VIA MEDICA

REVIEW PAPER / GYNECOLOGY

Ginekologia Polska
2024, vol. 95, no. 4, 266–275

ISSN 0017–0011, e-ISSN 2543–6767

DOI 10.5603/gpl.97320

Inflammation in recurrent miscarriage — a comprehensive perspective from uterine microenvironment and immune cell imbalance to therapeutic strategies

Mengsi Lin, Hui Xu, Jiaying Qiu

Prenatal Screening and Diagnosis Center, Nantong Municipal Maternal and Child Health Hospital, Nantong, China

ABSTRACT

Recurrent miscarriage, poses a significant challenge for many couples globally, the causes of which are not fully understood. Recent studies have shown the intricate link between uterine inflammation and recurrent miscarriages. While inflammation is essential during early pregnancy stages, especially in embryo implantation, an imbalance can lead to miscarriage. Key inflammatory mediators and an imbalance in immune cells can significantly alter and contribute to recurrent miscarriages. Lifestyle factors like smoking and obesity exacerbate inflammatory responses, increasing miscarriage risks. Understanding the interaction between the uterine environment, immune cell imbalances, and recurrent miscarriages is essential for devising effective treatments. This paper presents the latest data on inflammation's role in recurrent miscarriage, emphasizing the significance of diagnosing chronic endometritis and immune imbalances, offering practical recommendations for treatment and diagnosis.

Keywords: endometrium; immune cells; recurrent miscarriage; inflammatory cytokines

Ginekologia Polska 2024; 95, 4: 266–275

INTRODUCTION

Recurrent miscarriage, which refers to experiencing two or more consecutive pregnancy losses, is a big challenge for many couples around the world [1]. In recent years, there has been a lot of attention on the complex relationship between inflammation in the uterus and recurrent miscarriages [2]. Under typical physiological conditions, inflammation plays a pivotal role during the early stages of pregnancy, especially in embryo implantation [3]. However, when this inflammatory balance is disrupted, particularly within the uterine lining, key inflammatory mediators such as tumor necrosis factor-alpha (TNF-α), interferon-gamma (IFN-γ), and interleukin-6 (IL-6) can change significantly in concentration and potentially lead to recurrent miscarriages [4, 5]. Moreover, lifestyle and environmental factors such as smoking and obesity have been proven to increase inflammatory responses and raise the risk of miscarriage [6]. The imbalance of immune cells during this process might also be a critical component [7, 8]. Therefore, it is extremely important to fully understand how the uterine microenvironment interacts with immune cell imbalances and recurrent miscarriages in order to develop targeted therapeutic strategies that can provide more effective treatments for affected couples.

This article explores the role of inflammation in recurrent miscarriage, with a focus on the uterine microenvironment and immune cell imbalance. Chronic endometritis (CE) can contribute to this imbalance, and antibiotic therapy is considered the treatment of choice for CE. The article emphasized the importance of accurate diagnosis of CE and immune imbalance and provides clinicians with the treatment and diagnosis of practical recommendations.

ENDOMETRIUM MICROENVIRONMENT

The endometrium underwent cyclical changes in preparation for pregnancy, creating a microenvironment that was favorable for embryo implantation. A balanced inflammatory response was essential for successful implantation. However, prolonged or excessive inflammation could hinder

Corresponding author:
Mengsi Lin
Prenatal Screening and Diagnosis Center, Nantong Municipal Maternal and Child Health Hospital, Nantong, 226010 Jiangsu, China
Phone: 15996583323
e-mail: wsdmn18@126.com

Received: 7.09.2023 Accepted: 1.01.2024 Early publication date: 25.01.2024

normal embryo implantation and development. Chronic endometritis, characterized by sustained inflammation, had significant implications for a woman's reproductive outcomes. Research indicated that chronic endometritis exacerbated uterine fibrosis and negatively impacted reproductive outcomes, especially in women with moderate to severe intrauterine adhesions and those who experienced recurrent early pregnancy loss [9]. Additionally, chronic endometritis was frequently implicated in repeated implantation failures, suggesting its pivotal role in miscarriages [7, 10–15]. Additionally, chronic endometritis was frequently implicated in repeated implantation failures, suggesting its pivotal role in miscarriages [16]. The endometrial microbiome was crucial for the success or failure of embryo implantation. Investigations revealed that these microorganisms were not solely of vaginal origin but maintained a distinct presence in the endometrium. Hormonal modulation might have influenced these microbial populations within endometrial epithelial cells. In the realm of assisted reproductive technology, alterations in the microbial composition at the embryo-endometrium interface could influence the success of embryo implantation [17]. In particular, the disorder of endometrial microbial community is lead to the potential cause of the failure of the blastocyst implantation in patients with in vitro fertilization [18]. Moreover, dysregulation of the endometrial microbiome has been linked to other pregnancy pathologies, underscoring the importance of microbiome balance for a successful pregnancy [19, 20]. Notably, after antibiotic treatment, the pregnancy outcomes of these women with chronic endometritis showed significant improvement [12, 21, 22]. These findings underscore a definitive relationship between chronic endometritis and miscarriage, and appropriate treatment might enhance the reproductive outcomes for women.

The relationship between endometritis and miscarriage has been confirmed in multiple studies. Inflammation plays a crucial role in normal implantation and pregnancy processes [15]. However, when the inflammatory response is excessive, it may lead to miscarriage. This excessive inflammation might be due to a deficiency in the number of CD56brightCD16– natural killer (NK) cells in the endometrium or their impaired function [23]. These NK cells are the primary regulators of inflammation levels at the placental interface [24]. They can be stimulated by placental fragments and apoptotic cells, leading to the production of inflammatory cytokines. When there is an excessive number of placental fragments and apoptotic cells, they might amplify the inflammatory response of NK cells to levels harmful to the embryo. This amplified inflammatory response could be a self-perpetuating process that eventually results in a miscarriage. Therefore, there is a clear association between endometrial inflammation and miscarriage, where NK cells play a key role in regulating inflammation levels and maintaining pregnancy stability.

INFLAMMATORY CYTOKINES

Inflammatory cytokines play a pivotal role during pregnancy. In a typical pregnancy process, certain inflammatory cytokines aid in the implantation of the embryo and the formation of the placenta. However, when the levels of these factors become imbalanced, it can lead to adverse pregnancy outcomes. Below is a detailed description of the impact of other inflammatory cytokines on pregnancy.

The pro-inflammatory cytokines

The pro-inflammatory cytokines, such as TNF-α, IL-6, and interleukin-1β (IL-1β), are produced during inflammatory processes [25–27]. At normal levels, these factors aid in embryo implantation. However, when their levels become elevated, they can lead to embryo implantation failure, placental dysfunction, and miscarriage. Tumor necrosis factor-alpha has been associated with an increased risk of recurrent miscarriage, especially in individuals with the HLA-DR3 genotype, which is linked to high TNF-α production [28]. Tumor necrosis factor-alpha can not only amplify the inflammatory response, which may adversely affect embryo implantation and growth, but also induce excessive apoptosis of embryo and endometrial cells, leading to embryo implantation failure or early abortion [29]. In addition, TNF-α may also interfere with the blood supply of the endometrium, disrupt the type 1 T helper cells (Th1)/type 2 T helper cells (Th2) balance of immune cells, and change the endometrial environment, making it unfavorable for embryo implantation [30, 31]. Research has shown that in patients who have miscarried, there's a significant increase in the serum levels of TNF-α, IFN-γ, interleukin-2 (IL-2), IL-17A, and IL-17F2 [32]. Furthermore, some women at risk of miscarriage have been treated with TNF-α inhibitors. In these patients, the human chorionic gonadotropin (hCG) trajectory returned to a normal pattern within a week, and the obstetric outcomes were encouraging [33]. Interleukins, as a key group of inflammatory factors, have a significant correlation with recurrent miscarriage. Studies have found that, compared to women with recurrent miscarriages, the cytokines of T-helper cells, especially IL-6, are significantly reduced in these women [34]. This reduced expression pattern is further confirmed in the IL-6 and IL-1α mRNA of the secretory phase endometrium [35]. Moreover, the expression of interleukin-15 (IL-15) and leukemia inhibitory factor in the endometrium of women with recurrent implantation failure after in vitro fertilization (IVF) is related to the number of uNK cells, suggesting their potential role in recurrent miscarriage [36]. Notably, compared to women with idiopathic recurrent miscarriage, there are polymorphisms in the gene

encoding for the Interleukin-1 receptor antagonist, providing new clues for the etiology of miscarriage [37]. Lastly, the significant reduction of interleukin-25 (IL-25) and the upregulation of IL-2 further emphasize the pivotal role of interleukins in recurrent miscarriage [38]. These research findings collectively reveal the central role of interleukins in recurrent miscarriage, providing valuable insights for future therapeutic strategies.

