

The role of cytokines in immune regulation of female reproductive physiology*

O papel das citocinas na imunorregulação da fisiologia reprodutiva da fêmea

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Abstract

Cytokines act as protein mediators of the immune system and exert pleiotropic effects on the source cells and/or on target cells. Cytokines are formed in a cascade, bind to specific receptors, and influence the activity, differentiation, proliferation, and survival of immune cells of both T helper 1 (Th1) type (which has proinflammatory properties) and Th2 type (with an anti-inflammatory function). The female reproductive system is regulated by the immune system via cytokines at various physiological stages: during the ovarian cycle, maternal recognition, embryo implantation, gestation, and birth, participating in homeostasis and protection from pathogens. These processes interact under the hormonal influence of the hypothalamic–pituitary–gonadal axis. This review is aimed at addressing the involvement of some cytokines in female reproductive physiology, highlighting the maternal recognition of the embryo and implantation as immunologically important steps for fetal survival. The scientific knowledge on the role of cytokines in female reproduction processes, such as the Th1/Th2 balance and immune tolerance should advance the research in various fields of assisted reproduction in humans and animals, such as artificial insemination, embryo transfer, and *in vitro* fertilization. The same is true for the development of contraceptive methods and understanding of pathological processes such as uterine infections and autoimmune diseases.

Keywords: implantation, immune tolerance, inflammatory cascade, maternal recognition.

Resumo

Citocinas funcionam como mediadores proteicos do sistema imunológico, que exercem efeitos pleiotrópicos nas próprias células e/ou em células-alvo; formadas em cascata e ligando-se a receptores específicos, influenciam a atividade, diferenciação, proliferação e sobrevivência da célula imunológica, tanto tipo Th1 (*Helper1*), de ação pró-inflamatória, quanto tipo Th2 (*Helper2*), de ação anti-inflamatória. O sistema reprodutivo das fêmeas é imunorregulado pelas citocinas em seus diversos estágios fisiológicos: ciclos ovarianos, reconhecimento materno e implantação do embrião, avanço da gestação e parto, auxiliando na homeostase e prevenção contra patógenos, interagindo sob influência hormonal do eixo hipotalâmico-hipofisário-gonadal. Esta revisão tem como objetivo abordar o envolvimento de algumas citocinas na fisiologia reprodutiva feminina, destacando o reconhecimento materno do embrião e a implantação como etapas imunologicamente importantes à sobrevivência fetal. É possível constatar que o conhecimento científico sobre as citocinas na reprodução de fêmeas, como o balanço Th1/Th2 e a imunotolerância, permite um sólido avanço de pesquisas nas áreas de Reprodução Assistida em humanos e animais, a exemplo da inseminação artificial, transferência de embriões e fertilização *in vitro*, bem como no desenvolvimento de métodos contraceptivos e compreensão de processos patológicos, como infecções uterinas e doenças auto-imunes.

Palavras-chave: cascata inflamatória, implantação, imunotolerância, reconhecimento materno

Introduction

Reproductive physiology of mammalian females is influenced by hypothalamic–pituitary–gonadal axis via feedback system of peptides and steroidal hormones. This physiological interaction harmonically and sequentially enables follicular development, oocyte maturation, mating acceptance, ovulation, fertilization,

corpus luteum formation, gestation, birth, and puerperium (Reynolds et al., 1994; Findlay et al., 2009). On the other hand, the immune system has a decisive role during various stages of reproduction. The immune system provides protection from external pathogens and modulates the fetal rejection process, since the fetus may be considered an allograft due to the paternal genetic material (Shechter et al., 2013).

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In this context, a group of cytokines is receiving research attention because they perform a strategic function in the regulation of reproductive events. Cytokines are heterogeneous, water-soluble, extracellular, animal-origin polypeptides or glycoproteins and serve as mediators in the immune system. Cytokines are pleiotropic (acting on several types of cells) and have a molecular weight ranging between 5,000 and 100,000 Da. They can be produced by cells of the immune system via the mitogen-activated protein kinase pathways and exert specific effects on the source cells or on target cells (Rice and Chard, 1998).

