



T Cell Exhaustion and Immune Dysfunction in Spontaneous Abortion: A Targeted Review

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Authors' contributions

This work was carried out in collaboration among all authors. Authors WW and GB conceived the idea. Authors WW, GB, JS and HM performed a literature search. All authors reviewed and made significant contributions to finalise the manuscript and agreed to the submission of this manuscript for consideration. All authors read and approved the final manuscript.

Article Information

DOI: <https://doi.org/10.9734/aji/2025/v8i1170>

Open Peer Review History:

This journal follows the Advanced Open Peer Review policy. Identity of the Reviewers, Editor(s) and additional Reviewers, peer review comments, different versions of the manuscript, comments of the editors, etc, are available here: <https://pr.sdiarticle5.com/review-history/139815>

Review Article

**Received: 10/05/2025
Published: 15/07/2025**

ABSTRACT

Background: Immune tolerance is established between the foetus and the mother in normal pregnancies. However, this tolerance may be breached, resulting in undesired pregnancy outcomes such as spontaneous abortion, foetal anomalies, and maternal complications. Reported

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studies suggest a potential link between immune response and unplanned pregnancy termination. A comprehensive understanding of immune responses in pregnancy loss harbours the potential to control the associated mechanisms.

Objective: This review synthesised existing studies on T cell exhaustion (TCE) in spontaneous abortion and pregnancy complications.

Methodology: A comprehensive database search from Scopus, Google Scholar, PubMed, and Web of Science identified 21 eligible studies that reported original data on spontaneous abortion and pregnancy complications and TCE.

Results: The review has shown that TCE is common in spontaneous abortion, characterised by the upregulation of inhibitory receptors and a suboptimal or lack of T-cells to perform their normal functions, such as proliferation, cytokine production, and cytotoxicity. Decreased expression of PD-1, LAG-3 and Tim-3 may contribute to an enhanced inflammatory response. Increased proportions of Th1 and Th17 cells are associated with pro-inflammatory responses and decreased immune regulatory function, resulting from altered PD-1/PD-L1 expression, which may contribute to pregnancy loss. Decreased anti-inflammatory cytokines (TGF- β 1, IL-10, and IL-4) promote an imbalanced homeostasis, which can lead to pregnancy loss. These anomalies are partly anchored on chronic antigen exposure, oxidative stress, and hormonal changes, phenomena frequently associated with recurrent spontaneous abortion or poor pregnancy outcomes.

Conclusion: Optimal modulation of immune response to control TCE may prevent or minimise the occurrence of spontaneous abortion and promote successful pregnancies.

Keywords: T cell exhaustion; immune exhaustion; spontaneous abortion; pregnancy; immune regulation; reproductive immunology; systematic review.

1. INTRODUCTION

Pregnancy is a complex immune state where tolerance and immune activation coexist (Hu et al., 2016). Despite its prevalence, the mechanisms governing maternal-foetal immune tolerance remain unclear. Pregnancy failure affects approximately 15% of known pregnancies, with more than 50% attributed to immune tolerance defects (Kuon et al., 2015). Research has shown that natural killer cells expressing Tim-3 play a defensive role in the early stages of pregnancy, promoting immunosuppressive activities and the induction of regulatory T cells (Kuon et al., 2015).

Spontaneous abortion, also known as miscarriage, is the unplanned termination of a pregnancy before the foetus can survive outside the womb, typically before the 20th week of gestation (Miller et al., 2020). Spontaneous abortion can occur due to various reasons, including chromosomal abnormalities, hormonal imbalance, infections, immune system disorders, uterine or cervical abnormalities, and advanced maternal age, among others (Miller et al., 2020). Spontaneous abortion, affecting close to 30% of pregnancies, is a common complication, with recurrent pregnancy loss affecting 1 in 100 women (Miller et al., 2020). While chromosomal abnormalities and thrombotic complications are established causes, immunologic factors, such

as T-cell exhaustion, have also been implicated (Miller et al., 2020).

Programmed Cell Death Protein 1 (PD-1), T Cell Immunoglobulin and Mucin-Domain Containing-3 (TIM-3), and Cytotoxic T-lymphocyte-associated Protein 4 (CTLA-4) are critical immune checkpoint receptors (Catakovic et al., 2017). Their dysregulation can contribute to spontaneous abortion by disrupting immune tolerance during pregnancy. These markers maintain a balance of T helper cells (Th1/Th2) and regulatory T cells (Tregs), along with their respective cytokines, which are essential for pregnancy success (Li et al., 2017). Altered expression of these markers can lead to T-cell exhaustion and recurrent miscarriages, underscoring their importance in maintaining the delicate balance of the maternal-foetal immune system (Li et al., 2020).