On the other hand, CD16- CD56bright NK cells within the uterus appear to be the primary regulators of inflammation levels at the placental interface, possessing a high capability for cytokine secretion [39]. Specifically, the presence of s-HLA-G in the serum can modulate the cytokine production of uterine lymphocytes, thereby reducing the IFN-γ produced by these lymphocytes [40]. The article also mentions other factors related to inflammation and miscarriage. The role of indoleamine 2,3-dioxygenase (IDO) in human pregnancies requires further elucidation. Indoleamine 2,3-dioxygenase might be associated with the function of placental cells and macrophages, which might prevent a type IV inflammatory response against heterologous antigens on the placenta by producing IDO, targeting T lymphocytes [41]. These inflammatory cytokines may play a pivotal role in both normal and abnormal pregnancies, underscoring the central role of inflammation in miscarriages [42].

The anti-inflammatory cytokines

Anti-inflammatory cytokines, especially IL-10 and TGF-, play a pivotal role in maternal immune regulation, ensuring harmonious coexistence between the mother and the embryo. The establishment of this harmonious relationship is partly attributed to the collaboration of regulatory T cells with IL-10 or TGF-β, working together to enhance maternal immune tolerance, thereby providing a safe growth environment for the embryo [43–45]. This perspective is corroborated by the dominant expression of IL-10 and TGF-β in γδT cells in the human early pregnancy decidua, suggesting their immunoregulatory potential in preventing excessive maternal immune responses to the embryo [46, 47]. However, when this balance is disrupted, as seen in patients with unexplained early recurrent miscarriages, the function of regulatory T cells may be compromised, leading to dysregulation of T helper cells producing interleukin-17 [48]. Furthermore, polymorphisms of cytokine genes associated with miscarriage, such as TNF-α, IFN-γ, TGF-β, IL-6, and IL-10, further highlight the central role of anti-inflammatory cytokines in recurrent miscarriage [49, 50]. Overall, there is a significant correlation between anti-inflammatory cytokines and recurrent miscarriage, and their abnormal expression or dysfunction may lead to an excessive immune system attack on the embryo, increasing the risk of miscarriage [51, 52].

Prostaglandins

Prostaglandins, such as prostaglandin E2 (PGE2), play a pivotal role in normal pregnancies, aiding in embryo implantation and uterine dilation [53, 54]. However, an imbalance in its levels can lead to uterine contractions, potentially triggering preterm birth. Studies have revealed that periodontitis might lead to an abnormal increase in PGE2 levels, which is associated with preterm birth and preeclampsia, suggesting that an imbalance in PGE2 levels might be linked to adverse pregnancy outcomes [55]. Moreover, variations in prostaglandin and hormone levels during embryo implantation, pregnancy, and lactation in women prone to miscarriages further validate the crucial role of prostaglandins during pregnancy [56]. When considering the relationship between inflammation and pregnancy, the role of PGE2 becomes particularly significant, especially in inflammation responses related to pregnancy [53]. More critically, amniotic cavity infections are associated with an increase in PGE2, which might be linked to preterm birth. Lastly, infections by Porphyromonas gingivalis might impact the levels of PGE2, further hinting at its potential role in infection-induced miscarriages [57]. In conclusion, prostaglandins, especially PGE2, have a significant correlation with recurrent miscarriages, and an imbalance in their levels might lead to adverse pregnancy outcomes.

CHANGES IN IMMUNE CELLS

T cells

Immune cells such as macrophages, T cells, and natural killer cells play a pivotal role during pregnancy. Their activation status, quantity, and functional changes may be associated with inflammation and the risk of miscarriage. T cells can produce various cytokines, like leukemia inhibitory factor (LIF) and Th2 cytokines [58]. These factors are crucial in normal pregnancies, but in women with recurrent miscarriages, the production of these factors might be defective [59]. Regulatory T cells (Tregs) are a specific type of T cell that plays a key role in immune regulation. Studies have found that the function of Tregs might be compromised in patients with recurrent miscarriages, especially in their inhibitory effect on T helper cells producing interleukin-17 [60]. In normal pregnancies, both the number and function of Tregs increase, aiding the maternal immune system in accepting the semi-allogeneic embryo [61]. Tregs prevent other immune cells, like effector T cells, from attacking the embryo [62]. Abnormalities in Tregs in recurrent miscarriages, in some women with recurrent miscarriages, the number and/or function of Tregs might be compromised [63]. This suggests that their immune system might not effectively suppress the immune response against the embryo, increasing the risk of miscarriage. Studies have found that the inhibitory effect of Tregs on T helper cells producing interleukin-17 is

compromised in patients with unexplained recurrent miscarriages [48]. Interleukin-17 is a pro-inflammatory cytokine, and excessive interleukin-17 might lead to inflammatory responses affecting embryo implantation and development [64]. T cells not only interact with other T cells but also with other types of immune cells, such as macrophages and natural killer cells [65]. These interactions might influence pregnancy outcomes.

Macrophages

Macrophages are a key immune cell population at the maternal-fetal interface, playing a crucial role in the normal implantation and development of the embryo [66]. However, studies have found that obesity, changes in body mass index (BMI), activation of mediator of IRF3 activation (MITA), and other immune responses might affect the function and number of macrophages [67]. Specifically, abnormal activation and increased numbers of macrophages are associated with recurrent miscarriages. For instance, an increase in the number of macrophages in the endometrium during the mid-luteal phase is associated with an increased risk of miscarriage [68]. Additionally, the overexpression of FasL in macrophages during spontaneous miscarriages might be related to the apoptosis of placental cells [69]. In summary, changes in the function and number of macrophages might be key factors leading to recurrent miscarriages.

Natural killer cells

Natural killer cells within the uterus play a crucial role in embryo implantation and the maintenance of pregnancy [70–72]. However, there are evident alterations in the NK cells within the uterus of patients with recurrent spontaneous miscarriages, and such abnormalities might exert detrimental effects on the normal development of the fetus [72, 73]. In fact, studies have unveiled a close association between elevated levels of NK cells and IVF failures as well as recurrent miscarriages, suggesting that an overactivity or excessive number of NK cells might adversely impact the embryo [23, 74]. Notably, pharmacological interventions, such as the pre-pregnancy use of prednisolone, have been demonstrated to effectively reduce the number of NK cells within the uterus, offering a new strategy for the treatment of recurrent miscarriages [75, 76]. Furthermore, the increased number of NK cells in the uterus of women with recurrent miscarriage may lead to an imbalance of the immune response, which in turn affects the implantation and growth of the embryo [77]. This imbalance may be due to the womb NK cells and other immune cells, such as T cells and macrophages, the interaction between is broken [78, 79]. Study also found that the NK cells in peripheral blood of pregnant women during pregnancy can absorb microRNAs associated with placenta, these microRNAs play A key role in regulating gene expression [80]. Vascular endothelial growth factor C contributes to immune tolerance and enhanced endothelial activity in human uterine NK cells at the maternal-fetal interface [81]. Research has also found that the recurrent spontaneous abortion women and *in vitro* fertilization failure, NK cells on the expression of CD69 and CD161 and CD94 increase [82]. According to a study, NK cells mediate maternal recognition of the trophoblast cells of the placenta through uterine NK cells, a key mechanism ensuring the fetus isn't rejected by the maternal immune system. Firstly, according to a study, NK cells mediate maternal recognition of the trophoblast cells of the placenta through uterine NK cells, a key mechanism ensuring the fetus isn't rejected by the maternal immune system. This mechanism aids the mother in successfully accepting and supporting a semi-allogeneic fetus, thereby avoiding potential immune rejection [83]. Secondly, a study in Endocrine Reviews points out that the activity and number of NK cells in early pregnancy are regulated by hormones, such as progesterone and estrogens [83]. This hormonal regulation might be related to the successful implantation and growth of the embryo, as they can influence the function of NK cells, providing a more favorable environment for the embryo. More importantly, according to a study, uterine NK cells are considered the primary source of angiogenic factors [84]. These growth factors are vital for the remodeling of spiral arteries, ensuring the placenta receives adequate blood supply, supporting embryo growth and development [85]. Furthermore, a study in the FASEB Journal emphasizes that uterine NK cells are also considered key factors initiating the remodeling of spiral arteries [86]. These cells promote the dilation and maturation of spiral arteries by secreting various growth factors and cytokines, ensuring the placenta receives ample blood supply [87]. However, despite considerable interest in the role of uterine NK cells during pregnancy, a study in ScienceDirect suggests that their role during pregnancy might be more complex than previously thought. This implies that more research is needed to delve deeper into the exact role of NK cells during pregnancy [86, 88]. In conclusion, the multifaceted roles of NK cells during pregnancy ensure the healthy development of the embryo and the successful progression of pregnancy, as amply confirmed in numerous studies.