Cytokines production occurs in cascades fashion, i.e., one cytokine causes its target cells to produce more cytokines; these substances bind to specific receptors, thereby activating intracellular messengers that regulate gene transcription. Cytokines have several biological effects: they influence activity, differentiation, proliferation, and survival of immune cells and regulate the production and activity of other cytokines, which may either increase or reduce the inflammatory response (Oliveira et al., 2011). The T helper 1 (Th1) cytokines are thought to be proinflammatory, and Th2 cytokines are considered to be anti-inflammatory. In the reproductive tract, they are involved in communication among cells; cytokines are not only secreted by the embryo but also by peripheral blood lymphocytes, macrophages, endometrial and uterine tube cells (Schäfer-Somi, 2003).

The objective of this review is to describe the role of some cytokines in female reproduction linking them to some reproductive phases (from the ovarian cycle to pregnancy and birth) in order to emphasize the importance of the immunological stages in embryo maternal recognition and embryo implantation, given the need for the maternal organism to undergo immunoendocrine changes in Th1/Th2 balance.

Cytokines in female reproductive physiology

Cytokines participate in various female reproductive phases and are under strong influence of endocrine regulation by hormones of the hypothalamic–pituitary–gonadal axis as well as by hormones secreted by the endometrium. This immunological and endocrine relation ensures—in the reproductive tract—the development of both inflammatory cascades that cause tissue remodeling and immune regulatory barriers that can prevent fetal rejection [because a fetus can be considered an “allograft” (Mitchell et al., 2002; Shechter et al., 2013)]. Some cytokine–hormone interactions are evident at distinct physiological stages, as explained below.

Ovarian growth, luteolysis and endometrial dynamic

The dynamics of ovarian follicular growth until ovulation is also directly influenced by a blood supply due to vasodilatory effect of nitric oxide (NO), thereby allowing the supply of these inflammatory cells and activation of the cytokine cascade. NO stimulates synthesis of PGE and PGF₂α, which causes

inflammation of the preovulatory follicle and subsequent rupture. A study involving Doppler ultrasonography in sheep during the ovulation period showed a progressive increase in the blood flow area at the follicular base, from follicle deviation to ovulation, which was also influenced by a progressive increase in plasmatic concentrations of NO and 17β estradiol up to its peak at ovulation (El Sherry et al., 2013).

The estrous cycle of domestic ruminants is directly uterus dependent since endometrium produces prostaglandins, such as PGE₂ and PGF₂α, which play a strategic role in reproductive cyclicity. PGE₂ has luteotrophic and luteoprotective activities, whereas PGF₂α is luteolytic. Thus, the PGE₂:PGF₂α ratio is more important than the absolute concentrations of each prostaglandin, and modulation of this ratio is performed by cytokines (Tatcher et al., 1997; Weems et al., 2006).

In cattle, tumor necrosis factor α (TNF-α) serves as a trigger of prostaglandin synthesis and release. Although it stimulates the production of PGF₂α during luteolysis, TNF-α also regulates PGE₂ production in the endometrial stroma, controlling the PGE₂:PGF₂α ratio and thus preventing premature luteolysis (Murakami et al., 2001). Interleukin 1α (IL-1α), produced in endometrium, also affects the proportion of these prostaglandins, stimulating PGE₂ production, especially between days 8 and 12 of the estrous cycle, participating with the process of maintaining the corpus luteum (CL). On the other hand, between days 15 and 17 of the estrous cycle, IL-1α preferentially stimulates PGF₂α synthesis (Tanikawa et al., 2005).

