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REVIEW ARTICLE

MONOCYTES IN MENSTRUATION: CONTRIBUTIONS TO BOTH IMMUNITY AND FERTILITY

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Abstract

Monocytes, a fundamental component of the innate immune system, play an important role in menstruation by promoting immunity and fertility. These immune cells are aggressively attracted to the endometrium, where they play roles in tissue remodeling, immunological monitoring, and pathogen protection. Their ability to phagocytose apoptotic cells and produce cytokines maintains a balanced inflammatory response, limiting excessive tissue damage and promoting regeneration. Aside from their role in menstrual immunity, monocytes influence fertility by promoting implantation and maintaining immunological tolerance during pregnancy. They promote endometrial angiogenesis by secreting growth factors such as vascular endothelial growth factor (VEGF), which creates an environment conducive to embryo implantation.

Furthermore, monocytes help with immune regulation by regulating the maternal response to fetal antigens, preventing immunological rejection, and promoting successful gestation. Monocyte dysregulation has been linked to a variety of reproductive diseases, including endometriosis, recurrent pregnancy loss, and implantation failure. Aberrant monocyte recruitment or function can cause chronic inflammation, decreased endometrial receptivity, and disturbed immunological tolerance, all of which have a deleterious influence on fertility.

Keywords: Monocytes, menstruation, immunity, fertility, endometrial remodeling.

INTRODUCTION

Menstruation is a very dynamic and cyclical process that involves the shedding and rebuilding of the uterine lining. This process is strictly controlled by a combination of hormonal, immunological, and vascular variables that maintain normal endometrial remodeling. Among the immune cells involved, monocytes are critical in maintaining this delicate balance, regulating both immunological defense and reproductive success. Their ability to develop into macrophages and dendritic cells enables them to aid in tissue healing, inflammation control, and immunological surveillance[1-4]. Monocytes, a kind of leukocyte produced from bone marrow, are rapidly attracted to the endometrium during menstruation. Their key tasks include apoptotic cell phagocytosis, cytokine release, and tissue regeneration. Monocytes regulate inflammatory responses, preventing excessive tissue damage and promoting uterine lining regeneration, providing normal menstrual cycles. Their participation in endometrial remodeling is critical for preparing the uterus for possible implantation in the next cycle[4-6]. In addition to immunological control, monocytes play a crucial role in endometrial vascularization. Monocyte-derived macrophages secrete VEGF, which promotes angiogenesis and ensures an adequate blood supply for endometrial healing. Furthermore, monocytes contribute to the breakdown and removal of extracellular matrix components, which aids in tissue remodeling and regeneration. These processes are essential for sustaining a healthy endometrial environment that promotes reproductive success[7].

Monocytes also play an important function in developing immunological tolerance during pregnancy. When fertilization occurs, monocytes help to regulate maternal-fetal immunity by inhibiting excessive immune responses to fetal antigens. They stimulate the differentiation of regulatory macrophages, which aids in the creation of an immunosuppressive environment required for successful implantation and fetal development. Disruptions in immunological homeostasis can lead to implantation failure and pregnancy loss[7,8]. Despite their beneficial effects, dysregulated monocyte activity has been associated to a variety of reproductive issues. Monocytes contribute to chronic inflammation in endometriosis, which causes aberrant tissue development and infertility. Similarly, in recurrent pregnancy loss (RPL), impaired monocyte-mediated immune tolerance can cause an

excessive maternal immune response, resulting in fetal rejection. Understanding how monocyte function is affected in various illnesses may bring fresh insights into potential therapeutic strategies[9,10]. Recent studies have underlined the significance of monocyte plasticity in reproductive health. Depending on the local milieu, monocytes can develop into pro-inflammatory or anti-inflammatory macrophages, regulating pregnancy and menstrual health. The ability of monocytes to transition between different states demonstrates their versatility in response to changing physiological requirements. However, an imbalance in the differentiation process can lead to pathological disorders that impact fertility and menstrual health[11,12].

This review will look at the critical role of monocytes in menstruation and fertility, focusing on their contributions to immunological control, endometrial remodeling, and reproductive success.