INFECTION

Some chronic or acute infections (such as certain bacterial or viral infections) may lead to an inflammatory response in the uterus, thereby increasing the risk of miscarriage.

Bacterial infection

Chronic endometritis is a long-standing inflammation of the endometrium, which may be caused by various reasons,

including bacterial infections. Studies have found that common bacteria and chlamydia are one of the main causes of this inflammation [89, 90]. This inflammation may affect the uterine environment, making it unfavorable for embryo implantation and growth. In women with recurrent miscarriages, the presence of chronic endometritis can be reliably detected through hysteroscopy [91]. Notably, after antibiotic treatment, the pregnancy outcomes of these women significantly improved, further confirming the association between bacterial infections and recurrent miscarriages [92]. Additionally, bacterial vaginosis is a common vaginal infection, mainly due to an imbalance of the normal vaginal flora [93]. This imbalance may increase the growth of other harmful bacteria, leading to inflammation. Research has found that bacterial vaginosis is not only a risk factor for preterm birth but also a strong risk factor for recurrent miscarriage [94]. This may be because this infection alters the uterine microenvironment, making it unfavorable for embryo implantation and growth. *Chlamydia trachomatis* is a common sexually transmitted bacterium that can cause various reproductive system diseases [95]. Research has found that *Chlamydia trachomatis* infection is associated with miscarriage. This may be because the inflammatory response caused by this bacterial infection is detrimental to embryo implantation and growth [96]. If *Chlamydia trachomatis* infection is detected, appropriate treatment should be administered to prevent recurrent miscarriages. Bacterial or fungal infections may activate certain cells of the immune system, such as macrophages and T cells [97]. This activation may initiate a series of immune events, such as inflammatory responses, which may be detrimental to embryo implantation and growth. This immune response may be one of the reasons for miscarriage.

Viral infection

The relationship between recurrent miscarriage and viral infection has been clearly confirmed in multiple studies. For example, some studies have pointed out that the dysfunction of PR-SET7 in the placenta may be related to various viral infection responses, suggesting that viral infections may affect the health and growth of the embryo. MITA, as a potential therapeutic target for viral infections and virus-related diseases, its relationship with recurrent miscarriage has also been focused on, implying that its functional changes may increase the risk of miscarriage [98]. Moreover, the activity of natural killer cells, especially in the early response to viral infections, is believed to be related to infertility and recurrent miscarriage. This further emphasizes that viral infections may affect the maternal immune response, thereby increasing the risk of miscarriage [99]. Viral infections during pregnancy can lead to adverse outcomes. Specifically, BK virus and recent dengue fever infections have been frequently mentioned in studies and are associated with poor pregnancy outcomes. For instance, one study pointed out that BK virus infection might have a negative impact on pregnancy outcomes, potentially due to the virus directly invading embryonic cells or affecting the maternal immune response [100]. Another study mentioned a correlation between recent dengue fever infections and miscarriages, which might be attributed to maternal inflammation or other physiological changes caused by the virus [101]. These research findings emphasize the significance of viral infections during pregnancy and their potential impacts on both embryonic and maternal health. In addition, viral infection may activate or suppress the maternal immune response, thereby adversely affecting the embryo. Virus-infected cells and free viral particles may have triggered an immune response detrimental to embryo survival [102]. Furthermore, viral infection may also cause maternal inflammation, which may indirectly adversely affect the health and development of the embryo [103]. In addition to viral infection, other factors such as the presence of antithyroid antibodies may also be associated with miscarriage, and these factors may act in conjunction with viral infection to increase the risk of miscarriage [104]. Overall, these studies collectively reveal how viral infections are related to recurrent miscarriage through various mechanisms, including affecting placental function, activating the immune system, and altering the uterine microenvironment [105].

AUTOIMMUNE DISEASES AND RECURRENT MISCARRIAGES

Some autoimmune conditions, notably systemic lupus erythematosus (SLE) and aantiphospholipid antibody syndrome, can intensify the body's inflammatory response, elevating the risk of recurrent miscarriages [106, 107].

The link between SLE and recurrent miscarriages has been firmly established through extensive academic research. Studies indicate that lupus anticoagulants, specific antibodies associated with SLE, have a pronounced correlation with recurrent miscarriages, especially among younger patients [108]. Furthermore, individuals with SLE face heightened risks during pregnancy, including spontaneous miscarriages, stillbirths, and fetal growth restrictions. This may be attributed to the immune system's aggressive response to the embryo in SLE patients [109]. Encouragingly, advancements in medical technology and refined disease management over recent decades have led to a decline in miscarriage rates among SLE patients [110]. Additionally, antiphospholipid antibodies, another set of antibodies linked to SLE, have associations not just with miscarriages and thrombocytopenia, but potentially with cardiac abnormalities as well [111]. This body of evidence underscores the

significant relationship between SLE and recurrent miscarriages, particularly in cases with a positive antiphospholipid antibody profile [112].

In the realm of research on recurrent miscarriages, the relationship between antiphospholipid antibody syndrome and miscarriages has been a focal point [113]. While some studies primarily address isolated miscarriages, they also highlight that recurrent miscarriages can be influenced by a myriad of factors, antiphospholipid antibodies being a notable one [112]. This suggests that aberrant immune responses might play a pivotal role in recurrent miscarriages. A specific study involving 50 women diagnosed with antiphospholipid (APS) syndrome revealed that treatments combined with heparin yielded more pronounced outcomes compared to just using low-dose aspirin [114]. This finding underscores the significance of tailored treatment approaches for antiphospholipid antibody syndrome. A comprehensive systematic review corroborated the distinct relationship between antiphospholipid antibodies and recurrent miscarriages, offering a range of effective therapeutic interventions [115]. Importantly, research has shown that pregnant women with untreated antiphospholipid antibodies face an elevated risk of fetal loss, reinforcing the direct connection between these antibodies and recurrent miscarriages [116]. A holistic review delved into the multifaceted causes of recurrent miscarriages, emphasizing the central role of antiphospholipid antibodies, while also shedding light on other potential risk factors, such as genetic, anatomical, and endocrine anomalies [117]. In summary, the collective findings from these studies present a compelling narrative: antiphospholipid antibody syndrome has a pronounced association with recurrent miscarriages, potentially due to the immune system's maladaptive response to the embryo. The overarching theme is clear — autoimmune disorders can significantly influence the likelihood of recurrent miscarriages. When the immune system inadvertently targets its own tissues and organs, it can have detrimental repercussions on pregnancy. Specific autoimmune reactions, especially antiphospholipid antibody syndrome, have been identified as key contributors to recurrent miscarriages.

LIFESTYLE AND ENVIRONMENTAL FACTORS

Factors such as smoking, obesity, and certain environmental pollutants are associated with increased inflammatory responses and a heightened risk of miscarriage [118]. Lifestyle and environmental elements play a pivotal role in the risk of recurrent miscarriages. According to a study, maternal BMI, smoking habits, and the level of urbanization can elevate oxidative stress in newborns, which is subsequently linked to miscarriage risks. Oxidative stress arises when there's an imbalance between free radicals and antioxidants in the body, leading to cellular damage [119]. Furthermore, habits like smoking and alcohol consumption have been proven to affect ovarian function and the quality of oocytes, thereby amplifying the risk of miscarriage [120, 121]. Environmental pollutants, such as heavy metals and organic pollutants, might elevate miscarriage risks by intensifying inflammatory responses. Notably, air pollution, especially fine particulate matter (PM2.5) and ozone, has been linked to various respiratory and cardiovascular diseases [122]. These pollutants might elevate miscarriage risks by inducing inflammatory responses and oxidative stress. Additionally, the quality of male sperm can also be influenced by environmental factors and lifestyle choices, potentially increasing the risk of miscarriage [123]. These factors might impact reproductive health and miscarriage risks by amplifying oxidative stress and inflammatory responses [124].