The immune system contribute to the transient nature of the CL (development, maintenance and regression), for example, with regulation of leukocytes in the ovary and secretion of regulatory cytokines. T cells, macrophages, eosinophils, and neutrophils produce and secrete interleukins, prostaglandins, interferon γ (IFN-γ), TNF-α, and angiogenic factors such as vascular endothelial growth factor A (VEGF-A) and fibroblast growth factor 2 (FGF2) (Reynolds et al., 1994; Shirasuma et al., 2012; Galvão et al., 2013). Therefore, during luteolysis, there is a significant increase in the number of these cells in the CL, with luteal cell apoptosis and subsequent phagocytosis of the debris; these events characterize the luteolytic cascade as an immune and inflammatory-like response. Based on this, Shirasuma et al. (2012) suggested that luteolysis is an acute inflammatory-like response, in terms of immune cell infiltration and a drastic change in the vascular diameter and blood supply: PGF₂α stimulates vasoconstriction and increases expression of P-selectin, which is a protein that functions as a cell adhesion molecule for neutrophils and tethers them to endothelial cells of the CL. After this step, vasodilation is initiated under the influence of NO produced by the neutrophils; as blood volume and flow increases, the supply of neutrophils reaching the site also increases, thereby causing greater adhesion of neutrophils to this endothelium, greater production of proinflammatory cytokines (IL-8, TNF-α, and IFN-γ), and recruitment of lymphocytes and macrophages to the site (Figure 1).

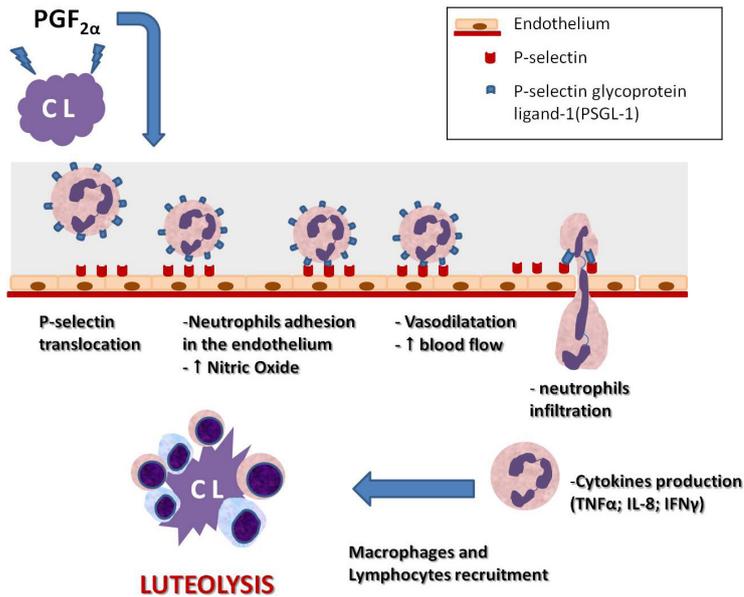


Figure 1: Schematic model of Corpus Luteum (CL) regression from inflammatory response induced by increase of PGF_{2α} secretion

Cytokines and growth factors, when modulated by hormonal variations, directly interfere with female endometrial dynamics (proliferation, differentiation, and degradation). This effect is due to their influence on the cyclicity of leukocyte population in endometrial stroma, both cellular immunity level, represented by macrophages, T cells, and uterine natural killer cells (uNK) as well as humoral immunity level (B cells and mastocytes). In addition, this balance of immunity is seriously compromised by multifactorial autoimmune diseases such as systemic lupus erythematosus, which is mediated by a Th2 inflammatory response and can result in infertility, embryonic loss, or miscarriage in women (Cutolo et al., 1998; Pereira et al., 2005). In the Murinae subfamily, the recruitment, proliferation, and differentiation stages of macrophages in reproductive tissues are influenced by the colony-stimulating factor 1 (CSF-1): mutant mice lacking CSF-1 (*csfm^{op}/csfm^{op}*) show impaired cellular immunity and consequent reduction in reproductive efficiency, which is identified by deficits in the estrous cycle and low ovulation rates (Cohen et al., 1997).