This systematic review synthesised existing literature on TCE in spontaneous abortion and pregnancy, exploring its prevalence, mechanisms, and clinical implications to identify knowledge gaps and areas for future research.

2. METHODOLOGY

2.1 Study Design

This systematic review spanned from January 2014 to March 2024, adhering to the PRISMA

2020 guidelines for a comprehensive and transparent approach. The research process involved a structured identification, screening, eligibility, and inclusion framework conducted independently to minimise errors and bias. Studies were selected based on their relevance to understanding T cell exhaustion in pregnancy, with a focus on peer-reviewed journals. Data extraction encompassed T cell functionality, inhibitory receptor expression, cytokine profiles, and outcomes related to spontaneous abortion. Furthermore, a comprehensive review of animal models and clinical studies was conducted to gain a deeper insight into the role of T cell exhaustion in spontaneous abortion and pregnancy complications, providing a more complete understanding of this complex phenomenon.

2.2 Search Strategy

A systematic literature search was conducted, encompassing a range of databases, including Scopus, Google Scholar, PubMed, and Web of Science, to identify and synthesise the findings of previous studies.

Applicable keywords, utilising Medical Subject Headings (MeSH) for PubMed, were combined using logical operators to develop a comprehensive search strategy. A combination of keywords from the title was used to construct Boolean search strings (“T cell exhaustion”) OR (“Immune exhaustion”) AND (“Spontaneous abortion”) OR (“Miscarriage”) AND (“Pregnancy”) in order to search and identify relevant studies. This methodology ensured a rigorous and systematic approach to understanding T cell exhaustion in the context of spontaneous abortion and pregnancy.

2.3 Inclusion Criteria

Available studies and data were included based on the following predefined criteria: (1) original research papers published between January 2014 and March 2024, (2) experimental and Observational studies, (3) availability of full text, and (4) articles written and published in English.