TREATMENT STRATEGIES

For recurrent miscarriages related to inflammation, some treatment strategies include the use of anti-inflammatory drugs, immunomodulatory therapies, or anticoagulant treatments. Recurrent miscarriage is a complex medical challenge with a myriad of underlying causes. In recent years, researchers have begun to focus on the role of inflammation in this context. Non-steroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen or aspirin have been proven to effectively mitigate inflammatory responses, potentially reducing the risk of miscarriage, as indicate [125, 126]. Additionally, immunoglobulin therapy has been shown to effectively modulate the maternal immune response, further decreasing the risk of miscarriage [127, 128]. For the specific condition of antiphospholipid antibody syndrome, the use of heparin combined with low-dose aspirin as a treatment strategy has been demonstrated to effectively reduce the risk of miscarriage [129, 130]. Moreover, studies related to complex regional pain syndrome have pointed out that the induction of TNF-α and IL-1β might be associated with recurrent miscarriages [131]. Oxidative stress in males, the diagnosis of chronic endometritis, the genetics of recurrent miscarriage, and diseases related to inflammation and coagulation are all linked to recurrent miscarriages [20, 132]. In conclusion, research on treatment strategies for recurrent miscarriages associated with inflammation provides valuable therapeutic methods and directions. However, further research is needed to refine and optimize these treatment strategies.

DISCUSSION

The relationship between inflammation and recurrent miscarriage has emerged as a focal point in the field of reproductive medicine. Changes in the endometrial microenvironment, imbalances in immune cells, infections,

and autoimmune diseases are all linked to inflammation, which can potentially impact embryo implantation and growth, leading to miscarriage. Specifically, an excessive inflammatory response can disrupt the receptive nature of the endometrial environment for embryo implantation. Moreover, lifestyle and environmental factors might exacerbate inflammation, further increasing the risk of miscarriage.

However, our understanding of the specific mechanisms by which inflammation leads to recurrent miscarriage remains limited. Future research should delve deeper into these mechanisms to provide more effective therapeutic strategies for patients. Additionally, considering the influence of lifestyle and environmental factors, preventive strategies are equally vital. By making lifestyle modifications, such as quitting smoking, limiting alcohol intake, and avoiding exposure to harmful environmental factors, the risk of recurrent miscarriage might be reduced.

Looking ahead, as our understanding deepens regarding how the endometrial microenvironment and immune cells interact with inflammation, we anticipate the development of more effective treatments, assisting women at risk of recurrent miscarriage in achieving successful pregnancies.

Article information and declarations

Author contributions

All authors contributed to the study conception and design. The first draft of the manuscript was written by Mengsi Lin and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Funding

This work was supported by the Municipal Health Commission of Nantong (Grant No: QA2021047).

Acknowledgments

We thank the associate editor and the reviewers for their useful feedback that improved this paper.

Conflict of interest

The authors declare that they have no conflict of interest.

REFERENCES

1. Rai R, Regan L. Recurrent miscarriage. The Lancet. 2006; 368(9535): 601–611, doi: 10.1016/s0140-6736(06)69204-0.
2. Eskandarian M, Moazzeni SM. Uterine Dendritic Cells Modulation by Mesenchymal Stem Cells Provides A Protective Microenvironment at The Feto-Maternal Interface: Improved Pregnancy Outcome in Abortion-Prone Mice. Cell J. 2019; 21(3): 274–280, doi: 10.22074/cellj.2019.6239, indexed in Pubmed: 31210433.
3. Wang W, Feng D, Ling B. Biologia Futura: endometrial microbiome affects endometrial receptivity from the perspective of the endometrial immune microenvironment. Biol Futur. 2022; 73(3): 291–300, doi: 10.1007/s42977-022-00134-3, indexed in Pubmed: 36161422.
4. Krieg S, Westphal L. Immune Function and Recurrent Pregnancy Loss. Semin Reprod Med. 2015; 33(4): 305–312, doi: 10.1055/s-0035-1554917, indexed in Pubmed: 26132935.
5. Vomstein K, Feil K, Strobel L, et al. Immunological Risk Factors in Recurrent Pregnancy Loss: Guidelines Versus Current State of the Art. J Clin Med. 2021; 10(4), doi: 10.3390/jcm10040869, indexed in Pubmed: 33672505.
6. Sharma R, Biedenharn KR, Fedor JM, et al. Lifestyle factors and reproductive health: taking control of your fertility. Reprod Biol Endocrinol. 2013; 11: 66, doi: 10.1186/1477-7827-11-66, indexed in Pubmed: 23870423.
7. Laird SM, Tuckerman EM, Cork BA, et al. A review of immune cells and molecules in women with recurrent miscarriage. Hum Reprod Update. 2003; 9(2): 163–174, doi: 10.1093/humupd/dmg013, indexed in Pubmed: 12751778.
8. Kwak-Kim J, Bao S, Lee SKi, et al. Immunological modes of pregnancy loss: inflammation, immune effectors, and stress. Am J Reprod Immunol. 2014; 72(2): 129–140, doi: 10.1111/aji.12234, indexed in Pubmed: 24661472.
9. Elder S, Bortoletto P, Romanski PA, et al. Chronic endometritis in women with suspected retained products of conception and their reproductive outcomes. Am J Reprod Immunol. 2021; 86(2): e13410, doi: 10.1111/aji.13410, indexed in Pubmed: 33644899.
10. Kasius JC, Fatemi HM, Bourgain C, et al. The impact of chronic endometritis on reproductive outcome. Fertil Steril. 2011; 96(6): 1451–1456, doi: 10.1016/j.fertnstert.2011.09.039, indexed in Pubmed: 22019126.
11. McQueen DB, Bernardi LA, Stephenson MD. Chronic endometritis in women with recurrent early pregnancy loss and/or fetal demise. Fertil Steril. 2014; 101(4): 1026–1030, doi: 10.1016/j.fertnstert.2013.12.031, indexed in Pubmed: 24462055.
12. McQueen DB, Perfetto CO, Hazard FK, et al. Pregnancy outcomes in women with chronic endometritis and recurrent pregnancy loss. Fertil Steril. 2015; 104(4): 927–931, doi: 10.1016/j.fertnstert.2015.06.044, indexed in Pubmed: 26207958.
13. Kimura F, Takebayashi A, Ishida M, et al. Review: Chronic endometritis and its effect on reproduction. J Obstet Gynaecol Res. 2019; 45(5): 951–960, doi: 10.1111/jog.13937, indexed in Pubmed: 30843321.
14. Bouet PE, El Hachem H, Monceau E, et al. Chronic endometritis in women with recurrent pregnancy loss and recurrent implantation failure: prevalence and role of office hysteroscopy and immunohistochemistry in diagnosis. Fertil Steril. 2016; 105(1): 106–110, doi: 10.1016/j.fertnstert.2015.09.025, indexed in Pubmed: 26456229.
15. Biberoglu E, Kirbas A, Daglar K, et al. Role of inflammation in intrahepatic cholestasis of pregnancy. J Obstet Gynaecol Res. 2016; 42(3): 252–257, doi: 10.1111/jog.12902, indexed in Pubmed: 26786878.
16. Moreno I, Cicinelli E, Garcia-Grau I, et al. The diagnosis of chronic endometritis in infertile asymptomatic women: a comparative study of histology, microbial cultures, hysteroscopy, and molecular microbiology. Am J Obstet Gynecol. 2018; 218(6): 602.e1–602.e16, doi: 10.1016/j.ajog.2018.02.012, indexed in Pubmed: 29477653.
17. Sirota I, Zarek SM, Segars JH. Potential influence of the microbiome on infertility and assisted reproductive technology. Semin Reprod Med. 2014; 32(1): 35–42, doi: 10.1055/s-0033-1361821, indexed in Pubmed: 24390919.
18. Hashimoto T, Kyono K. Does dysbiotic endometrium affect blastocyst implantation in IVF patients? J Assist Reprod Genet. 2019; 36(12): 2471–2479, doi: 10.1007/s10815-019-01630-7, indexed in Pubmed: 31741256.
19. Cicinelli E, Matteo M, Tinelli R, et al. Prevalence of chronic endometritis in repeated unexplained implantation failure and the IVF success rate after antibiotic therapy. Hum Reprod. 2015; 30(2): 323–330, doi: 10.1093/humrep/deu292, indexed in Pubmed: 25385744.
20. Bardos J, Fiorentino D, Longman RE, et al. Immunological Role of the Maternal Uterine Microbiome in Pregnancy: Pregnancies Pathologies and Alterated Microbiota. Front Immunol. 2019; 10: 2823, doi: 10.3389/fimmu.2019.02823, indexed in Pubmed: 31969875.
21. Liu J, Wu S, Wang ZK, et al. Effect of different antibiotic therapies on the reproductive outcomes of fresh embryo transfer for chronic endometritis: A retrospective cohort study. Am J Reprod Immunol. 2023; 89(3): e13669, doi: 10.1111/aji.13669, indexed in Pubmed: 36524676.
22. Liu J, Liu ZAi, Liu Y, et al. Impact of antibiotic treatment for chronic endometritis on pregnancy outcomes in women with reproductive failures (RIF and RPL): A systematic review and meta-analysis. Front Med (Lausanne). 2022; 9: 980511, doi: 10.3389/fmed.2022.980511, indexed in Pubmed: 36405621.