Monocytes in Menstruation

Menstruation is a cyclical and complex physiological process that involves the shedding and rebuilding of the uterine lining. This process is carefully controlled by a dynamic interaction of endocrine, immunological, and vascular components. Monocytes, one of the core immune cells engaged in this process, perform an important role in maintaining the immunological balance required for tissue repair and reproduction. These innate immune cells act as progenitors to macrophages and dendritic cells, allowing them to contribute to a variety of immunological and inflammatory responses that are critical for endometrial homeostasis. Monocytes are actively recruited to the endometrium during menstruation, where they help with immunological defense, tissue remodeling, and vascularization. Their ability to phagocytose dead cells, release pro-inflammatory and anti-inflammatory cytokines, and stimulate angiogenesis makes them critical for normal menstrual function. Furthermore, monocytes assist create immunological tolerance during pregnancy, ensuring that the mother immune system does not react negatively to the developing fetus. However, deregulation of monocyte activity has been linked to a variety of reproductive diseases, including endometriosis, recurrent pregnancy loss (RPL), and implantation failure[13,14].

Monocytes and immune regulation in menstruation

The endometrium goes through cyclical periods of proliferation, differentiation, and shedding, necessitating a strong immune response to preserve tissue integrity and avoid infections. Monocytes serve an important function in maintaining the immunological balance. Menstruation causes extensive tissue disintegration, resulting in the release of cellular waste and potential exposure to infections. Monocytes are attracted to the uterine lining in response to chemokines such monocyte chemoattractant protein-1 (MCP-1), and they serve as the first line of defense against infections. One of the key activities of monocytes during menstruation is to remove apoptotic cells and necrotic tissue. This is accomplished through phagocytosis, a process in which monocytes consume and breakdown dead cells, minimizing excessive inflammation and tissue damage. Monocytes release cytokines such as IL-6, IL-10, and TNF-α, which regulate the local immune system. The balance of pro-inflammatory and anti-inflammatory cytokines is critical for ensuring that menstruation occurs without excessive inflammation, which can lead to pathological disorders like endometriosis[15-17].

Monocytes and endometrial remodeling

Monocytes have an important part in endometrial remodeling, in addition to immunological protection. After menstruation, the endometrial lining must renew in preparation for potential embryo implantation in the following month. When monocytes differentiate into macrophages, they contribute to this process by promoting angiogenesis and modifying the extracellular matrix. Angiogenesis, or the development of new blood vessels, is required for re-establishing the endometrial blood supply after menstruation. Monocyte-derived macrophages release VEGF, an important angiogenic agent that promotes endothelial cell proliferation and migration. This guarantees that the newly produced endometrial tissue receives sufficient oxygen and nutrients, allowing for regeneration. Furthermore, monocytes create matrix metalloproteinases (MMPs), which destroy extra-cellular matrix components, allowing for regulated tissue remodeling. Monocytes also work with stromal and epithelial cells in the endometrium to stimulate healing processes. Their capacity to modulate fibrosis through TGF-β prevents excessive scarring and preserves endometrial receptivity for subsequent embryo implantation. These restorative actions underscore monocytes' critical involvement in maintaining a healthy and functional endometrium[18-20].

Monocytes and fertility

Beyond menstruation, monocytes have an important role in fertility, notably in preparing the endometrium for implantation and maintaining immunological tolerance during pregnancy. The shift from menstruation to the luteal phase is characterized by decidualization, in which endometrial stromal cells undergo morphological and functional changes to become receptive to an embryo. Monocytes participate to this process by secreting growth factors and cytokines that help decidual cells differentiate and function. A major difficulty during pregnancy is the necessity for immunological tolerance toward the semi-allogeneic fetus, which contains paternal antigens that the mother immune system may perceive as foreign. Monocytes contribute to immunological tolerance by developing into anti-inflammatory macrophages and regulatory dendritic cells. These immune cells reduce overactive maternal immunological responses, thereby protecting the developing fetus from being rejected. Furthermore, monocytes stimulate the growth of regulatory T cells (Tregs), which are essential for maintaining the maternal-fetal immunological balance. Impaired monocyte function can have serious implications for fertility. For example, insufficient monocyte-mediated immunological tolerance has been linked to RPL and implantation failure. Abnormal monocyte activity can also lead to uterine conditions such chronic endometritis, which can impair endometrial receptivity and embryo implantation.

Understanding monocytes' immune role during pregnancy can lead to new therapeutic options for infertility[21-23].