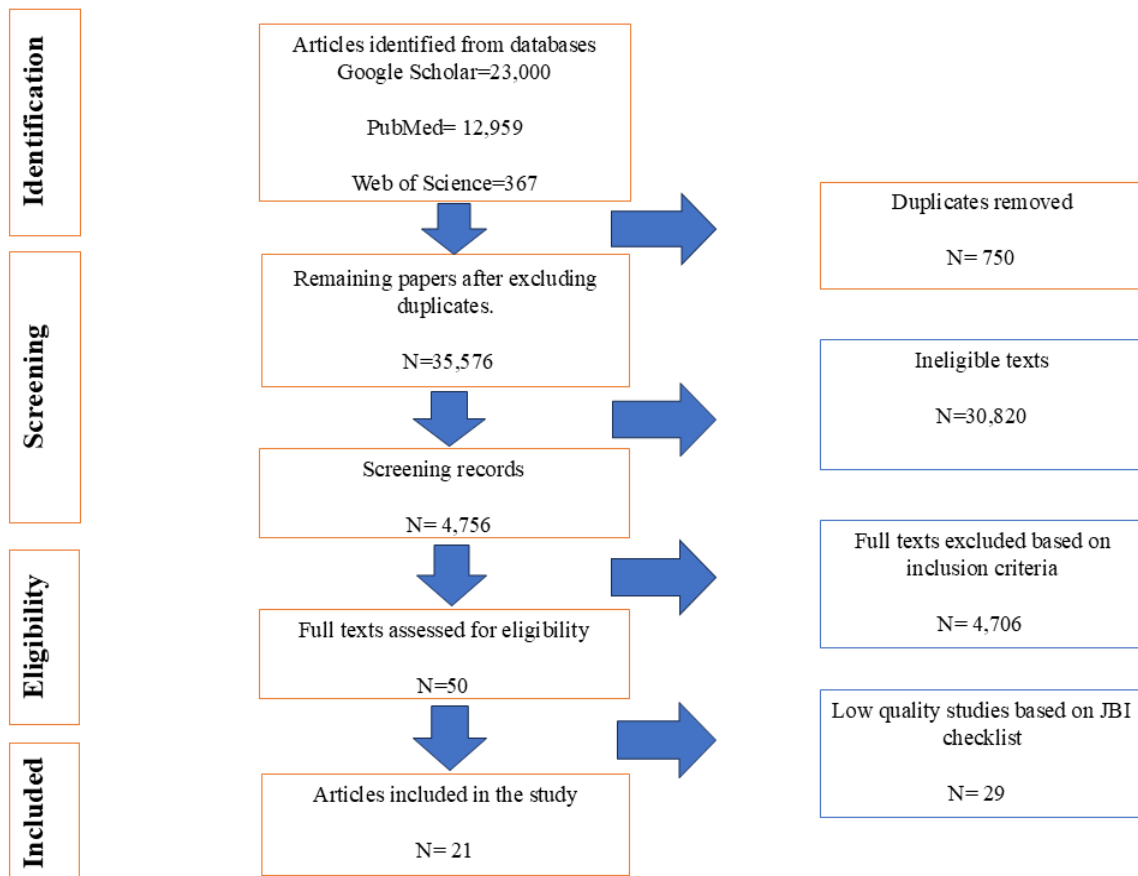


Fig. 1. Schematic flow diagram of the study retrieval process

Table 1. Summary of included articles. RSA: recurrent spontaneous abortion: RSA is defined as three or more consecutive spontaneous miscarriages before the 22nd week of gestation; WRSA: women with RSA; IPL: induced pregnancy loss; HC-P: healthy control pregnant; HC-NP: healthy control non-pregnant; decidual macrophages- M ϕ s; NK-cells: natural killer cells

Authors; Year	Population Characteristics	T-Cells & Exhaustion Markers	Practical implications
Observational			
(Zych et al., 2024)	N = 50; 20 = WRSA, 20 = HC-P, and 10 = HC-NP	RSA women exhibit decreased expression of PD-1 and LAG-3 on various T cells and increased expression of TIGIT on NKT cells.	<ul style="list-style-type: none"> The decreased expression of PD-1 and LAG-3 may contribute to an enhanced inflammatory response. In women with RSA, elevated TIGIT expression on NKT cells compensates for reduced PD-1 and LAG-3 expression.
(Zargar et al.,2024)	N = 57; 22 = WRSA, 18 = recurrent implantation failure, and 17 = HC-P	The mean numbers of NK cells (CD16+ and CD56+) and IFN- γ levels were significantly higher in the RSA	<ul style="list-style-type: none"> A significant correlation was found between the levels of IFN-γ and NK cells in the RPL group, indicating that immune dysfunction and IFN-related cytotoxicity may contribute to pregnancy loss.
(Zhang et al., 2022)	N=98, 17 = WRSA, 81 HC-P	Decreased levels of Tim-3+ peripheral NK-cells and PD-1 in women with miscarriage	<ul style="list-style-type: none"> Lower Tim-3 levels in WRSA cases may indicate poor immune adaptation to pregnancy, suggesting Tim-3 could be a marker for predicting miscarriage risk.
(Talukdar et al., 2018)	N = 43; 26 women with idiopathic recurrent pregnancy loss (RPL) and 17 healthy fertile controls	Significantly elevated frequencies of $\gamma\delta$ T cells correspond to elevated IFN- γ and TNF- α , but decreased IL-10, in RPLs.	<ul style="list-style-type: none"> These findings suggest a shift in $\gamma\delta$ T cell cytokine profile toward a pro-inflammatory phenotype, which may contribute to immune dysregulation and pregnancy failure in women with idiopathic recurrent pregnancy loss.
(Zych et al., 2021)	N = 36, 24 = WRSA, 12 = HC-P	Elevated PD-1 expression was observed on T helper (CD4+) cells in WRSA, while TIM-3 expression was decreased on T cytotoxic (CD8+) cells.	<ul style="list-style-type: none"> The dysregulation of the maternal immune system in RSA is characterised by a shift towards a Th1 cytokine profile and increased cytotoxicity, which may contribute to pregnancy loss.
(Liu et al., 2021)	N = 150; 50 = WRSA, 50 = HC-P and 50 = HC-NP	WRSA had increased naïve CD4+ T cells, central memory CD4+ T cells, and mature NK cells, while terminally differentiated CD4+ T cells and effective memory CD4+ T cells were decreased.	<ul style="list-style-type: none"> Higher naïve CD4+ T cells may weaken the immune system, while increased central memory CD4+ T cells suggest altered immune responses. Elevated mature NK cells can cause cytotoxic effects, potentially leading to pregnancy loss. Decreased terminally differentiated and effective memory, CD4+ T cells, indicate reduced

