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Definition Of Endometrial Immune Dysfunction In Recurrentpregnancy Loss

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ABSTRACT

Recurrent miscarriage (RMP) is an unsolved problem in modern gynecology and obstetrics. A growing body of experimental research suggests that endometrial immune dysregulation may be responsible for many, if not all, cases of PNL of unknown etiology. This article discusses the main immunological disorders that occur in PNL.

KEYWORDS

Recurrent pregnancy loss; endometrium; decidua; immunologicdysfunction.

INTRODUCTION

Habitual miscarriage (PNB), according to the European Society for Human Reproduction and Embryology, is: the loss of two or more pregnancies at up to 24 weeks. The Committee of the American Society of Reproductive Medicine defines PNB as two or more unsuccessful clinical pregnancies. In fact, only in about 50% of cases of PNB, certain causes of the pathology can be detected, including: old age of the mother, genetic anomalies, individual maternal auto antibodies, endocrine disorders and uterine anomalies. The

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remaining cases of PNB currently remain unexplained.

It is believed that a significant part of PNB has an immunological etiology.

And, in this case, pregnancy loss occurs due to persistent disruptions in several immune pathways. In this context, the endometrium may play an important role. The endometrial plays a crucial role in the reproduction process. It is the mother's tissue that comes into direct contact with the embryo and ensures its proper implantation and further development. In recent decades, extensive research has been conducted to elucidate the biomolecular mechanisms that make the endometrium susceptible to the embryo, as well as specific cell types and cellular mechanisms involved in endometrial reception. However, our knowledge of these mechanisms is still largely incomplete. Currently available information indicates that the endometrium is a unique tissue in which a number of events occur, called in the aggregate decidualization, in order to dynamically provide the necessary environment for conception and further development of the embryo. Recent data suggest that a key role in endometrial remodeling and mother-embryo tolerance is played by several types of immune system cells that have or acquire specific characteristics when they enter the endometrium along with a growing number of immunoregulatory molecules. Experimental and clinical data also suggest that disorders occurring in the endometrial immune environment can lead to several important reproductive dysfunctions, such as recurrent implantation failure and habitual miscarriage of unclear etiology. This review summarizes the main effects of the immune system on endometrial physiology and current knowledge about the main immunological changes in the endometrium of women with PNB.

1. Physiological function of the endometrium and the immune system

2.1. Endometrial remodeling and decidualization

The endometrium is the maternal tissue that comes into direct contact with the embryo, which is immunologically different from the mother. The embryo is usually considered as a semi-allograft or even as a full allograft in the case of egg donation [1]. The primary function of the endometrium is to create and provide an optimal endocrine / paracrine, immune, and molecular environment that enables attachment, implantation, invasion, and embryo development.

To accomplish this task, the endometrium must undergo a series of unique and striking adaptive changes, collectively called decidualization.This leads to deep morphological and functional reprogramming of endometrial stromal cells, which differentiate into highly specialized cells with secretory capabilities. Among placental mammals, these changes are especially significant in species with an invasive placenta type, in particular in humans, who have the most invasive placentation type. In fact, the degree of decidualization is proportional to the degree of embryo invasiveness [2]. While in most animal species, endometrial transformation occurs in response to the presence of an embryo, in some species, including humans, it occurs long before the embryo appears and, therefore, is initially under exclusive maternal hormonal control. If conception does not occur, then in response to a drop in the level of circulating progesterone, desquamation of the decidualized endometrium occurs and menstruation occurs. This initiates the beginning of a new menstrual cycle. Most recent data on the role of the