Dysregulation of monocyte function in reproductive disorders

Monocyte dysregulation has been linked to a variety of reproductive problems, including menstrual health and fertility issues. Endometriosis is a chronic inflammatory ailment marked by the presence of endometrial-like tissue outside the uterus. Monocytes in women with endometriosis have altered cytokine profiles, resulting in chronic inflammation and immunological failure. Endometriosis can cause infertility and pelvic pain due to elevated levels of pro-inflammatory cytokines such TNF-α and IL-1β. RPL is another disorder that has been associated to monocyte dysfunction. Monocytes play an important role in immunological tolerance throughout pregnancy, and defects in their development can cause an excessive maternal immune response, culminating in fetal rejection. According to studies, women with RPL frequently have a skewed monocyte response, which includes increased inflammatory cytokine production and decreased regulatory function. This immunological imbalance can impede embryo implantation, resulting in pregnancy failure. In addition, altered monocyte function can lead to implantation failure. Inadequate monocyte recruitment to the endometrium can lead to reduced endometrial receptivity, lowering the chances of successful implantation. Similarly, excessive monocyte-driven inflammation can disrupt the uterine environment, inhibiting embryo attachment and growth. These findings highlight the significance of monocyte homeostasis in reproductive health and the necessity for additional research into monocyte-targeted treatments[24,25].

Immune regulation in menstruation

Menstruation is a distinct immunological event requiring a careful balance of inflammation, immune tolerance, and tissue repair. The endometrial lining sheds through controlled immune activation, allowing for the elimination of necrotic and apoptotic cells while minimizing excessive inflammation that could lead to pathological diseases. This process is heavily influenced by immune cells, cytokines, and signaling pathways that coordinate endometrial breakdown and regeneration. Monocytes, macrophages, natural killer (NK) cells, and T cells are among the essential immunological actors that ensure menstruation runs smoothly while preserving local and systemic immune homeostasis[26,27].

Inflammatory triggers and the recruitment of immune cells

Menstruation begins with a rapid fall in progesterone levels, which causes destabilization of the endometrial vasculature and destruction of the endometrium's functional layer. Withdrawal of progesterone causes an increase in pro-inflammatory mediators like prostaglandins, TNF-α, and IL-1β, leading to an inflammatory cascade. The infiltration of immune cells, notably monocytes, macrophages, and neutrophils, into endometrial tissue is critical for cleaning cellular waste and preventing infection. Monocytes, which are recruited in response to chemokines like MCP-1, develop into macrophages once they enter the endometrium. These macrophages play a dual role, increasing inflammation during the first phase of menstruation and then switching to an anti-inflammatory phenotype to aid in tissue healing. Neutrophils, another type of immune cell, contribute to the inflammatory response by producing enzymes and reactive oxygen species (ROS), which break down the extracellular matrix and aid in endometrial shedding[28,29].

Phagocytosis and clearance of cellular debris

The elimination of apoptotic cells and necrotic tissue during menstruation is an important function of immune control because it prevents excessive inflammation and autoimmune. Monocytes and macrophages are the principal phagocytic cells that consume and degrade these cellular leftovers. Phagocytosis removes debris and releases anti-inflammatory cytokines including IL-10 and TGF-β, promoting tissue regeneration. During the menstrual cycle, macrophages undergo functional plasticity, transitioning from a pro-inflammatory M1 phenotype to an anti-inflammatory M2 phenotype. M1 macrophages produce cytokines including TNF-α and IL-6, which promote inflammation and attract more immune cells. As menstruation proceeds, the M2 macrophage phenotype dominates, promoting angiogenesis, extracellular matrix remodeling, and epithelium regeneration via VEGF and MMP production. The change from an inflammatory to a reparative immunological milieu is essential for repairing endometrial function and preparing for the next reproductive cycle[30,31].

Role of natural killer cells and T cells in endometrial immunity

NK cells make up a large component of the immune cell population in the endometrium, and their function goes beyond immune surveillance to tissue remodeling. Unlike peripheral NK cells, which are largely cytotoxic, uterine NK (uNK) cells have a more regulatory nature. They produce cytokines such as interferon-gamma (IFN-γ), which contribute to vascular remodeling and tissue homeostasis. During menstruation, uNK cells help to remove senescent endometrial cells and regulate local immune responses to prevent excessive inflammation. T cells, particularly Tregs, play an important role in immunological control during menstruation. These cells support immunological tolerance by decreasing excessive inflammatory responses and preventing autoimmunity. Tregs help to resolve inflammation by preventing the activation of effector T cells and regulating cytokine levels. Treg function imbalances have been associated to menstruation illnesses including endometriosis, in which excessive inflammation and immunological malfunction contribute to abnormal tissue growth beyond the uterine wall[32,33].