Authors; Year	Population Characteristics	T-Cells & Exhaustion Markers	Practical implications
(Wang et al., 2020)	N=65; 45 =WRSA; 20 = HC-P	Increased Th1 and Th17 cells, and decreased regulatory Treg cells, were associated with a significant decrease in the expression of PD-1 on Th1 and Th17 cells in WRSA.	immune protection and a weaker response to pregnancy-related antigens. <ul style="list-style-type: none"> Increased proportions of Th1 and Th17 cells are associated with pro-inflammatory responses and decreased immune regulatory function due to altered PD-1/PD-L1 expression, which may have led to pregnancy loss.
(Zhu et al., 2019)	N=68; 33 = WRSA; 35 = HC-P	WRSA exhibits an activated immune system, characterised by high levels of cytotoxic NK cells and low levels of immunoregulatory IL-10+ CD56bright NK cells. NK cells also spontaneously produce a high amount of TGFβ1.	<ul style="list-style-type: none"> This indicates a persistent inflammatory response that cannot be efficiently counter-regulated. This suggests that down-regulating the cytotoxic immune response and enhancing immunoregulatory mechanisms could be beneficial for WRSA
(Abdolmohammadi Vahid et al., 2019)	N= 100; 50 = WRSA and 50 = HC-P	Treg and exhausted T cells were decreased, while Th17 and exhausted Treg cells were increased in WRSA.	<ul style="list-style-type: none"> The decrease in Treg cells and exhausted T-cells suggests a failure in the regulatory mechanisms that prevent the maternal immune system from attacking the foetus. Increase in Th17 and exhausted Treg cells indicates a shift towards a pro-inflammatory immune environment.
(Qian et al., 2018)	N = 75; 37 = WRSA, 38 = HC-P	WRSA has a higher Th17/Treg cell ratio at the maternal-foetal interface compared to women with normal pregnancies	<ul style="list-style-type: none"> WRSA exhibited elevated pro-inflammatory cytokine levels due to the skewed Th17/Treg cell ratio at the maternal-foetal interface, contributing to immune tolerance failure in WRSA.
(Kuon et al., 2015)	N = 123; 97 = WRSA; 26 = HC-NP	WRSA showed higher levels of activated T-cells (CD3+DR+, CD4+DR+, and CD8+DR+) that were less responsive to mitogens than the controls. A significant increase in neopterin levels and Lower levels of CD16+CD56+ NK cells and CD19+ B lymphocytes	<ul style="list-style-type: none"> The chronic activation of T-cells and the deficiency in NK and B-cells in WRSA may contribute to the inability of the maternal immune system to tolerate the developing foetus, leading to miscarriage.

Authors; Year	Population Characteristics	T-Cells & Exhaustion Markers	Practical implications
Experimental			
(Li et al., 2022)	N = 135, 40 = WRSA, 86 HC-P, 9 HC-NP	Tim-3 expression is significantly decreased in WRSA, while it is increased in normal pregnancies.	<ul style="list-style-type: none"> Decreased Tim-3 results in the dysfunction of dMφs, which leads to an increase in pro-inflammatory cytokines and a decrease in anti-inflammatory cytokines, subsequently increasing foetal loss.
(Huang et al., 2020)	N = 43; 8 = WRSA, 35 = HC-P	The proportion of CD69+CD103+ resident and memory T-cells is significantly higher in women with RSA than in HC-P.	<ul style="list-style-type: none"> The Resident Memory T-cells expressed high levels of chemokine receptors such as CXCR3 and CXCR6. They had an enhanced capacity to produce both effector cytokines, TNF-α and IFN-γ, which may have led to pregnancy loss.
(Liu et al., 2020)	200 specific pathogen-free female CBA/J mice	Decreased PD-1 and PD-L1 expression in the placenta and spleen	<ul style="list-style-type: none"> Thyroiditis in mice led to reduced PD-1 and PD-L1 expression in the placenta and spleen, resulting in a decrease in Treg cells and an increase in Th17 cells at the maternal-foetal interface, resulting in miscarriage.
(Luo et al., 2020)	N = 12; 60 WRSA and 60 HC-P	Decreased expression of FOXP3 both at the protein and mRNA levels and reduced frequency of CD4+CD25highCD127low/- regulatory T cells in patients with RSA	<ul style="list-style-type: none"> In WRSA, there is a reduction in the number and function of Tregs, which may lead to the immune system attacking the foetus, resulting in miscarriage.
(Yu et al., 2021)	N = 42; 10 = WRSA-P; 11 = RSA-UP; 11 = HC-P; 10 = HC-UP	RSA patients exhibit increased CD107a expression on gdT cells, a higher frequency of IL-17A-secreting Vδ2+ gdT cells, upregulated CCL8 expression, and enhanced infiltration of CD8+ T cells and M2 macrophages. Additionally, PD1 expressions on Vd2+ gdT cells are elevated in these patients.	<ul style="list-style-type: none"> Activated gdT cells, particularly those expressing CD107a and IL-17A, may contribute to inflammation at the maternal-foetal interface; these cells have an enhanced ability to kill other cells, potentially leading to RSA.
(Wang et al., 2019)	N = 37 18 Normal pregnancies 19 Abortion-prone model	Decreased frequency of splenic T cells co-expressing CTLA-4 and Tim-3 in miscarriage models	<ul style="list-style-type: none"> In the Abortion Prone Model, there is a decrease in splenic T cells co-expressing CTLA-4 and Tim-3, which is linked to changes in cytokine; there is an increase in