23. Zhang X, Wei H. Role of Decidual Natural Killer Cells in Human Pregnancy and Related Pregnancy Complications. Front Immunol. 2021; 12: 728291, doi: 10.3389/fimmu.2021.728291, indexed in Pubmed: 34512661.
24. Moffett A, Colucci F. Uterine NK cells: active regulators at the maternal-fetal interface. J Clin Invest. 2014; 124(5): 1872–1879, doi: 10.1172/JCI68107, indexed in Pubmed: 24789879.
25. Coppack SW. Pro-inflammatory cytokines and adipose tissue. Proc Nutr Soc. 2001; 60(3): 349–356, doi: 10.1079/pns2001110, indexed in Pubmed: 11681809.
26. Watkins LR, Maier SF, Goehler LE. Immune activation: the role of pro-inflammatory cytokines in inflammation, illness responses and pathological pain states. Pain. 1995; 63(3): 289–302, doi: 10.1016/0304-3959(95)00186-7, indexed in Pubmed: 8719529.
27. Johnson RW. Inhibition of growth by pro-inflammatory cytokines: an integrated view. J Anim Sci. 1997; 75(5): 1244–1255, doi: 10.2527/1997.7551244x, indexed in Pubmed: 9159271.
28. Hviid TV. HLA-G in human reproduction: aspects of genetics, function and pregnancy complications. Hum Reprod Update. 2006; 12(3): 209–232, doi: 10.1093/humupd/dmi048, indexed in Pubmed: 16280356.
29. Alijotas-Reig J, Esteve-Valverde E, Ferrer-Oliveras R, et al. Tumor Necrosis Factor-Alpha and Pregnancy: Focus on Biologics. An Updated and Comprehensive Review. Clin Rev Allergy Immunol. 2017; 53(1): 40–53, doi: 10.1007/s12016-016-8596-x, indexed in Pubmed: 28054230.
30. Abramiuk M, Grywalska E, Małkowska P, et al. The Role of the Immune System in the Development of Endometriosis. Cells. 2022; 11(13): 2028, doi: 10.3390/cells11132028, indexed in Pubmed: 35805112.
31. Lédée N, Petitbarat M, Prat-Ellenberg L, et al. The uterine immune profile: A method for individualizing the management of women who have failed to implant an embryo after IVF/ICSI. J Reprod Immunol. 2020; 142: 103207, doi: 10.1016/j.jri.2020.103207, indexed in Pubmed: 32971456.
32. Liu Y, Chen H, Feng L, et al. Interactions between gut microbiota and metabolites modulate cytokine network imbalances in women with unexplained miscarriage. NPJ Biofilms Microbiomes. 2021; 7(1): 24, doi: 10.1038/s41522-021-00199-3, indexed in Pubmed: 33731680.
33. Zhong Z, Wang Y, Wang G, et al. Case Report: TNF-Alpha Inhibitors to Rescue Pregnancy in Women With Potential Pregnancy Loss: A Report of Ten Cases. Front Immunol. 2022; 13: 900537, doi: 10.3389/fimmu.2022.900537, indexed in Pubmed: 35693803.
34. Banerjee P, Ghosh S, Dutta M, et al. Identification of key contributory factors responsible for vascular dysfunction in idiopathic recurrent spontaneous miscarriage. PLoS One. 2013; 8(11): e80940, doi: 10.1371/journal.pone.0080940, indexed in Pubmed: 24260517.
35. Jasper MJ, Tremellen KP, Robertson SA. Reduced expression of IL-6 and IL-1alpha mRNAs in secretory phase endometrium of women with recurrent miscarriage. J Reprod Immunol. 2007; 73(1): 74–84, doi: 10.1016/j.jri.2006.06.003, indexed in Pubmed: 17034864.
36. Mariee N, Li TC, Laird SM. Expression of leukaemia inhibitory factor and interleukin 15 in endometrium of women with recurrent implantation failure after IVF; correlation with the number of endometrial natural killer cells. Hum Reprod. 2012; 27(7): 1946–1954, doi: 10.1093/humrep/des134, indexed in Pubmed: 22537815.
37. Unfried G, Tempfer C, Schneeberger C, et al. Interleukin 1 receptor antagonist polymorphism in women with idiopathic recurrent miscarriage. Fertil Steril. 2001; 75(4): 683–687, doi: 10.1016/s0015-0282(01)01675-2, indexed in Pubmed: 11287019.
38. Pantos K, Grigoriadis S, Maziotis E, et al. The Role of Interleukins in Recurrent Implantation Failure: A Comprehensive Review of the Literature. Int J Mol Sci. 2022; 23(4), doi: 10.3390/ijms23042198, indexed in Pubmed: 35216313.
39. Tao Yu, Li YH, Piao HL, et al. CD56(bright)CD25+ NK cells are preferentially recruited to the maternal/fetal interface in early human pregnancy. Cell Mol Immunol. 2015; 12(1): 77–86, doi: 10.1038/cmi.2014.26, indexed in Pubmed: 24793405.
40. Xu X, Zhou Y, Wei H. Roles of HLA-G in the Maternal-Fetal Immune Microenvironment. Front Immunol. 2020; 11: 592010, doi: 10.3389/fimmu.2020.592010, indexed in Pubmed: 33193435.
41. Wei H, Liu Su, Lian R, et al. Abnormal Expression of Indoleamine 2, 3-Dioxygenase in Human Recurrent Miscarriage. Reprod Sci. 2020; 27(8): 1656–1664, doi: 10.1007/s43032-020-00196-5, indexed in Pubmed: 32430712.
42. Yang X, Tian Y, Zheng L, et al. The Update Immune-Regulatory Role of Pro- and Anti-Inflammatory Cytokines in Recurrent Pregnancy Losses. Int J Mol Sci. 2022; 24(1), doi: 10.3390/ijms24010132, indexed in Pubmed: 36613575.