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normal endometrium and functional changes occurring in it are derived from histological studies performed in vivo on native human endometrium, as well as in vitro on baboon endometrial cells and cultures of primary human endometrial stroma cells .Despite significant differences between species, the overall picture is that endometrial decidualization is a process involving deep cell reprogramming, tissue remodeling, changes in gene expression and post-translational regulation, as well as changes in cellular signaling pathways. There are also significant changes in the modulation of immune cell activity at the local level. These events involve a large number of molecular mediators and effectors. A detailed description of all changes and intermediaries involved in decidualization is beyond the scope of this article. This article is devoted to assessing the significance of endometrial changes, in particular decasualization, that occur under the influence of the human immune system. Decidualization can be considered evolutionarily as having two non-mutually exclusive functions. On the one hand, it can be considered as a biological solution to the conflict between mother and fetus, in which the embryo's invasiveness, aimed at maximizing the expansion of fetal genes (partially different from maternal ones), is contrasted with the need of maternal genes to ensure their own expansion in present and future pregnancies. On the other hand, it can be considered as an adaptive response to the maternal need to control its corresponding contribution to pregnancy, during gestation for a long period of time. This concept is supported by robust evidence indicating that the decidualized endometrium acts as a biosensor of embryo quality. In this regard, implantation is characterized by cooperation between the embryo and the decidualized endometrium and that loss of endometrial plasticity can lead to idiopathic PNB. Many key events that occur in the endometrium during implantation are realized by the corresponding contribution of immune cells and are mediated by many immunoregulatory molecules. Emerging evidence suggests that abnormalities in normal immune function may occur in these tissues in women with different etiologies of PNB. In recent years, a large amount of experimental work has been carried out to study specific populations of immune cells in the endometrium during various phases of the menstrual cycle, during implantation and in the early stages of pregnancy; their specific role in the early stages of pregnancy together with the expressed regulatory molecules is characterized. In addition, a large number of mechanisms are proposed to explain the development of maternal tolerance to immunologically different concepts. The emerging general picture strongly suggests that in normal pregnancy, the maternal immune system undergoes significant modulation in at least many (if not all) key components, in order to develop tolerance to foreign paternal antigens of the fetus and an immunologically favorable environment for the fetus while maintaining full adaptive capacity to other foreign antigens. Pregnancy-related changes in immune cells and the system occurring in the endometrium and decidua can only be partially determined. However, with regard to successful implantation, the most important changes related to endometrial cells, immune system cells (macrophages, natural killer cells of the uterus, dendritic cells (DC), T cells (especially cytolytic T cells (CTL)) are already well understood.

2.2. Immune dysregulation of the endometrium and the decidual membrane of prnb

Data indicating the fundamental role of proper immunological interaction between the mother and the embryo during the physiological development of pregnancy have

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prompted a large number of studies aimed at studying the effect of dysregulations in the immune relations of the mother and fetus in PNB. This is especially true for the so-called "unexplained" PNB , which accounts for about 52% of cases of PNB. Many of the abnormalities found in this context occur within the endometrium and decidual tissue, which are the primary interface between mother and fetus. In this section, for reasons of clarity, the relevant findings will be divided according to the specific types of cells involved, and then by their own network of immunoregulatory molecules.

3. Endometrial cells in PNB have a specific effect on the regulation of local immune function.

It has been suggested that there are evolutionarily adapted control points during early pregnancy that are designed to terminate pregnancy if the fetus or maternal endometrium is compromised [3]. For example, in the case of an insufficiently developed decidualized endometrium. Several studies have shown that the transformation of stromal fibroblasts into the decidual phenotype is impaired in patients with PNB. The importance of proper decidualization of endometrial stromal cells during implantation and maintenance of early pregnancy has been elucidated by a series of observations supporting the concept that the endometrium is a fine biosensor of the quality of the implanted embryo. In particular, studies conducted on stromal cells of the human endometrium have shown that these cells, differentiating into decidual cells, become sensitive to embryonic signals, to which they respond differently, depending on the quality of the embryo. In normal women, low-quality embryos inhibit the secretion of factors that play a key role in implantation; conversely, developing healthy embryos produce signals that promote implantation. These studies provide experimental evidence that the endometrium of healthy fertile women is selective with respect to the embryo and that low-quality embryos are subject to early rejection. Conversely, the endometrium of a woman with PNB is less sensitive and allows the implantation of low-quality embryos that will be rejected later in pregnancy. Although the specific mechanisms underlying these disorders are still unclear, it is likely that the disordered decidual response observed in women with PNB involves the production of mediators and immune system cells.Since this response is observed in endometrial stroma insufficiency, the cells do not begin to transition from an initially pro-inflammatory phenotype to an anti-inflammatory one during recidualization, as is usually the case in normal pregnancy.