Authors; Year	Population Characteristics	T-Cells & Exhaustion Markers	Practical implications
(Li et al., 2017)	N = 18; 10 = WRSA, HC-P = 8	Tim-3+ NK cells from WRSA produce fewer anti-inflammatory cytokines and have increased cytotoxicity compared to those from normal pregnancies	<p>pro-inflammatory cytokines (e.g., TNF-α) and a decrease in anti-inflammatory cytokines (e.g., IL-4, IL-10).</p> <ul style="list-style-type: none"> • Tim-3+ NK produces more anti-inflammatory cytokines (TGF-β1, IL-10, IL-4) and fewer pro-inflammatory cytokines (TNF-α), fostering immune tolerance, and WRSA produces fewer anti-inflammatory cytokines, resulting in pregnancy loss
(Xu et al., 2017)	N=18; 9 mice were normal, and nine were abortion-prone matings in the study.	Tim-3 and PD-1 pathways were blocked in pregnant mice.	<ul style="list-style-type: none"> • TIM-3 and PD-1 regulate CD8+ T cell function to maintain early pregnancy in mice • CD8+ T cells that co-express Tim-3 and PD-1 were reduced in the decidua of mice with abortion-prone matings • Blocking TIM-3 and PD-1 in normal pregnant mice led to increased foetal resorption
(Wang et al., 2016)	36 normal pregnant mice 45 abortion-prone mice	Decreased PD-1 and Tim-3 expression on CD4+ T cells in Abortion prone Mice.	<ul style="list-style-type: none"> • Blocking PD-1 and Tim-3 pathways in experimental models led to decreased Th2 cytokine production and increased foetal resorption.
(Sun et al., 2016)	N = 80; 20 = WRSA, 30 = HC-NP and 30 HC-P	Tim-3 levels are lower in NK cells from WRSA than in normal pregnancies. Tim-3 is more abundant in dNK cells during early pregnancy than pNK cells. Blocking Tim-3 reduces cytokine production in dNK cells.	<ul style="list-style-type: none"> • Tim-3 influences the production of cytokines like IFN-γ and TNF-α in dNK cells, essential for immune tolerance and vascular remodelling. • Tim-3's interaction with Galectin-9 inhibits NK cell cytotoxicity towards trophoblasts, preventing placental damage and supporting foetal development.

3. RESULTS AND DISCUSSION

3.1 Study Identification and Retrieval

Fig. 1 illustrates the step-by-step processes of identifying, retrieving, and selecting studies for this review. Our literature search yielded 23,000 articles from Google Scholar, 12,959 from PubMed, and 367 from Web of Science. After filtering to remove duplicates and irrelevant studies, 50 articles qualified for a thorough full-text evaluation. Upon further assessment, 21 of these studies met the predetermined inclusion criteria and were included in the review.

4. DISCUSSION

Recurrent Spontaneous Abortion (RSA) is a multifaceted condition where maternal immune dysregulation is a pivotal factor. Evidence consistently highlights an imbalance between pro-inflammatory and regulatory immune responses central to RSA pathophysiology. For example, reduced expression of immune checkpoints, such as PD-1 and Tim-3, on T cells—crucial for suppressing inflammation—has been observed in RSA cases, suggesting impaired immune tolerance at the maternal-foetal interface (Zych et al., 2021; Wang et al., 2020). Additionally, elevated levels of Th17 cells and a reduction in regulatory T cells (Tregs) further underscore a shift towards a pro-inflammatory immune environment that may lead to pregnancy loss (Vahid et al., 2018; Qian et al., 2018).