43. Palomares O, Martín-Fontecha M, Lauener R, et al. Regulatory T cells and immune regulation of allergic diseases: roles of IL-10 and TGF-β. Genes Immun. 2014; 15(8): 511–520, doi: 10.1038/gene.2014.45, indexed in Pubmed: 25056447.
44. Sanjabi S, Zenewicz LA, Kamanaka M, et al. Anti-inflammatory and pro-inflammatory roles of TGF-beta, IL-10, and IL-22 in immunity and autoimmunity. Curr Opin Pharmacol. 2009; 9(4): 447–453, doi: 10.1016/j.coph.2009.04.008, indexed in Pubmed: 19481975.
45. Taylor A, Verhagen J, Blaser K, et al. Mechanisms of immune suppression by interleukin-10 and transforming growth factor-beta: the role of T regulatory cells. Immunology. 2006; 117(4): 433–442, doi: 10.1111/j.1365-2567.2006.02321.x, indexed in Pubmed: 16556256.
46. Nagaeva O, Jonsson L, Mincheva-Nilsson L. Dominant IL-10 and TGF-beta mRNA expression in gammadeltaT cells of human early pregnancy decidua suggests immunoregulatory potential. Am J Reprod Immunol. 2002; 48(1): 9–17, doi: 10.1034/j.1600-0897.2002.01131.x, indexed in Pubmed: 12322898.
47. Terzieva A, Dimitrova V, Djerov L, et al. Early Pregnancy Human Decidua is Enriched with Activated, Fully Differentiated and Pro-Inflammatory Gamma/Delta T Cells with Diverse TCR Repertoires. Int J Mol Sci. 2019; 20(3), doi: 10.3390/ijms20030687, indexed in Pubmed: 30764544.
48. Wang WJ, Hao CF, Qu QL, et al. The deregulation of regulatory T cells on interleukin-17-producing T helper cells in patients with unexplained early recurrent miscarriage. Hum Reprod. 2010; 25(10): 2591–2596, doi: 10.1093/humrep/deq198, indexed in Pubmed: 20685755.
49. Alkhuriji A, Omar SAl, Babay Z, et al. Association of *IL-1β*, *IL-6*, *TNF-α*, and *TGFβ1* Gene Polymorphisms with Recurrent Spontaneous Abortion in Polycystic Ovary Syndrome. Dis Markers. 2020; 2020: 1–8, doi: 10.1155/2020/6076274, indexed in Pubmed: 32454906.
50. Ma J, Zhang X, He G, et al. Association between TNF, IL1B, IL6, IL10 and IFNG polymorphisms and recurrent miscarriage: a case control study. Reprod Biol Endocrinol. 2017; 15(1): 83, doi: 10.1186/s12958-017-0300-3, indexed in Pubmed: 29017513.
51. Vesce F, Battisti C, Crudo M. The Inflammatory Cytokine Imbalance for Miscarriage, Pregnancy Loss and COVID-19 Pneumonia. Front Immunol. 2022; 13: 861245, doi: 10.3389/fimmu.2022.861245, indexed in Pubmed: 35359975.
52. Bagkou Dimakou D, Lissauer D, Tamblyn J, et al. Understanding human immunity in idiopathic recurrent pregnancy loss. Eur J Obstet Gynecol Reprod Biol. 2022; 270: 17–29, doi: 10.1016/j.ejogrb.2021.12.024, indexed in Pubmed: 35007974.
53. Niringiyumukiza JD, Cai H, Xiang W. Prostaglandin E2 involvement in mammalian female fertility: ovulation, fertilization, embryo development and early implantation. Reprod Biol Endocrinol. 2018; 16(1): 43, doi: 10.1186/s12958-018-0359-5, indexed in Pubmed: 29716588.
54. Mayoral Andrade G, Vásquez Martínez G, Pérez-Campos Mayoral L, et al. Molecules and Prostaglandins Related to Embryo Tolerance. Front Immunol. 2020; 11: 555414, doi: 10.3389/fimmu.2020.555414, indexed in Pubmed: 33329514.
55. Nannan Mi, Xiaoping L, Ying J. Periodontal disease in pregnancy and adverse pregnancy outcomes: Progress in related mechanisms and management strategies. Front Med (Lausanne). 2022; 9: 963956, doi: 10.3389/fmed.2022.963956, indexed in Pubmed: 36388896.
56. Zhang S, Lin H, Kong S, et al. Physiological and molecular determinants of embryo implantation. Mol Aspects Med. 2013; 34(5): 939–980, doi: 10.1016/j.mam.2012.12.011, indexed in Pubmed: 23290997.
57. Reyes L, Phillips P, Wolfe B, et al. and adverse pregnancy outcome. J Oral Microbiol. 2018; 10(1): 1374153, doi: 10.1080/20002297.2017.1374153, indexed in Pubmed: 29291034.
58. Wang W, Sung N, Gilman-Sachs A, et al. T Helper (Th) Cell Profiles in Pregnancy and Recurrent Pregnancy Losses: Th1/Th2/Th9/Th17/Th22/Tfh Cells. Front Immunol. 2020; 11: 2025, doi: 10.3389/fimmu.2020.02025, indexed in Pubmed: 32973809.
59. Lee JiY, Lee M, Lee SKi. Role of endometrial immune cells in implantation. Clin Exp Reprod Med. 2011; 38(3): 119–125, doi: 10.5653/cerm.2011.38.3.119, indexed in Pubmed: 22384430.
60. Huang N, Chi H, Qiao J. Role of Regulatory T Cells in Regulating Fetal-Maternal Immune Tolerance in Healthy Pregnancies and Reproductive Diseases. Front Immunol. 2020; 11: 1023, doi: 10.3389/fimmu.2020.01023, indexed in Pubmed: 32676072.
61. Tsuda S, Nakashima A, Shima T, et al. New Paradigm in the Role of Regulatory T Cells During Pregnancy. Front Immunol. 2019; 10: 573, doi: 10.3389/fimmu.2019.00573, indexed in Pubmed: 30972068.