Endometrial repair and immune modulation

Following the breakdown and loss of the endometrial lining, immune modulation changes to tissue repair and regeneration. This phase includes angiogenesis, extracellular matrix remodeling, and epithelial cell

proliferation, all of which are aided by immune cell-derived growth factors and cytokines. Monocytes and macrophages secrete VEGF, TGF-β, and MMPs, which help generate new blood vessels and rebuild endometrial tissue. Endometrial stem cells, which live in the basal layer of the endometrium, also help with tissue regeneration. These stem cells work with immune cells to stimulate wound healing and epithelial cell growth. The interaction of immune and stromal cells guarantees that newly produced endometrial tissue is functional enough for implantation in subsequent cycles. Immune-mediated tissue repair dysregulation can result in disorders like Asherman's syndrome, which is characterized by intrauterine adhesions and poor endometrial regeneration[34,35].

Immune dysregulation and menstrual disorders

While immune modulation in menstruation is normally well-coordinated, changes in this balance can result in a variety of menstrual diseases. Excessive immunological activation, characterized by increased inflammatory responses and defective resolution mechanisms, has been linked to illnesses like endometriosis, adenomyosis, and heavy menstrual hemorrhage. In contrast, insufficient immune activation might lead to insufficient endometrial debris clearance, resulting in chronic endometritis and implantation failure. Endometriosis is a chronic inflammatory illness characterized by abnormal immune responses that allow endometrial-like tissue to grow outside the uterus. Endometriotic lesions and persistent pelvic discomfort persist due to elevated pro-inflammatory cytokines, dysregulated macrophage polarization, and reduced Treg activity. Similarly, severe monthly bleeding (menorrhagia) is frequently associated with an imbalance in pro-coagulant and anti-coagulant factors, which are controlled by immune-mediated interactions inside the endometrium. Another immune-related menstruation illness is polycystic ovarian syndrome (PCOS), in which chronic low-grade inflammation disrupts hormonal and immunological homeostasis. Women with PCOS frequently have higher levels of inflammatory cytokines and altered monocyte/ macrophage activity, which can lead to monthly abnormalities and infertility[36-38].

Monocytes and endometrial remodeling

Endometrial remodeling is a dynamic and cyclical process required for reproductive health. Each menstrual cycle includes stages of endometrial proliferation, differentiation, breakdown, shedding, and regeneration. Monocytes, as critical components of the innate immune system, play an important part in these processes by reducing inflammation, removing cellular debris, boosting tissue healing, and assisting with vascular remodeling. Their ability to develop into macrophages and dendritic cells enables them to respond to the changing needs of the endometrium throughout the menstrual cycle.

Monocyte recruitment and activation during the menstrual cycle

Monocytes are actively recruited to the endometrium in response to chemotactic signals sent out by endometrial stromal and immunological cells. During the late secretory phase, dropping progesterone levels cause the release of inflammatory mediators such as MCP-1, interleukin-8 (IL-8), and colony-stimulating factors, allowing monocytes to infiltrate the endometrial tissue. When these recruited monocytes contact the local milieu, they develop into specialized macrophages that play varied functional roles depending on the stage of the menstrual cycle. During menstruation, the endometrium experiences substantial tissue disintegration, and monocytes contribute to the inflammatory response required for proper shedding. These cells produce pro-inflammatory cytokines such TNF-α, IL-6, and IL-1β, which recruit more immune cells and degrade the extracellular matrix. MMPs, which are released in part by activated monocytes, aid in tissue breakdown by efficiently removing necrotic cells and damaged matrix components[39,40].

Monocyte-mediated phagocytosis and clearance of apoptotic cells

Monocytes play an important role in endometrial remodeling by clearing apoptotic cells and cellular debris, which prevents excessive inflammation and secondary tissue damage. As the menstrual cycle proceeds, inflammation must be resolved in order to restore tissue integrity. Monocytes and differentiated macrophages adopt an anti-inflammatory character, encouraging the removal of apoptotic cells via efferocytosis, a process in which dead cells are ingested and digested. Macrophages derived from monocytes recognize apoptotic cells through the expression of scavenger receptors and engage in phagocytosis, releasing immunomodulatory cytokines such as TGF-β andIL-10. These cytokines contribute to dampening inflammation and initiating the repair phase of endometrial remodeling. The efficient clearance of cellular debris not only prevents excessive immune activation but also facilitates the transition from tissue breakdown to regeneration[41-43].

