged instead is a revised model where each stage of early pregnancy requires timely and differential activation or suppression of these cytokines (Table 1). Ongoing research focuses on the distinct pathways of dysregulation that predict pregnancy failure as well as potential therapies that can target these pathways to reduce recurrent pregnancy loss and increase IVF/ICSI success.

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Compliance with Ethical Standards

Conflict of Interest The authors declare no conflict interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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