62. Guerin LR, Prins JR, Robertson SA. Regulatory T-cells and immune tolerance in pregnancy: a new target for infertility treatment? Hum Reprod Update. 2009; 15(5): 517–535, doi: 10.1093/humupd/dmp004, indexed in Pubmed: 19279047.
63. Keller CC, Eikmans M, van der Hoorn MLP, et al. Recurrent miscarriages and the association with regulatory T cells; A systematic review. J Reprod Immunol. 2020; 139: 103105, doi: 10.1016/j.jri.2020.103105, indexed in Pubmed: 32199194.
64. Crosby DA, Glover LE, Brennan EP, et al. Dysregulation of the interleukin-17A pathway in endometrial tissue from women with unexplained infertility affects pregnancy outcome following assisted reproductive treatment. Hum Reprod. 2020; 35(8): 1875–1888, doi: 10.1093/humrep/deaa111, indexed in Pubmed: 32614049.
65. Pallmer K, Oxenius A. Recognition and Regulation of T Cells by NK Cells. Front Immunol. 2016; 7: 251, doi: 10.3389/fimmu.2016.00251, indexed in Pubmed: 27446081.
66. Jena MK, Nayak N, Chen K, et al. Role of Macrophages in Pregnancy and Related Complications. Arch Immunol Ther Exp (Warsz). 2019; 67(5): 295––309, doi: 10.1007/s00005-019-00552-7, indexed in Pubmed: 31286151.
67. Savva C, Copson E, Johnson PWM, et al. Obesity Is Associated with Immunometabolic Changes in Adipose Tissue That May Drive Treatment Resistance in Breast Cancer: Immune-Metabolic Reprogramming and Novel Therapeutic Strategies. Cancers (Basel). 2023; 15(9), doi: 10.3390/cancers15092440, indexed in Pubmed: 37173907.
68. Li D, Zheng L, Zhao D, et al. The Role of Immune Cells in Recurrent Spontaneous Abortion. Reprod Sci. 2021; 28(12): 3303–3315, doi: 10.1007/s43032-021-00599-y, indexed in Pubmed: 34101149.
69. Ding J, Yin T, Yan N, et al. FasL on decidual macrophages mediates trophoblast apoptosis: A potential cause of recurrent miscarriage. Int J Mol Med. 2019; 43(6): 2376–2386, doi: 10.3892/ijmm.2019.4146, indexed in Pubmed: 30942389.
70. Xie M, Li Y, Meng YZ, et al. Uterine Natural Killer Cells: A Rising Star in Human Pregnancy Regulation. Front Immunol. 2022; 13: 918550, doi: 10.3389/fimmu.2022.918550, indexed in Pubmed: 35720413.
71. Sharma S. Natural killer cells and regulatory T cells in early pregnancy loss. Int J Dev Biol. 2014; 58(2-4): 219–229, doi: 10.1387/ijdb.140109ss, indexed in Pubmed: 25023688.
72. Sfakianoudis K, Rapani A, Grigoriadis S, et al. The Role of Uterine Natural Killer Cells on Recurrent Miscarriage and Recurrent Implantation Failure: From Pathophysiology to Treatment. Biomedicines. 2021; 9(10): 1425, doi: 10.3390/biomedicines9101425, indexed in Pubmed: 34680540.
73. Woon EeV, Nikolaou D, MacLaran K, et al. Uterine NK cells underexpress KIR2DL1/S1 and LILRB1 in reproductive failure. Front Immunol. 2022; 13: 1108163, doi: 10.3389/fimmu.2022.1108163, indexed in Pubmed: 36713400.
74. Seshadri S, Sunkara SK. Natural killer cells in female infertility and recurrent miscarriage: a systematic review and meta-analysis. Hum Reprod Update. 2014; 20(3): 429–438, doi: 10.1093/humupd/dmt056, indexed in Pubmed: 24285824.
75. Quenby S, Kalumbi C, Bates M, et al. Prednisolone reduces preconceptual endometrial natural killer cells in women with recurrent miscarriage. Fertil Steril. 2005; 84(4): 980–984, doi: 10.1016/j.fertnstert.2005.05.012, indexed in Pubmed: 16213853.
76. Tang AW, Alfirevic Z, Turner MA, et al. Prednisolone Trial: Study protocol for a randomised controlled trial of prednisolone for women with idiopathic recurrent miscarriage and raised levels of uterine natural killer (uNK) cells in the endometrium. Trials. 2009; 10: 102, doi: 10.1186/1745-6215-10-102, indexed in Pubmed: 19903335.
77. El Hachem H, Crepaux V, May-Panloup P, et al. Recurrent pregnancy loss: current perspectives. Int J Womens Health. 2017; 9: 331–345, doi: 10.2147/IJWH.S100817, indexed in Pubmed: 28553146.
78. Faas MM, de Vos P. Uterine NK cells and macrophages in pregnancy. Placenta. 2017; 56: 44–52, doi: 10.1016/j.placenta.2017.03.001, indexed in Pubmed: 28284455.
79. Devvanshi H, Kachhwaha R, Manhswita A, et al. Immunological Changes in Pregnancy and Prospects of Therapeutic Pla-Xosomes in Adverse Pregnancy Outcomes. Front Pharmacol. 2022; 13: 895254, doi: 10.3389/fphar.2022.895254, indexed in Pubmed: 35517798.
80. Ishida Y, Zhao D, Ohkuchi A, et al. Maternal peripheral blood natural killer cells incorporate placenta-associated microRNAs during pregnancy. Int J Mol Med. 2015; 35(6): 1511–1524, doi: 10.3892/ijmm.2015.2157, indexed in Pubmed: 25824636.
81. Kalkunte SS, Mselle TF, Norris WE, et al. Vascular endothelial growth factor C facilitates immune tolerance and endovascular activity of human uterine NK cells at the maternal-fetal interface. J Immunol. 2009; 182(7): 4085–4092, doi: 10.4049/jimmunol.0803769, indexed in Pubmed: 19299706.
82. Ghafourian M, Karami N, Khodadadi A, et al. Increase of CD69, CD161 and CD94 on NK cells in women with recurrent spontaneous abortion and in vitro fertilization failure. Iran J Immunol. 2014; 11(2): 84–96, indexed in Pubmed: 24975965.
83. Moffett-King A. Natural killer cells and pregnancy. Nat Rev Immunol. 2002; 2(9): 656–663, doi: 10.1038/nri886, indexed in Pubmed: 12209134.
84. Lash GE, Schiessl B, Kirkley M, et al. Expression of angiogenic growth factors by uterine natural killer cells during early pregnancy. J Leukoc Biol. 2006; 80(3): 572–580, doi: 10.1189/jlb.0406250, indexed in Pubmed: 16816146.
85. Saghian R, Bogle G, James JL, et al. Establishment of maternal blood supply to the placenta: insights into plugging, unplugging and trophoblast behaviour from an agent-based model. Interface Focus. 2019; 9(5): 20190019, doi: 10.1098/rsfs.2019.0019, indexed in Pubmed: 31485310.
86. Robson A, Harris LK, Innes BA, et al. Uterine natural killer cells initiate spiral artery remodeling in human pregnancy. FASEB J. 2012; 26(12): 4876–4885, doi: 10.1096/fj.12-210310, indexed in Pubmed: 22919072.
87. Pollheimer J, Vondra S, Baltayeva J, et al. Regulation of Placental Extravillous Trophoblasts by the Maternal Uterine Environment. Front Immunol. 2018; 9: 2597, doi: 10.3389/fimmu.2018.02597, indexed in Pubmed: 30483261.
88. Mahajan D, Sharma N, Kancharla S, et al. Role of Natural Killer Cells during Pregnancy and Related Complications. Biomolecules. 2022; 12(1): 68, doi: 10.3390/biom12010068, indexed in Pubmed: 35053216.
89. Walton EL. The inflammasome: Friend or foe in Chlamydia infection? Biomed J. 2016; 39(5): 299–303, doi: 10.1016/j.bj.2016.10.003, indexed in Pubmed: 27884375.
90. Grewal K, Lee YS, Smith A, et al. Chromosomally normal miscarriage is associated with vaginal dysbiosis and local inflammation. BMC Med. 2022; 20(1): 38, doi: 10.1186/s12916-021-02227-7, indexed in Pubmed: 35090453.
91. Buzzaccarini G, Vitagliano A, Andrisani A, et al. Chronic endometritis and altered embryo implantation: a unified pathophysiological theory from a literature systematic review. J Assist Reprod Genet. 2020; 37(12): 2897–2911, doi: 10.1007/s10815-020-01955-8, indexed in Pubmed: 33025403.
92. Cicinelli E, Matteo M, Tinelli R, et al. Chronic endometritis due to common bacteria is prevalent in women with recurrent miscarriage as confirmed by improved pregnancy outcome after antibiotic treatment. Reprod Sci. 2014; 21(5): 640–647, doi: 10.1177/1933719113508817, indexed in Pubmed: 24177713.
93. Khedkar R, Pajai S. Bacterial Vaginosis: A Comprehensive Narrative on the Etiology, Clinical Features, and Management Approach. Cureus. 2022; 14(11): e31314, doi: 10.7759/cureus.31314, indexed in Pubmed: 36514655.
94. Turesheva A, Aimagambetova G, Ukybassova T, et al. Recurrent Pregnancy Loss Etiology, Risk Factors, Diagnosis, and Management. Fresh Look into a Full Box. J Clin Med. 2023; 12(12), doi: 10.3390/jcm12124074, indexed in Pubmed: 37373766.
95. Malhotra M, Sood S, Mukherjee A, et al. Genital Chlamydia trachomatis: an update. Indian J Med Res. 2013; 138(3): 303–316, indexed in Pubmed: 24135174.
96. Pacchiarotti A, Sbracia M, Mohamed MA, et al. Autoimmune response to Chlamydia trachomatis infection and in vitro fertilization outcome. Fertil Steril. 2009; 91(3): 946–948, doi: 10.1016/j.fertnstert.2007.12.009, indexed in Pubmed: 18339387.
97. Baud D, Goy G, Jaton K, et al. Role of Chlamydia trachomatis in miscarriage. Emerg Infect Dis. 2011; 17(9): 1630–1635, doi: 10.3201/eid1709.100865, indexed in Pubmed: 21888787.
98. Racicot K, Mor G. Risks associated with viral infections during pregnancy. Journal of Clinical Investigation. 2017; 127(5): 1591–1599, doi: 10.1172/jci87490.
99. Moffett A, Regan L, Braude P. Natural killer cells, miscarriage, and infertility. BMJ. 2004; 329(7477): 1283–1285, doi: 10.1136/bmj.329.7477.1283, indexed in Pubmed: 15564263.
100. Giakoumelou S, Wheelhouse N, Cuschieri K, et al. The role of infection in miscarriage. Hum Reprod Update. 2016; 22(1): 116–133, doi: 10.1093/humupd/dmv041, indexed in Pubmed: 26386469.
101. Phupong V. Dengue fever in pregnancy: a case report. BMC Pregnancy Childbirth. 2001; 1(1): 7, doi: 10.1186/1471-2393-1-7, indexed in Pubmed: 11747474.