3.2. Immune cells in the endometrium in PNB.

3.2.1. Macrophages

Macrophages are found in small numbers in the endometrium of non-pregnant women, although their number increases significantly during the luteal phase of the cycle. Their number increases dramatically with the onset of pregnancy, reaching 20-25% of all white blood cells in the decidual membrane. There is evidence that macrophages in the decidual envelope differentiate towards the immunoregulatory type M2, since they express several M2 markers [13]. It has been suggested that a proinflammatory subpopulation of macrophages is present, although to a much lesser extent, in the early decidual envelope. In early pregnancy, macrophages are localized mainly near invasive trophoblast cells and spiral arteries and are believed to play several important roles and functions in early pregnancy: enhancing blastocyst implantation and trophoblast invasion, remodeling spiral

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arteries, removing apoptotic cells and cellular debris, and protecting the fetus from foreign pathogens [5,6,7,8,9,10,13,14,15]. It has been shown that remodeling of the decidual spiral artery begins prior to cellular interaction with cytotrophoblasts[16] and that matrix remodeling in spiral arteries is initiated by infiltration of leukocytes, including macrophages, while extravascular trophoblasts (EVT) are involved at later stages [17]. Four discrete stages of vascular remodeling were described in accordance with the degree of destruction of smooth muscle cells in human decidual vessels [18]. Vascular infiltration by macrophages is more pronounced at intermediate stages II and III [18].

3.2.2. Dendritic cells of the uterus

Dendritic cells perform a dual role - they can differentiate into powerful antigen-presenting cells that can activate effector T cells, or, in the immature state, they can increase immune tolerance by inducing Treg formation [19]. In the decidual envelope, dcs are believed to play an important role in the recognition of paternal antigens by the mother both before and during implantation. In particular, seminal fluid has the ability to attract DC (as well as macrophages) to the decidual membrane; dcs, in turn, can capture and represent seminal soluble T cells of the major histocompatibility complex (MHC) in regional draining lymph nodes and induce the growth of the Treg population [4,20,21]. dcs in a specific cytokine environment are characterized by the predominance of G-CSF, GM-CSF, IL-4, IL-10, and TGFß, and in the presence of IDO acquire the phenotype of tolerant dcs (tdc) and become capable of stimulating the differentiation of native Tho cells towards tolerant regulatory T cells (Treg), rather than towards cytotoxic effector T cells [8,11]. In addition to the above immunological actions, dcs are assumed to play a relevant trophic role, enhancing differentiation and proliferation of endometrial stromal cells, as well as local angiogenesis [22].

3.2.3. Tged

Treg (CD4 + CD25 + Foxp3 +) are a subset of CD4 + T cells and are important components of adaptive immunity because their primary function is to limit the immune response. Tregs are involved in immunological tolerance to self and graft and play an important role in preventing autoimmune responses against autoantigens [23,24]. Recent studies strongly demonstrate the key role of these cells in early pregnancy [4,8,11,12,25]. Thus, it has been shown that in both mice and humans, during normal pregnancy, there is an increase in the population of decidual Tregs, which have several pregnancy-stimulating effects [11]: prevention of immune rejection of paternal antigens of the fetus by the T cell effector, induction of decidual support for embryo implantation due to their effect on other leukocyte and non-leukocyte cell types [26], as well as by enhancing proper remodeling of maternal vessels [27]. There is evidence to support the concept that the pregnancy-stimulating effects of Tregs are particularly important in the peri-implantation period and in the earliest stages of pregnancy, whereas the role of Treg in later stages seems to be more limited [28].

3.2.4. Other components of the immune system

The role of other components of the immune system, such as granulocytes, CD8 + cells, and B cells, is still largely unexplored, especially in relation to PNB; further research is needed to better determine the potential significance of these important components of innate and adaptive immunity. However, when specifically applied to B cells and plasma cells, evidence appears to support the concept that regulatory

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B(Breg) cells, a subset of B cells with immunosuppressive properties, mainly studied in autoimmunity, cancer, and transplant tolerance, may also play a role in pregnancy, as they are the main cellular source of the potent anti-inflammatory cytokine IL-10. Moreover, Breg cells cause suppression of other immune cell populations and can enhance the induction and maintenance of Treg [29]. A decrease in the number of Breg cells was observed in women with spontaneous abortion [110]. In normal pregnancy, HCG causes the expansion of Breg, as well as their production of IL-10; in addition, HCG increases the formation of plasma cells capable of producing specific antibodies that protect pregnancy [30].