Maternal recognition of the embryo

This reproductive phase is the most intriguing because the placenta and fetus evade rejection by the immune system of the dam. The placenta is believed to be the predominant source of antigens for T cells as well as a direct target of any active immune response. Thus, the preimplantation period involves fetal-maternal interactions that lead to maternal recognition of pregnancy and its maintenance. The fetus synthesizes and secretes a surprising amount of cytokines as well as enzymes, prostaglandins, and hormones.

Paracrine and endocrine signs of pregnancy recognition secreted by the fetus into the maternal system are either antiluteolytic,

aimed at interrupting intraovarian/endometrial PGF_{2α} production, or luteotrophic, exerting a direct effect on the CL. One example is human chorionic gonadotropin (hCG) in primates; in swine, estrogen secretion by the fetus promotes this maternal recognition, so that in the presence of estrogen, the direction of PGF_{2α} secretion is exocrine to the uterine lumen, where it is sequestered and metabolized to prevent luteolysis (Bazer et al., 1998; Spencer et al., 2004).

The immune regulation of maternal recognition in humans is initiated by a fertilized ovum, which promotes intrauterine predominance of Th2 cells, whereas a greater presence of Th1 cytokines would result in interruption of embryonic development and placental growth. Therefore, to maintain the pregnancy, some mechanisms contribute to the Th1/Th2 balance, such as the *in vitro* blockade of the Th1 response to human trophoblast via secretion of progesterone and IL-10 by decidual and embryonic leukocytes during the preimplantation phase (Schäfer-Somi, 2003). These cells inhibit the proliferation of and secretion by Th1 lymphocytes as well as IL-4 production by cytotrophoblasts, which promote Th2 lymphocyte differentiation (Schäfer-Somi, 2003).

As for ruminants, it became clear in the late 1980s that the main indication of maternal recognition of pregnancy is a type 1 interferon, interferon tau (IFN-τ), which has a structure homologous to that already known IFN-α and -β. However, IFN-τ is restricted to embryonic trophectoderm (Roberts et al., 2008). The action mechanisms of IFN-τ in the endometrium are based on regulation and stabilization of progesterone receptors and direct inhibition of the receptors of estrogen and oxytocin and thus decrease the release of oxytocin-induced PGF_{2α}; similarly, IFN-τ induces the endometrium to inhibit the production of enzymes necessary for PGF_{2α} synthesis (Schäfer-Somi, 2003; Spencer et al., 2015), as shown in Figure 2A. Spencer et al. (2004) demonstrated the paracrine action of ovine IFN-τ in the luminal and glandular epithelium of the endometrium, where IFN-τ suppresses transcription of the genes of estrogen and oxytocin receptors. The increase in the expression of these genes—that is detected at this site during days 11–17 post-estrus in sheep—does not occur during pregnancy, nor does it happen in cyclic sheep if they are subjected to IFN-τ infusion. Majewska et al. (2012) reported that cortisol can serve as an IFN-τ modulator during the antiluteolytic process in cattle, in particular, by upregulating PGE₂ and luteoprotective action, thereby raising the PGE₂:PGF_{2α} ratio in the endometrium. The strong secretion of bovine IFN-τ (bIFN-τ) occurs prior to luteolysis in the estrous cycle of the animals and seems to depend on uterine environment for this amplification and sustenance. As reported by Thatcher et al. (1997), bovine embryos that are produced by *in vitro* fertilization express and secrete bIFN-τ up to blastocyst stage, but *in vitro* secretion is limited in extended culture. In contrast, with morulae or hatched blastocysts (after *in vitro* fertilization) that were transferred to the uterus of synchronized cows and recovered four days later, greater quantities of bIFN-τ in extended culture were secreted.

