

Review

## The role of myeloid differentiation of hematopoietic stem cells in pregnancy immunological tolerance: a systematic review

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### Article Info



#### Article history:

**Received:** January 19, 2024

**Accepted:** April 13, 2024

**Published:** June 30, 2024

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### Abstract

The present research aimed to conduct a comprehensive critical analysis of existing literature, focusing on the differentiation of myeloid cells from hematopoietic stem cells within the context of immunological tolerance during pregnancy. A comprehensive systematic review was conducted by searching databases including PubMed, Scopus Biomedicine, EBSCOhost, ScienceDirect, Embase, Cochrane Library, and Web of Science. The focus was on the role of myeloid differentiation from hematopoietic stem cells in modulating immune tolerance, particularly during pregnancy and in certain disease states where they act to suppress the immune response. The quality of the evidence gathered was assessed using the GRADE rating system. Our analysis maintains objectivity and independence from the outcomes presented. The current systematic review offers a synthesis of existing research on the transformation of hematopoietic stem cells into fibroblasts across different tissue types. A thorough search of databases such as PubMed, EBSCOhost, Embase, ScienceDirect, Cochrane Library, and Web of Science was performed in conjunction with a specialist in medical information to identify original research on the derivation of fibroblasts following hematopoietic stem cell transplantation. This search yielded a total of 159 studies, of which 10 met the criteria for inclusion in this review. Reflecting on the constraints of this preliminary review, further in-depth and scientific investigations are warranted to comprehensively assess the impact of varied treatments, with a recommendation for clinicians to proceed with increased circumspection. The myeloid differentiation pathway of hematopoietic stem cells is pivotal in modulating the immune environment during pregnancy, supporting the sustenance of a healthy gestational period. Future research in this domain is expected to advance our understanding of the immunological processes occurring at the maternal-fetal boundary.

**Keywords:** Myeloid, Hematopoietic stem cells, Pregnancy, Immunological tolerance

### 1. Introduction

A successful pregnancy necessitates a dynamic adjustment in the maternal immune system, fostering a state of immune tolerance to avoid rejecting the fetus. Concurrently, the maternal immune defense must remain vigilant against a spectrum of potential pathogens and diverse pathologies, including infections of viral and bacterial nature. This necessitates a finely tuned immune equilibrium to maintain a healthy pregnancy. Disruptions to this equilibrium may precipitate various complications, such as implantation failures, premature labor, preeclampsia, and restrictions in fetal development [1]. Immune responses are categorized into innate and adaptive defenses, with the former involving effector cells like myeloid and natural killer (NK) cells, complemented by the actions of the complement system. Hematopoietic stem cells (HSCs) contribute to this defense network through their inherent abilities for self-renewal and generating a spectrum of differentiated cells. Genetic anomalies within HSCs, whether inherited or acquired, can result in diverse hematological

disorders, affecting either the stem cells themselves or their cellular descendants. Given that such mutations are at the root of numerous hereditary hematologic conditions, therapeutic strategies targeting these HSC mutations hold potential for curative interventions [2].

Hematopoietic stem cells (HSCs) serve as the foundational elements of the hematopoietic system, preserving its integrity throughout an individual's lifespan. In the adult stage, HSCs intermittently enter an active cycle from a quiescent state to partake in asymmetric divisions, spawning a lineage of multipotent and unipotent progenitors. These progenitors are instrumental in the continuous generation of diverse blood and immune cells. As organisms age, the diversity within the HSC and progenitor cell populations broadens, with a bias in differentiation typically skewing towards either myeloid or lymphoid lineages, yet still upholding long-term hematopoiesis. The reservoir of genuinely multipotent HSCs diminishes over time. Concurrently, age-associated deficits in DNA repair mechanisms culminate in the accrual of mutations, alongside

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Doi: <http://dx.doi.org/10.14715/cmb/2024.70.6.30>

alterations at the epigenetic, transcriptomic, and proteomic levels, leading to metabolic imbalances and perturbations in the differentiation pathways of HSCs [3].