4. The imbalance of cytokines in the endometrium of PNB.

Consistent experimental data indicate that PNB is associated with an imbalance in the endometrial and decidual cytokine environment typical of normal pregnancy. The general concept is that in women with PNB, as well as in animals predisposed to PNB, a violation of the regulation of the production of several cytokines important for implantation and early pregnancy stimulation occurs in both immune and non-immune cells present or recruited into the endometrium and decidual membrane. This creates an unfavorable cytokine environment, which, in turn, can disrupt the tolerance of the maternal immune system to trophoblast and lead to rejection of the concept. Due to the complexity of the endometrial cytokine network, which also undergoes profound changes during pregnancy, it is difficult to identify all the cytokines involved in the determination of PNB and determine the relative importance of each specific substance. Moreover, there is a difficulty in pinpointing the specific cellular source of these factors, which are likely secreted by a wide range of both immune and non-immune cells. Despite the above limitations, several of the following cytokines are considered to play an important role in this context. These cytokines include at least IL-1, IL-1α, IL-1β, IL-2, IL-4, IL-6, IL-7, IL-8, IL-10, IL-12, IL-17, IL. -18, IL-22, IL-23, IL-27, TGF-β, TGF-β1, IFN-γ, TNF-α, LIF and MIF.

5. Conclusions and future directions

Over the past three decades, tremendous progress has been made in understanding

mechanisms underlying maternal adoption of genetically and immunologically distinct embryos. The emerging picture can be summarized as follows: a) the mother's immune system is directly involved in the establishment, maintenance and development of a normal pregnancy. In this context, it is logical and very plausible that the immune system is used to regulate all phases of pregnancy b) there are numerous mechanisms to prevent immune dysfunction in the mother's body, leading to pregnancy loss. These mechanisms are aimed at inducing general immunological tolerance of the mother to the fetus while maintaining complete immunological reactivity against all other foreign antigens. To achieve this goal, the maternal immune system must undergo modulation, which includes many, if not all, of the main cellular and molecular mechanisms, components of the adaptive and innate immune system; c) the involvement of the mother's immune system is not limited to the correct immunological dialogue between the mother and the fetus, but also extends to uterine (endometrial) tissue destruction, vascular remodeling and placentation; d) the mother's immune response to the fetus undergoes significant changes depending on the duration of pregnancy. In fact, recent data

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support the concept that embryo implantation triggers an initial, early inflammatory response, followed quickly by the creation of an anti-inflammatory-decidual environment that allows the embryo to survive. The latter, even more powerful, inflammatory reaction occurs in late pregnancy and leads to childbirth and fetal birth. All these events fully affect the maternal immune system. In this context, it is highly likely that immune system disorders may occur, at least in some women with unexplained PNB who have no other clinical causes or explanations. In these women, it is very likely that the immune dysfunction occurs in the endometrium and the vdecidual membrane. However, it is possible that different disorders of the immune system lead to the same end effect—PNB—in different women; in other words, it is possible that there are different immunological modes of PNB. Further research is needed to answer this urgent question and help develop effective immunological treatments for this subgroup of women with PNB. In fact, the currently available methods of treating PNB of immune etiology are quite limited, empirical in most cases and have low effectiveness, with the rare exception of cases associated with the use of a combination of Aspirin and Heparin in women with antiphospholipid antibodies. Future prospects in the treatment of PNB of immune etiology can be directed to the correction of abnormal recidualization, as well as dysfunctions of immune mechanisms occurring in the endometrial decidual membrane, based on emerging data. For example, the recently introduced innovative method of influencing seminal plasma on Tregs expansion is already being used in assisted reproductive technologies (ART), although with conflicting results.

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