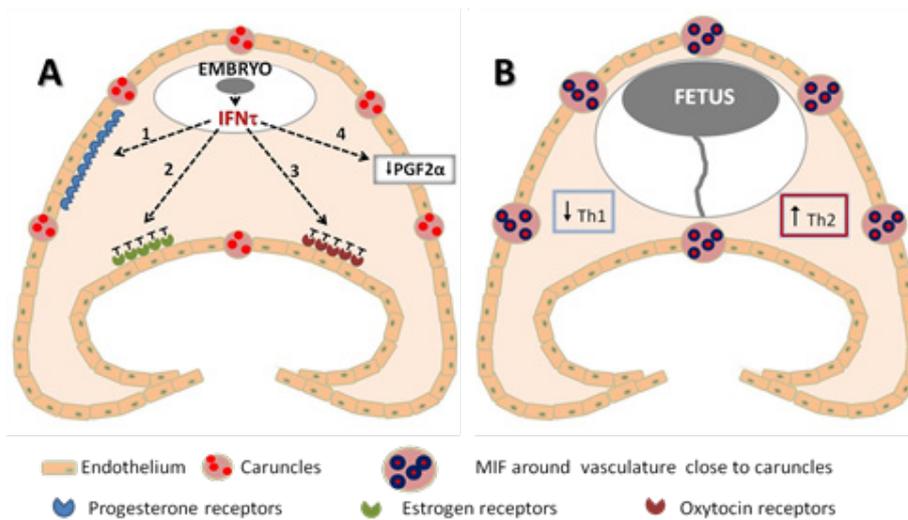


Figure 2: Involvement of cytokines in two distinct reproductive stages in ruminants. During maternal recognition (A), the interferon- tau (IFN τ) produced by the embryo acts on the endometrium promoting the transcription of genes for progesterone receptors (1), direct inhibition of estrogen (2) and oxytocin (3) receptors and production of inhibitors of enzymes necessary for the synthesis of PGF2 α (4). With the advancement of pregnancy (B), there is a progressive increase of anti-inflammatory cytokines Th2 in contrast to a decrease in proinflammatory cytokines Th1; around the vasculature close to caruncles, occurs accumulation of the macrophage migration inhibitory factor (MIF), also as a measure of maternal-fetal immunotolerance.

Implantation

This complex process in the blastocyst development involves affixing, adhesion, and invasion by the trophoblast via proteolytic action on the maternal endometrium that in response to this interaction elicits cellular reactions that are similar to those resulting from invasion by tumor cells; these reactions have characteristics of an inflammatory response. The endometrium represents a critical tissue for normal fertility and reproductive success in all mammals, being a unique tissue that exhibits remarkable plasticity, with regeneration, reparation and remodeling occurring during estrous cycle, following pregnancy failures, and after parturition (Sandra, 2016). Therefore, at this implantation site, cytokines are crucial for successful establishment of pregnancy (Rice and Chard, 1998).

The implantation process in domestic farm animals (swine, cattle, goats, sheep, and horses) involves a prereceptive uterus phase, i.e., a long pre-implantation period in contrast to rodents and primates, where the embryo almost immediately attaches itself to the uterine epithelium after entering the uterus (Bowen and Burghant, 2000). Erlebacher (2013) reported that in humans and mice, the contact between maternal and placental tissues occurs via two distinct surfaces: i) the outer surface of the placenta is established inside the maternal decidua—a specialized stromal layer of tissue on the endometrium—for placental development. The juxtaposition of the placenta and decidua creates what is known as the maternal-fetal interface, where placental trophoblasts and uterine leukocytes make contact with each other, this forming a site for a direct immune attack. ii) The maternal blood irrigates the trophoblasts residing in the body of the placenta (placental villi in humans and labyrinths in rats), thereby allowing placental antigens and other materials to directly get into the maternal blood; this event elicits an immune response. Immunity-related genes regulate the implantation period through

many functions, such as chemotaxis, inhibition of the cytolytic activity of the NK cells, inhibition of T-cell and pathogen growth, with the ultimate purpose of adapting the maternal system for the accommodation of the embryo, which is immunologically foreign (Lobo et al., 2004).