The hematopoietic process facilitates the expansion and mobilization of hematopoietic stem cells (HSCs) in non-bone marrow sites such as the spleen, which leads to an augmented HSC count and amplified blood cell production. While the regulatory mechanisms of HSCs during homeostasis are well-documented, recent studies have shed light on how HSCs adaptively respond to augment the hematopoietic system in various physiological states, including pregnancy [4]. Concurrently, the maternal immune system not only defends against pathogenic threats but also engages in multiple immune tolerance strategies to support the in-utero development of the semi-allogenic fetus [5]. Additionally, HSCs possess the distinctive capability for self-renewal and differentiation into an array of cell types necessary for sustaining and reconstituting the hematopoietic system [6].

## 2. Methods

The methodology section of this analysis provides a synopsis of the approaches employed. To hone the selection criteria for our systematic review, the PICO framework—encompassing Population, Intervention, Comparison, and Outcomes—was applied. Furthermore, this research has been officially recorded with the International Prospective Register of Systematic Reviews.

### 2.1. Inclusion and Exclusion Criteria

The criteria for selecting studies in this review included: (1) Investigations focusing on the myeloid differentiation of hematopoietic stem cells during pregnancy; (2) Comprehensive reviews addressing patient experiences in pregnancy and aspects of immunological tolerance; (3) Case-control studies and prospective observational research with abstracts detailing differential expression patterns; and (4) Owing to resource constraints, the scope was narrowed to include only studies published in English.

The criteria for excluding studies from this review were established as: (1) Literature that was replicated or duplicated; (2) Analyses or reviews involving patients demonstrating immunological tolerance due to conditions other than pregnancy; (3) Summaries of experiences, individual case reports, abstracts from conferences, reviews for which full texts were inaccessible, and any literature deemed not directly relevant; (4) Types of publications lacking original data, including but not limited to editorials, additional case reports, proceedings from conferences, and narrative reviews.

### 2.2. Search Strategy

We conducted a thorough search of several databases, such as PubMed, EBSCOhost, ScienceDirect, Embase, Cochrane Library, and Web of Science, to identify relevant studies. This search was specifically focused on studies published in English from 2013 to the present, utilizing the earliest available records. We employed keywords and Medical Subject Headings (MeSH) such as 'myeloid differentiation' and 'hematopoietic stem cells in pregnancy immunological tolerance'. These terms were specifically targeted in the titles and abstracts of the publications to refine our search results.

The search strategy included keywords that were used

together with boolean operators such as "AND" and "OR" different search strategies were used for the different databases because of their peculiarities. The search terms used for journal that we use are "the role" AND "myeloid" OR "myeloid differentiation" AND "hematopoietic stem cells" OR "myeloid hematopoietic" OR "stem cells" OR "immunological tolerance" AND "pregnancy immunological tolerance" OR "pregnancy immunological tolerance in pregnancy" OR "immunological tolerance" AND "pregnancy".

### 2.3. Study risk of bias assessment

For the analysis, ten selected studies underwent a detailed evaluation using the Specialist Unit for Review Evidence (SURE) assessment tool, which is comprised of a 12-question framework. The scoring methodology is designed where a 'yes' answer is awarded 1 point, whereas a 'no' or 'uncertain' response is given 0 points, with the highest possible score being 12. Studies scoring 6 or above were considered high enough in quality to be included in this analysis. On the other hand, studies with a score lower than 6 were deemed of inferior quality and thus excluded. The comprehensive risk of bias for each study is delineated in Table 1 [4,7-15]. This quality evaluation was independently conducted by reviewers Zheng Zheng and Weng Tingsong, with Yao Jingxin resolving any arising disagreements.

### 2.4. Statistical analysis

As this is a systematic review, no statistical analyses were performed in this article.