Monocyte contribution to angiogenesis and tissue regeneration

As the menstrual period ends, the endometrium must renew in preparation for the following cycle. This stage of endometrial remodeling is distinguished by fast cell proliferation, extracellular matrix deposition, and angiogenesis. Monocytes and macrophage derivatives play an important part in this process by producing pro-angiogenic substances such as VEGF, PDGF, and bFGF. These substances increase endothelial cell proliferation, encourage new blood vessel development, and repair the uterine vasculature that was disturbed during menstruation. Macrophages produced from monocytes are classified as M1 (pro-inflammatory) or M2 (anti-inflammatory/reparative). While M1 macrophages predominate during menstruation to aid in tissue destruction, M2 macrophages become more common during the proliferative and secretory phases. These M2 macrophages aid wound healing by secreting extracellular matrix components and anti-inflammatory cytokines, which promote stromal cell proliferation and tissue remodeling. The balance of M1 and M2 macrophages is critical for effective inflammation resolution and healthy tissue regeneration[44-47].

Monocytes and regulation of extracellular matrix remodeling

The extracellular matrix (ECM) provides structural support for endometrial tissue and undergoes extensive modification during the menstrual cycle. Monocytes contribute to ECM turnover via regulating the activity of matrix metalloproteinases (MMPs) and their inhibitors. MMPs degrade ECM components like collagen and fibronectin, which aids in the breakdown of the functional layer during menstruation. TIMPs, on the other hand, aid in the regulation of MMP activity during the repair phase, ensuring that matrix deterioration does not continue unabated. Monocytes also interact with fibroblasts and stromal cells to influence the makeup of the extracellular matrix. Monocytes secrete TGF-β and other fibrogenic factors, which activate fibroblasts and deposit new ECM proteins to reconstruct the uterine lining. Monocyte-mediated ECM remodeling dysregulation has been linked to clinical illnesses such as endometriosis, in which excessive MMP activity causes aberrant tissue growth outside the uterus, and fibrosis-related disorders that impede endometrial receptivity[48-51].

Monocytes in endometrial immune tolerance and pregnancy readiness

In addition to their involvement in tissue remodeling, monocytes help build immunological tolerance in the endometrium, which is essential for successful embryo implantation and pregnancy maintenance. During the secretory phase, high levels of progesterone produce an immunosuppressive environment, encouraging the recruitment of monocytes with anti-inflammatory functions. These cells help regulate maternal immunological responses, minimizing over activation that could result in implantation failure or pregnancy problems. To maintain immunological homeostasis, monocyte-derived regulatory macrophages interact with uterine natural killer (uNK) cells and regulatory T cells. They release IL-10 and PGE2, which decrease inflammatory responses and promote trophoblast invasion. Monocytes orchestrate a fine-tuned immunological balance that keeps the endometrium receptive to embryo implantation while preventing the growing embryo from being rejected[51,52].

Dysregulation of monocyte function and endometrial disorders

Aberrant monocyte activity has been linked to a variety of endometrial illnesses, including endometriosis, adenomyosis, and recurring pregnancy loss. Endometriosis is characterized by increased monocyte recruitment and altered macrophage polarization, which lead to persistent inflammation and ectopic endometrial lesions. These lesions have increased levels of pro-inflammatory cytokines and growth factors, which promote pathological angiogenesis and fibrosis. Adenomyosis occurs when monocyte-derived macrophages invade the myometrium, causing excessive ECM remodeling and aberrant uterine wall thickening. Dysregulated monocyte function can also impair endometrial receptivity, leading to implantation failure and infertility. Furthermore, prolonged inflammation produced by defective monocyte-mediated clearance of apoptotic cells has been linked to recurrent pregnancy loss, emphasizing the relevance of well-regulated immune responses in reproductive success[53].