Cross et al. (1994) described the “window for implantation”: during the preimplantation, the fetus can develop without maternal intervention, but during the implantation phase, an active cross-talk between maternal cells and the blastocyst is necessary. This process requires synchrony in the development of the uterus and of the blastocyst: a fact that probably explains the high failure rate of embryo transfer in humans and animals. Energy metabolism and amino acid metabolism likely played an important role in the formation of endometrial receptivity; in dairy goats, a total of 810 mRNAs were discovered between pre-receptive and

receptive endometrium, demonstrating the great influence of this metabolism on the window for implantation (Zhang et al., 2017).

The development of the uterus undergoes changes during the preimplantation period that are controlled by steroid hormones: estrogen and progesterone (Schäfer-Somi, 2003). The estrogens trigger various events to facilitate embryo implantation, acting on the uterine epithelium and inducing the secretion of cytokines, including the leukemia inhibitory factor (LIF) and the transforming growth factor α (TGF- α) (Schäfer-Somi, 2003).

Rahman et al. (2004) studied cytokine expression in the endometrium of nonpregnant and pregnant sheep at 17–19 days post-breeding (dpb), 26–27 dpb, and 34–36 dpb. The results showed that the proinflammatory cytokines IL-1 β , IFN- γ , and TNF- α were present in nonpregnant sheep and in all implantation phases. In contrast, IL-2 and IL-8 were strongly upregulated only from 26–27 dpb onwards—when anti-inflammatory cytokines LIF, IL-6, and IL-10 were expressed at lower levels in nonpregnant sheep—but with a visible increase at 26–27 dpb, while IL-4 was expressed starting from 17–19 dpb. A broad and dynamic change involving the Th1/Th2 ratio in sheep was observed, which is conducive to the prevalence of anti-inflammatory cytokines.

This immunoregulated environment allows the concept modulates proteome profiles in caruncular endometrium during early pregnancy. For example, Arianmanesh et al. (2016) reported evidence that the sheep conceptus-derived factors exert local effects within the endometrium to control of L-Homocysteine (Hcy) production and counteract peri-implantation oxidative stress, which is a risk factor for the maintenance of pregnancy.

Ptak et al. (2006) demonstrated the importance of using LIF (human recombinant) in methods for fertilization, maturation, and *in vitro* culture of embryos; those authors reported beneficial effects on the blastocyst quality, albeit stressing the need for influence by steroid hormones when these hormones are present during *in vivo* regulation.

Pregnancy, birth, and puerperium

Successful pregnancy depends of an efficient vascular system in uteroplacental unit; this unit harmoniously modulates interactions among maternal vascular endothelium, local immune competent cells and antigenic determinants on the trophoblast surface. Thus, adhesion, activation, and cell migration processes are regulated, through changes in the cytokine cascade (Pereira et al., 2005).

The best-studied immune modulator of the maternal-fetal interface is progesterone, whose role in fetal survival is evident. The presence of progesterone has been reported to have such effects as blockade of the stimulation of lymphocyte mitogen production, modulation of antibody production, downregulation of monocyte metabolism, a reduction in the production of proinflammatory cytokines by macrophages in response to bacterial infections, and facilitation of IL-10 production (Peltier, 2003).

The Th1/Th2 ratio during pregnancy may point to an answer to the question why a fetus is not rejected by the maternal immune system despite the contact of paternal antigens with maternal cells. During existence of the maternal-fetal interface, the Th2 cytokines seem to be responsible for successful maintenance of pregnancy (Figure 2B): they are secreted not only by the competent immune cells but also by decidual and placental cells. This finding was proved by an experiment where IL-4, IL-10, and IL-3 were detected at increased levels during normal gestation in humans and animals; in addition, injection of Th2 cytokines prevents abortion in mice (Zenclussen et al., 2002).