Natural Killer (NK) cells also exhibit substantial dysregulation in RSA. Studies have documented increased cytotoxic NK cell activity alongside reduced levels of immunoregulatory subsets, a combination that disrupts the immune balance essential for successful pregnancy (Zhu et al., 2019; Li et al., 2017). Gamma-delta T ($\gamma\delta$ T) cells, which produce high levels of IL-17A and express cytotoxic markers, contribute to this inflammatory milieu, further compromising pregnancy outcomes (Yu et al., 2021; Talukdar et al., 2018).

Dysregulation of decidual macrophages (dM ϕ s) and T cells is critical at the maternal-foetal interface. Reduced Tim-3 expression in these cells correlates with increased production of pro-inflammatory cytokines and decreased production of anti-inflammatory cytokines, ultimately contributing to foetal loss (Li et al., 2022; Xu et al., 2017). Experimental models underscore the significance of immune checkpoints, showing that blocking the Tim-3 or

PD-1 pathways exacerbates pregnancy loss by inducing inflammatory and cytotoxic responses (Wang et al., 2016; Xu et al., 2017).

The immunological environment in RSA is characterised by heightened inflammation and impaired regulatory mechanisms. Targeting immune checkpoints such as PD-1 and Tim-3 offers a promising therapeutic approach to restore immune balance and improve pregnancy outcomes in RSA patients.

5. FUTURE PERSPECTIVE

Potential therapeutic strategies for preventing spontaneous abortion include targeting T-cell exhaustion. This can be achieved by enhancing Treg function, blocking inhibitory receptors on T cells, and modulating cytokine environments to restore immune balance in pregnancy. Diagnostic markers for T cell exhaustion, such as the expression of inhibitory receptors and cytokine profiles, could help predict and prevent spontaneous abortion. Non-invasive diagnostic tools, such as blood tests or imaging techniques, could be developed to monitor immune status during pregnancy.

Future research should focus on elucidating the detailed mechanisms of T cell exhaustion in pregnancy, identifying additional biomarkers, and developing targeted therapies. Collaborative efforts between researchers, clinicians, and pharmaceutical companies will be crucial for translating experimental findings into clinical practice.

6. CONCLUSION

Studies have identified T-cell exhaustion as a significant contributor to spontaneous abortion. This phenomenon is characterised by reduced T cell functionality and proliferation in women who have experienced spontaneous abortion. Studies have shown that T cell exhaustion is characterised by a decrease in the expression of stimulatory receptors and an increase in the expression of suppressive receptors, making it challenging for T cells to respond to infections. This highlights the critical role of T-cell exhaustion in spontaneous abortion.

Regulatory T cells (Tregs) have been seen to play a vital role in maintaining immune homeostasis and preventing foetal rejection. However, women with a history of repeated unexplained pregnancy loss have been found to

have reduced Treg presence and functionality, which may contribute to spontaneous abortion.

Furthermore, T-cell exhaustion and an overactive immune response have been linked to spontaneous abortion. Modulating the immune response and preventing T-cell exhaustion may be potential therapeutic strategies to prevent spontaneous abortion and promote successful pregnancy outcomes. Decidual natural killer cells (dNK) have been found to play a crucial role in maintaining pregnancy and preventing spontaneous abortion. However, an imbalance in dNK cells, particularly an overactivation of dNK1 cells, may contribute to spontaneous abortion.

In conclusion, T cell exhaustion and immune modulation play a critical role in spontaneous abortion and recurrent pregnancy loss. Targeting these cell populations or their associated pathways may be a promising therapeutic strategy for preventing or treating pregnancy complications. Further research is needed to fully understand the mechanisms underlying T cell exhaustion and spontaneous abortion and to develop practical therapeutic approaches.

DISCLAIMER (ARTIFICIAL INTELLIGENCE)

Author(s) hereby declare that NO generative AI technologies such as Large Language Models (ChatGPT, COPILOT, etc.) and text-to-image generators have been used during the writing or editing of this manuscript.

CONSENT

It is not applicable.

ETHICAL APPROVAL

This systematic review did not necessitate ethical clearance, as it relied on previously published studies and research works freely accessible in the public domain, eliminating the need for additional ethical oversight.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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