## 3. Results

### 3.1. Study selection

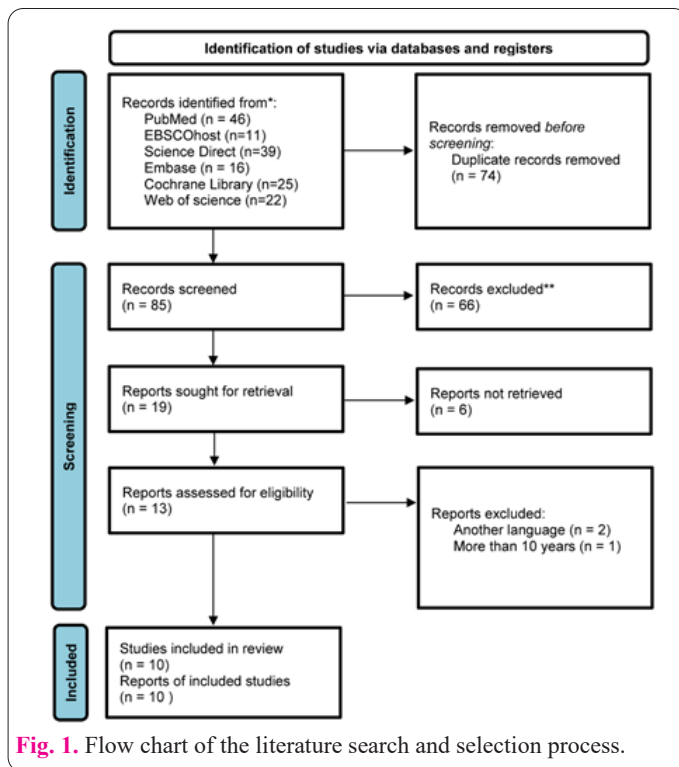
The search across various databases yielded a total of 159 references, with their distribution being 46 from PubMed, 11 from EBSCOhost, 39 from ScienceDirect, 16 from Embase, 25 from the Cochrane Library, and 22 from Web of Science. When duplicates present across multiple databases were removed, 74 references remained. Following the screening of titles and abstracts according to the previously stated criteria, 19 references were deemed suitable for in-depth, full-text review. This stage led to the exclusion of an additional 9 articles. Consequently, a total of 10 articles were included and critically reviewed in the results section, particularly focusing on the development of myelopoietic cells within a well-structured three-dimensional microenvironment under normal physiological conditions (Figure 1).

The bone marrow's architectural structure is an intricate network of various cell types, notably osteoblasts and stromal cells, along with their synthetic outputs like extracellular matrix elements, adhesion molecules, and factors promoting hematopoiesis. The niche for stem cells in bone marrow, crucial for hematopoietic processes, encompasses hematopoietic stem cells (HSCs) known for their self-renewal capacity and ability to generate diverse blood cell types. This niche is instrumental in managing the balance between the self-renewal and differentiation of stem cells. In bone marrow, two distinct niches have been identified: the osteoblast niche, which is pivotal in regulating HSC's quiescent state and asymmetric division, and the vascular niche, closely tied to myeloid differentiation. Hematopoietic regulation within these niches involves a variety of

**Table 1.** Critical Appraisal Using Specialist Unit for Review Evidence.

Authors	Study design stated?	Addressed clearly focused research question?	Study setting clearly stated?	Fair selection of study participants?	Participant characteristics provided?	Appropriateness of method of assessing outcomes	Appropriateness of sampling method	Appropriateness of methods of data analysis	Information provided on participant eligibility?	Are the results well described?	Conflict of interest reported?	Did the authors identify any limitations	Total (12)	Decision
Idris et al.,	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	No	Yes	Yes	10	Accepted
Uphadaya et al.,	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	11	Accepted
Feyen et al.,	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	12	Accepted
Oguro et al.,	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	No	10	Accepted
He, Suhai et al.,	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	12	Accepted
Natascha and Christian	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	No	10	Accepted
Nkemeh, Christine et al.,	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No	10	Accepted
Pessach et al.,	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	11	Accepted
Chen et al.,	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	11	Accepted
Shardina et al.,	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	11	Accepted