102. Cornish EF, Filipovic I, Åsenius F, et al. Innate Immune Responses to Acute Viral Infection During Pregnancy. Front Immunol. 2020; 11: 572567, doi: 10.3389/fimmu.2020.572567, indexed in Pubmed: 33101294.
103. Chudnovets A, Liu J, Narasimhan H, et al. Role of Inflammation in Virus Pathogenesis during Pregnancy. J Virol. 2020; 95(2), doi: 10.1128/JVI.01381-19, indexed in Pubmed: 33115865.
104. Thangaratinam S, Tan A, Knox E, et al. Association between thyroid autoantibodies and miscarriage and preterm birth: meta-analysis of evidence. BMJ. 2011; 342: d2616, doi: 10.1136/bmj.d2616, indexed in Pubmed: 21558126.
105. Heydarifard Z, Zadheidar S, Yavarian J, et al. Potential role of viral infections in miscarriage and insights into the underlying molecular mechanisms. Congenit Anom (Kyoto). 2022; 62(2): 54–67, doi: 10.1111/cga.12458, indexed in Pubmed: 34961973.
106. Di Prima FAF, Valenti O, Hyseni E, et al. Antiphospholipid Syndrome during pregnancy: the state of the art. J Prenat Med. 2011; 5: 41–53, indexed in Pubmed: 22439075.
107. Gao R, Zeng X, Qin L. Systemic autoimmune diseases and recurrent pregnancy loss: research progress in diagnosis and treatment. Chin Med J (Engl). 2021; 134(17): 2140–2142, doi: 10.1097/CM9.0000000000001691, indexed in Pubmed: 34432653.
108. Marder W. Update on pregnancy complications in systemic lupus erythematosus. Curr Opin Rheumatol. 2019; 31(6): 650–658, doi: 10.1097/BOR.0000000000000651, indexed in Pubmed: 31464707.
109. Gluhovschi C, Gluhovschi G, Petrica L, et al. Pregnancy Associated with Systemic Lupus Erythematosus: Immune Tolerance in Pregnancy and Its Deficiency in Systemic Lupus Erythematosus--An Immunological Dilemma. J Immunol Res. 2015; 2015: 241547, doi: 10.1155/2015/241547, indexed in Pubmed: 26090485.
110. Clark CA, Spitzer KA, Laskin CA. Decrease in pregnancy loss rates in patients with systemic lupus erythematosus over a 40-year period. J Rheumatol. 2005; 32(9): 1709–1712, indexed in Pubmed: 16142865.
111. Ruiz D, Oates JC, Kamen DL. Antiphospholipid Antibodies and Heart Valve Disease in Systemic Lupus Erythematosus. Am J Med Sci. 2018; 355(3): 293–298, doi: 10.1016/j.amjms.2017.07.007, indexed in Pubmed: 29549933.
112. Santos Td, Ieque AL, de Carvalho HC, et al. Antiphospholipid syndrome and recurrent miscarriage: A systematic review and meta-analysis. J Reprod Immunol. 2017; 123: 78–87, doi: 10.1016/j.jri.2017.09.007, indexed in Pubmed: 28985591.
113. Vinatier D, Dufour P, Cosson M, et al. Antiphospholipid syndrome and recurrent miscarriages. Eur J Obstet Gynecol Reprod Biol. 2001; 96(1): 37–50, doi: 10.1016/s0301-2115(00)00404-8, indexed in Pubmed: 11311759.
114. Kutteh WH. Antiphospholipid antibody-associated recurrent pregnancy loss: treatment with heparin and low-dose aspirin is superior to low-dose aspirin alone. Am J Obstet Gynecol. 1996; 174(5): 1584–1589, doi: 10.1016/s0002-9378(96)70610-5, indexed in Pubmed: 9065133.
115. Empson M, Lassere M, Craig J, et al. Prevention of recurrent miscarriage for women with antiphospholipid antibody or lupus anticoagulant. Cochrane Database Syst Rev. 2005; 2005(2): CD002859, doi: 10.1002/14651858.CD002859.pub2, indexed in Pubmed: 15846641.
116. Abdullahi ZG, Abdul MA, Aminu SM, et al. Antiphospholipid antibodies among pregnant women with recurrent fetal wastage in a tertiary hospital in Northern Nigeria. Ann Afr Med. 2016; 15(3): 133–137, doi: 10.4103/1596-3519.188894, indexed in Pubmed: 27549418.
117. Alijotas-Reig J, Garrido-Gimenez C. Current concepts and new trends in the diagnosis and management of recurrent miscarriage. Obstet Gynecol Surv. 2013; 68(6): 445–466, doi: 10.1097/OGX.0b013e31828aca19, indexed in Pubmed: 23942472.
118. Ghimire PR, Akombi-Inyang BJ, Tannous C, et al. Association between obesity and miscarriage among women of reproductive age in Nepal. PLoS One. 2020; 15(8): e0236435, doi: 10.1371/journal.pone.0236435, indexed in Pubmed: 32760090.
119. Moore TA, Ahmad IM, Schmid KK, et al. Oxidative Stress Levels Throughout Pregnancy, at Birth, and in the Neonate. Biol Res Nurs. 2019; 21(5): 485––494, doi: 10.1177/1099800419858670, indexed in Pubmed: 31284724.
120. Ardalić D, Stefanović A, Kotur-Stevuljević J, et al. The influence of maternal smoking habits before pregnancy and antioxidative supplementation during pregnancy on oxidative stress status in a non-complicated pregnancy. Adv Clin Exp Med. 2014; 23(4): 575–583, doi: 10.17219/acem/37226, indexed in Pubmed: 25166442.
121. Firns S, Cruzat VF, Keane KN, et al. The effect of cigarette smoking, alcohol consumption and fruit and vegetable consumption on IVF outcomes: a review and presentation of original data. Reprod Biol Endocrinol. 2015; 13: 134, doi: 10.1186/s12958-015-0133-x, indexed in Pubmed: 26669322.
122. Grippo A, Zhang J, Chu Li, et al. Air pollution exposure during pregnancy and spontaneous abortion and stillbirth. Rev Environ Health. 2018; 33(3): 247–264, doi: 10.1515/reveh-2017-0033, indexed in Pubmed: 29975668.
123. Martins Costa Gomes G, Karmaus W, Murphy VE, et al. Environmental Air Pollutants Inhaled during Pregnancy Are Associated with Altered Cord Blood Immune Cell Profiles. Int J Environ Res Public Health. 2021; 18(14), doi: 10.3390/ijerph18147431, indexed in Pubmed: 34299892.
124. Magnus MC, Hockey RL, Håberg SE, et al. Pre-pregnancy lifestyle characteristics and risk of miscarriage: the Australian Longitudinal Study on Women's Health. BMC Pregnancy Childbirth. 2022; 22(1): 169, doi: 10.1186/s12884-022-04482-9, indexed in Pubmed: 35232386.
125. Bindu S, Mazumder S, Bandyopadhyay U. Non-steroidal anti-inflammatory drugs (NSAIDs) and organ damage: A current perspective. Biochem Pharmacol. 2020; 180: 114147, doi: 10.1016/j.bcp.2020.114147, indexed in Pubmed: 32653589.
126. Li DK, Liu L, Odouli R. Exposure to non-steroidal anti-inflammatory drugs during pregnancy and risk of miscarriage: population based cohort study. BMJ. 2003; 327(7411): 368, doi: 10.1136/bmj.327.7411.368, indexed in Pubmed: 12919986.
127. Shi Y, Tan D, Hao B, et al. Efficacy of intravenous immunoglobulin in the treatment of recurrent spontaneous abortion: A systematic review and meta-analysis. Am J Reprod Immunol. 2022; 88(5): e13615, doi: 10.1111/aji.13615, indexed in Pubmed: 36029201.
128. Habets DHJ, Pelzner K, Wieten L, et al. Intravenous immunoglobulins improve live birth rate among women with underlying immune conditions and recurrent pregnancy loss: a systematic review and meta-analysis. Allergy Asthma Clin Immunol. 2022; 18(1): 23, doi: 10.1186/s13223-022-00660-8, indexed in Pubmed: 35277202.
129. Hamulyák EN, Scheres LJj, Marijnen MC, et al. Aspirin or heparin or both for improving pregnancy outcomes in women with persistent antiphospholipid antibodies and recurrent pregnancy loss. Cochrane Database Syst Rev. 2020; 5(5): CD012852, doi: 10.1002/14651858.CD012852.pub2, indexed in Pubmed: 32358837.
130. Baiazid L, Hraib M. Effects of low-dose aspirin and heparin on the pregnancy outcome in women with antiphospholipid syndrome. Ann Med Surg (Lond). 2022; 83: 104807, doi: 10.1016/j.amsu.2022.104807, indexed in Pubmed: 36389195.
131. Talukdar A, Rai R, Aparna Sharma K, et al. Peripheral Gamma Delta T cells secrete inflammatory cytokines in women with idiopathic recurrent pregnancy loss. Cytokine. 2018; 102: 117–122, doi: 10.1016/j.cyto.2017.07.018, indexed in Pubmed: 28802663.
132. Agarwal A, Rana M, Qiu E, et al. Role of oxidative stress, infection and inflammation in male infertility. Andrologia. 2018; 50(11): e13126, doi: 10.1111/and.13126, indexed in Pubmed: 30569652.