In sheep, the surface implantation and placentation begin on days 15–16 of the gestation, but they are not complete until days 50–60. During this period, the uterus grows and remodels itself to accommodate the fetus's rapid development and its growth during the final trimester of gestation. Due to the development of placentome in the caruncular areas of the endometrium and due to changes in uterine vascularization, the intercaruncular endometrial glands grow substantially in length and width. These changes are crucial for the synthesis, secretion, and transport of enzymes, hormones, growth factors, and cytokines (Spencer et al., 2004). During the third trimester of pregnancy, the physiological increase in concentrations of cortisol, progesterone, estradiol, and testosterone interferes with polarization of Th2 cytokines; at this gestation stage, less IFN- γ and IL-2 and more IL-4 and IL-10 are released, and one possible hormonal influence involves suppression of IL-12 and TNF (Th1 response) along with an increase in the Th2 response (Cutolo et al., 1998). Excessive production of proinflammatory cytokines, such as IL-1 β , TNF, and IFN- γ , at the maternal-fetal interface is detrimental to pregnancy and may even lead to miscarriage. IL-10 is an important cytokine because it suppresses the production of proinflammatory cytokines in other cells, although other immune modulators may also contribute to the survival of the fetal graft (Marzi et al., 1996; Peltier, 2003).

The macrophage migration inhibitory factor (MIF) is known to be a proinflammatory cytokine produced by macrophages, lymphocytes, and fibroblasts. It is involved in the establishment of maternal-fetal immune tolerance during placentation, according to the studies in hemochorial human and rodent and epitheliochorial porcine placentas. Paulesu et al. (2012) studied

the immune reactivity of MIF in cattle (epitheliochorial placenta); with nonpregnant animals as controls, immunohistochemical analysis during advancing gestation revealed growing coloration (greater presence of the cytokine) in the caruncular epithelium and in the vascularized area of this epithelium (Figure 2B). This finding suggests that MIF performs a regulatory function that is mainly active in the placental barrier, contributing to strong blood flow during new vascular development (in the placentome), in addition to reducing the cytotoxic action of endometrial NK cells and suppressing an immune reaction against fetal membranes during placentation.

Regarding birth, the immunity in the fetal-placental unit is withdrawn: the blockade of progesterone receptors can allow proinflammatory cascades to occur, which are stimulated by the elevated estradiol level during this period. These proinflammatory cytokines (IL-1 β , IL-6, IL-8, and TNF- α) induce maturation and dilatation in the cervical area in a number of ways, to raising the production of cyclooxygenase 2 and PGE2, promoting neutrophils and macrophage migration; the upregulation of PGE2 is related to vasodilation—as is the case with NO—and thus facilitates the flow of leukocytes to the site (Peltier, 2003).

Progesterone suppresses immune defenses and predisposes postpartum females to nonspecific infections by way of suppressing uterine synthesis of PGF2 α , eicosanoids, and leukotrienes. These effects appear to be a major factor at the beginning of uterine infections because eicosanoids can enhance immune defenses in the uterus. PGF2 α stimulates production of proinflammatory cytokines, in addition to increasing uterine production of leukotriene B4, which stimulates phagocytic activity of neutrophils; the latter is the typical first response to bacteria that reach the uterus. For this reason, the postpartum period is a crucial stage (mainly after the formation of the first corpus luteum), and consequent progesterone production downregulates IL-8, IL-6, IL-12, and IFN- γ (Lewis, 2004).

Conclusions

Because of the scientific advances over the last decades, it has been possible to recognize and understand the importance of the immune system for female reproductive physiology, in particular, in terms of the complexity of cytokines: their various types, origin, expression of their specific receptors, and immune modulatory functions. The knowledge that was acquired about the Th1/Th2 balance—and immune tolerance that is necessary for maintenance of pregnancy as well as comparative analysis of cytokines among various species—should facilitate the research in the area of reproductive biology. Accordingly, greater progress in the use of reproductive methods in humans and animals may be achieved, for example, in the use of artificial insemination, *in vitro* manipulation and fertilization, and embryo transfer, which require synchrony between the maternal organism and the biological material being introduced (semen/embryo). Similarly, such knowledge is obviously vital both for introduction of new contraceptive methods and for better understanding of and intervention in pathological processes, such as nonspecific uterine infections and even autoimmune diseases such as systemic lupus erythematosus (in the latter disease, it is possible that pregnancy is related to the flare-ups).

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