Yes is scored as 1 while No or I can't tell is scored as 0; A total score of the entire scale is 12. A score of 6 and above is considered a pass mark and accepted while a score of less than 6 is considered poor and rejected for inclusion.



cytokines that interact with specific cytokine receptors or activate Janus kinase-dependent receptors. Recent studies have also highlighted the role of novel receptor families, including G protein-coupled receptors and ion channels like the P2 receptor family, triggered by extracellular nucleotides, in hematopoietic regulation. These elements, secreted by endothelial and osteoblast cells, have potential implications for myeloid differentiation. Detailed characteristics of the study characteristic and findings are shown in Table 2.

#### 4. Discussion

This systematic review explored the extent to which cells from hematopoietic stem cells contribute to immunological tolerance during pregnancy. The results are presented by categorizing the investigated tissue types and species. Despite the significant variability in findings across different studies, there is consistent evidence of a small yet notable presence of fibroblasts from hematopoietic lineage in non-hematopoietic tissues, with an apparent increase in these cells following tissue damage.

Hematopoietic stem cells (HSCs) undergo extensive epigenetic remodeling during differentiation into various blood cells, a process mapped through genome-wide DNA methylation studies. Maternal extramedullary hematopoiesis (EMH) in pregnancy relies on HSC proliferation in bone marrow, migration to the spleen, and splenic erythropoiesis, influenced by estrogen receptor  $\alpha$  ( $ER\alpha$ ) functions within HSCs [16]. Interestingly, not only estradiol (E2) but also 27-hydroxycholesterol (27HC), an oxysterol, can bind and modulate estrogen receptors. EMH, essential for managing increased maternal blood volume during pregnancy, depends on  $ER\alpha$ -mediated HSC activity. Studies show different roles for estradiol and 27HC in HSC behavior, with 27HC specifically influencing recruitment and EMH. In pregnancy, 27HC levels rise in HSCs due to CYP27A1 activity, a cholesterol hydroxylase. Mice lacking *Cyp27a1* exhibit reduced 27HC levels, HSC recruitment, and EMH, highlighting different mechanisms for

EMH induction under various hematopoietic stresses. This finding underscores the complex interplay of hormonal, metabolic, and physiological functions of 27HC [4].

During pregnancy, maternal extramedullary hematopoiesis (EMH) involves the proliferation of hematopoietic stem cells (HSCs) in bone marrow, their migration to the spleen, and splenic erythropoiesis, dependent on estrogen receptor  $\alpha$  ( $ER\alpha$ ) function within HSCs [17]. HSCs are crucial for maintaining life, with control mechanisms being multifaceted, and influenced by both internal and external factors [6]. These cells can regenerate into all blood cell types and resume proliferation in the hematopoietic system. Research demonstrated their potential to restore the hematopoietic system post-radiation in mice [18], and their functionality is traditionally evaluated through transplantation assays involving radiation, setting the standard for assessing HSCs [19].

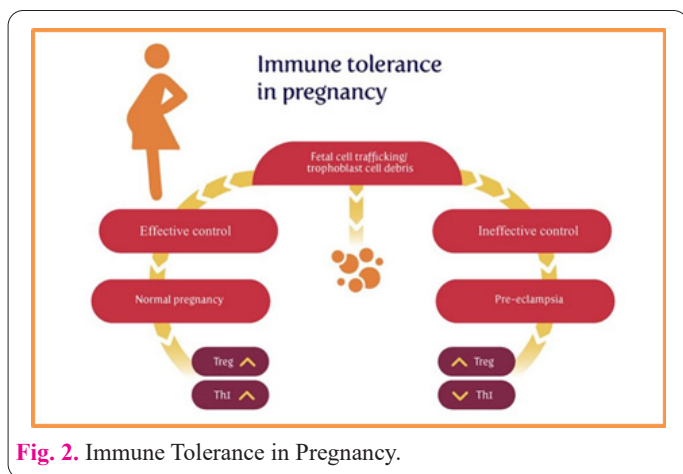
#### 4.1. Myeloid differentiation in pregnancy immunological tolerance