Monocytes and fertility

Fertility is a complex physiological process that necessitates a tightly controlled immunological milieu to facilitate embryo implantation and pregnancy maintenance. The endometrium, which changes cyclically throughout the menstrual cycle, must switch from an inflammatory condition during menstruation to an immunologically tolerant state during implantation. Monocytes, as critical actors in the innate immune system, play an important role in this process by regulating inflammation, tissue remodeling, and immunological tolerance. They can differentiate into macrophages and dendritic cells, allowing them to fulfill a variety of activities required for successful reproduction[54].

Monocyte recruitment and activation in the endometrium

Monocytes are recruited into the endometrium in response to hormonal signals and chemokines such as monocyte chemoattractant protein-1 (MCP-1) and interleukin-8 (IL-8). During the proliferative and secretory phases of the menstrual cycle, estrogen and progesterone influence the migration and differentiation of monocytes, shaping the local immune landscape. These monocytes infiltrate the endometrial stroma, where they differentiate into macrophages with distinct functional roles depending on the phase of the cycle. In the secretory phase, monocytes promote an immunosuppressive environment by producing anti-inflammatory cytokines such as interleukin-10 (IL-10) and transforming growth factor-beta (TGF-β). These cytokines facilitate the development of immune tolerance, which is essential for embryo implantation. Additionally, monocytes interact with other immune cells, such as uterine natural killer (uNK) cells and regulatory T cells (Tregs), to ensure a balanced immune response that prevents excessive inflammation while maintaining immune vigilance against infections[55,56].

Monocytes and endometrial receptivity

Endometrial receptivity is a crucial determinant of successful implantation, and monocytes play a central role in preparing the endometrial tissue for embryo attachment. One of the key contributions of monocytes to endometrial receptivity is their role in modulating extracellular matrix (ECM) remodeling. By secreting matrix metalloproteinases (MMPs) and tissue inhibitors of metalloproteinases (TIMPs), monocytes regulate the turnover of ECM components, ensuring that the endometrium maintains the necessary structural integrity for implantation. Abnormal ECM remodeling, often associated with dysregulated monocyte function, has been linked to conditions such as implantation failure and recurrent pregnancy loss[57-59].

Monocytes and implantation: Supporting trophoblast invasion

Successful implantation requires the invasion of trophoblast cells from the developing embryo into the maternal endometrium. Monocytes and their macrophage derivatives are instrumental in facilitating

this process by modulating immune responses and promoting tissue remodeling. These cells secrete factors such as vascular endothelial growth factor (VEGF), epidermal growth factor (EGF), and hepatocyte growth factor (HGF), which support trophoblast migration and invasion. Decidual macrophages derived from monocytes also contribute to the breakdown of the basement membrane, allowing trophoblast cells to penetrate deeper into the endometrium and establish a functional placenta. This process is tightly regulated to ensure that trophoblast invasion is neither excessive nor insufficient, as both extremes can lead to pregnancy complications such as preeclampsia or placenta accreta[60-62].

Monocyte-mediated angiogenesis and vascular adaptation

Proper vascular adaptation is essential for fetal development, and monocytes play a critical role in establishing and maintaining the maternal-fetal circulatory interface. During early pregnancy, monocytes and their macrophage derivatives contribute to angiogenesis by releasing pro-angiogenic factors such as VEGF and placental growth factor (PlGF). Monocyte-derived macrophages also interact with endothelial cells to modulate vascular tone and prevent excessive inflammation. By producing nitric oxide (NO) and prostaglandins, these cells help maintain vascular homeostasis, ensuring adequate blood flow to the developing embryo. Dysregulation of monocyte-mediated angiogenesis has been implicated in pregnancy complications such as intrauterine growth restriction (IUGR) and recurrent pregnancy loss, highlighting the importance of monocyte function in reproductive success[63-66].

Monocytes in immune tolerance and maternal-fetal immunoregulation

One of the most critical roles of monocytes in fertility is their involvement in maternal-fetal immune tolerance. The maternal immune system must recognize the developing fetus as a semi-allogeneic entity and prevent immune rejection. Monocytes contribute to this immunological balance by differentiating into regulatory macrophages that suppress excessive maternal immune activation. Decidual macrophages secrete IL-10 and TGF-β, which inhibit pro-inflammatory responses and promote the expansion of Tregs. Additionally, monocytes modulate the activity of uterine NK cells, ensuring that they support trophoblast invasion without inducing cytotoxic responses. This finely tuned immune environment is essential for maintaining pregnancy and preventing complications such as recurrent miscarriage or preterm labor[67-70].

Dysregulation of monocyte function and infertility

Imbalances in monocyte function have been linked to various infertility-related disorders, including endometriosis, polycystic ovary syndrome (PCOS), and implantation failure. In endometriosis, monocytes exhibit an aberrant inflammatory phenotype, contributing to chronic inflammation and the establishment of ectopic endometrial lesions. These lesions produce excessive levels of inflammatory cytokines and growth factors, leading to impaired implantation and reduced fertility. In PCOS, monocyte dysfunction has been associated with systemic inflammation and metabolic disturbances that negatively impact endometrial receptivity. Increased levels of pro-inflammatory cytokines such as TNF-α and IL-6 can alter the hormonal environment, disrupting the menstrual cycle and impairing ovulation. Furthermore, defective monocyte-mediated immune tolerance has been implicated in cases of unexplained infertility, where the endometrium fails to establish the necessary immune conditions for successful implantation[71-74].

Dysregulation of monocyte function in reproductive disorders

Monocytes play a pivotal role in maintaining immune homeostasis and supporting reproductive processes such as endometrial remodeling, implantation, and placental development. However, dysregulation of monocyte function can lead to a range of reproductive disorders, including endometriosis, polycystic ovary syndrome (PCOS), recurrent pregnancy loss (RPL), and implantation failure. Aberrant monocyte activity can result in excessive inflammation, impaired immune tolerance, defective angiogenesis, and abnormal tissue remodeling, all of which can negatively impact fertility and pregnancy outcomes. Understanding the mechanisms underlying monocyte dysfunction in reproductive disorders is essential for developing targeted therapeutic interventions[75].

Monocyte dysfunction in endometriosis

Endometriosis is a chronic inflammatory disease characterized by the presence of ectopic endometrial tissue outside the uterus. Monocytes and their macrophage derivatives play a crucial role in the pathogenesis of endometriosis by promoting a pro-inflammatory microenvironment that sustains the growth of ectopic lesions. Studies have shown that monocytes in women with endometriosis exhibit an altered phenotype, producing excessive amounts of pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), and interleukin-1β (IL-1β). These cytokines contribute to chronic inflammation, angiogenesis, and immune evasion, allowing ectopic endometrial implants to persist and proliferate. The impaired phagocytic capacity of monocytes and macrophages is associated with defective expression of scavenger receptors such as CD36 and CD163, which are essential for clearing apoptotic cells and tissue debris. This dysfunction perpetuates immune activation, resulting in pain, infertility, and disease progression. Moreover, monocyte derived macro-phages in endometriotic lesions promote neuro-angiogenesis by secreting nerve growth factor (NGF) and vascular endothelial growth factor (VEGF), contributing to the chronic pain experienced by affected individuals[75,76].

Monocyte dysregulation in Polycystic Ovary Syndrome (PCOS)

PCOS is a common endocrine disorder characterized by hyperandrogenism, ovulatory dysfunction, and metabolic abnormalities. Inflammatory processes play a significant role in the pathophysiology of PCOS, and monocytes have been implicated as key mediators of

systemic and local inflammation. Women with PCOS exhibit increased levels of circulating monocytes with an activated inflammatory phenotype, marked by elevated production of TNF-α, IL-6, and C-reactive protein (CRP). This chronic low-grade inflammation contributes to insulin resistance, a hallmark of PCOS that disrupts ovarian function and endometrial receptivity. Monocytes in PCOS also demonstrate altered migratory and adhesive properties, leading to endothelial dysfunction and impaired vascular remodeling. Increased expression of adhesion molecules such as intercellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1) promotes monocyte endothelial interactions, contributing to cardiovascular risk in PCOS patients. The dysregulated immune responses in PCOS highlight the critical role of monocyte homeostasis in reproductive health and underscore the need for immunomodulatory therapies to restore immune balance[77-79].

Monocyte-mediated inflammation in Recurrent Pregnancy Loss (RPL)

Recurrent pregnancy loss, defined as the loss of two or more consecutive pregnancies, has been linked to immune dysregulation, including abnormal monocyte activity. In a healthy pregnancy, monocytes play a protective role by facilitating immune tolerance and supporting trophoblast invasion. However, in cases of RPL, monocytes exhibit an aberrant pro-inflammatory phenotype, producing excessive levels of IL-1β, TNF-α, and interferon-gamma (IFN-γ), which can lead to placental dysfunction and fetal rejection. Monocytes from women with RPL show impaired differentiation into tolerogenic decidual macrophages, leading to an imbalance between pro-inflammatory and anti-inflammatory immune responses at the maternal-fetal interface. This disruption results in excessive activation of cytotoxic T cells and natural killer (NK) cells, increasing the risk of pregnancy loss. Additionally, monocyte-derived macrophages in RPL display reduced expression of programmed death-ligand 1 (PD-L1), a key molecule involved in immune tolerance. This deficiency exacerbates immune-mediated rejection of the embryo, further contributing to pregnancy failure[80,81].

Defective monocyte function in implantation failure

Successful implantation requires a precisely regulated immune microenvironment in which monocytes play a central role. In cases of implantation failure, monocytes may fail to adequately support endometrial receptivity and embryo adhesion. Dysregulated monocyte activity can result in excessive inflammation, leading to a hostile uterine environment that prevents successful embryo implantation. One of the primary mechanisms underlying implantation failure is the altered production of cytokines and growth factors by monocytes. Reduced levels of IL-10 and TGF-β, which are essential for immune tolerance, have been observed in women with recurrent implantation failure. Conversely, increased levels of TNF-α and IL-6 contribute to excessive inflammation, which disrupts the delicate balance required for implantation. Furthermore, monocyte-derived macrophages in implantation failure exhibit impaired angiogenic function, leading to insufficient vascularization of the endometrium. Without adequate blood supply, the endometrium cannot support embryo implantation, resulting in repeated implantation failure[82,83].

Monocyte dysregulation and preeclampsia

Preeclampsia is a pregnancy-related hypertensive disorder characterized by endothelial dysfunction, systemic inflammation, and impaired placental development. Monocytes play a key role in the pathogenesis of preeclampsia by contributing to excessive inflammation and vascular abnormalities. Studies have shown that monocytes from preeclamptic women exhibit heightened activation, producing elevated levels of TNF-α, IL-1β, and reactive oxygen species (ROS). Additionally, monocyte-derived macrophages in preeclampsia display an altered phenotype that promotes excessive trophoblast invasion inhibition. This imbalance impairs spiral artery remodeling, leading to poor placental perfusion and fetal growth restriction. Understanding the role of monocyte dysfunction in preeclampsia may help identify new biomarkers and therapeutic targets to improve pregnancy outcomes[84,85].

Therapeutic implications of targeting monocyte dysregulation

Given the importance of monocytes in reproductive diseases, addressing monocyte-mediated inflammation and immunological dysregulation offers a promising therapeutic option. Anti-inflammatory medications such TNF-α inhibitors, IL-6 blockers, and corticosteroids can improve immunological balance and fertility. Immunomodulatory medications that increase tolerogenic monocyte development, like TGF-β supplements or PD-L1 agonists, can improve immunological tolerance and decrease pregnancy loss. Lifestyle changes such as nutrition, exercise, and stress management can all have an impact on monocyte function and lower systemic inflammation. Nutritional therapies containing anti-inflammatory components such omega-3 fatty acids, vitamin D, and polyphenols may help regulate monocyte activity and improve fertility outcomes. More study is needed to identify novel therapeutic options that particularly target monocyte dysfunction in reproductive diseases[86-88].

CONCLUSIONS

Monocytes regulate immunological responses, assist endometrial remodeling, and facilitate implantation, all of which are essential for menstruation, fertility, and general reproductive health. Their ability to balance pro- and anti-inflammatory activities ensures that the menstrual cycle functions properly and that the pregnancy is successful. However, abnormal monocyte activity has been linked to a number of reproductive problems, including endometriosis, polycystic ovarian syndrome (PCOS), recurrent pregnancy loss (RPL), implantation failure, and preeclampsia. Anti-inflammatory drugs, immunomodulatory treatments, and lifestyle changes that target monocyte-mediated inflammation and immunological dysregulation may open up new paths for enhancing fertility and

pregnancy outcomes. Furthermore, additional study is required to discover precise biomarkers of monocyte dysfunction and to investigate novel immunotherapies that restore immunological balance in reproductive diseases.

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AUTHOR'S CONTRIBUTION

Obeagu EI: conceived the idea, writing the manuscript, literature survey, formal analysis, critical review.

DATA AVAILABILITY

Data will be made available on request.

CONFLICT OF INTEREST

There are no conflicts of interest in regard to this project.

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