Immune tolerance during pregnancy was once thought to be a matter of physical separation between mother and fetus. However, it's now understood that there is a significant exchange of fetal material across the placenta into the maternal circulation and vice versa. This exchange forms the foundation for non-invasive prenatal testing. Alloantigens from trophoblast cells enter the maternal bloodstream, particularly in the third trimester, and are linked to the occurrence of preeclampsia (PE). Thus, understanding immune tolerance is crucial. The immunobiology of the fetus is often likened to a transplanted graft, considering complications like uteroplacental insufficiency, preeclampsia, and intrauterine growth restriction (IUGR).

The discovery that HLA-G, a gene with limited alleles, plays a pivotal role at the placental interface has been crucial in understanding maternal immunotolerance. It is recognized that placental HLA-G proteins contribute to successful semiallogeneic pregnancies by dampening maternal immune reactions against foreign (paternal) antigens, acting on various immune cells. Additionally, regulatory T cells (Tregs) are acknowledged for their critical function in maintaining self-tolerance and in curbing harmful immune responses. Current research indicates that Tregs are vital in upholding immune tolerance during pregnancy, preventing the accumulation of effector T cells within the decidua, the tissue surrounding the fetus and placenta. In their comprehensive review, Williams et al. discuss the role of regulatory T cells (Tregs), a subset of CD4<sup>+</sup> helper T cells that regulate immune responses. They differentiate between thymic (tTreg) and extrathymic or peripheral (pTreg) developmental pathways of Tregs, each with distinct functions. A transcription factor, Foxp3, controls their differential production. Notably, pTregs, which are crucial for maternal-fetal tolerance, emerged in placental mammals and are dependent on a specific enhancer, CNS1. Williams et al. emphasize that maternal-fetal tolerance involves active pTreg response to paternal antigens. Their findings align with the observed increase in Tregs during pregnancy and its absence in cases of recurrent pregnancy loss, underscoring the importance of paternal alloantigen exposure and other mechanisms like haem oxygenase in maintaining pregnancy. They also note that autoimmune activity can often lead to pregnancy loss. Regulatory T cells (Tregs) play several critical roles in infection control,

**Table 2.** Overview of the articles selected in this systematic review.

Author	Years	Journal	Study	Samples	Outcome
Idris et al.,	2021	Frontiers in Medicine	Experimental design	80	The findings of these studies highlight the connection between cytokines, including osteopontin and various growth factors, with key neonatal parameters like birth weight, Apgar scores, hemoglobin levels, and hematocrit readings
Uphadaya et al.,	2018	Journal of experimental medicine	Experimental design	22	This research offers essential perspectives on the differentiation of HSCs and their progenitors, focusing on both the long-term outcomes and the consistent composition of these progenitor groups. Despite this, there is a notable gap in understanding the lineage trajectories, developmental processes, and real-time emergence of these progenitor groups from HSCs. Gaining insights into these dynamic aspects is vital for comprehending the process of adult hematopoiesis and the intricacies of its hierarchical organization.
Feyen et al.,	2022	Nature Communication Journal	Experimental design	18	The research indicates a significant role of myeloid cells in hematopoietic abnormalities, linked to the activation of interferon pathways, possibly through interactions between neutrophils and NK cells. This suggests that the establishment of innate immunity could potentially lead to systemic decline, driven by heightened chronic inflammatory responses affecting stem cells and their microenvironment.
Oguro et al.,	2017	The Journal of Clinical Investigation	Randomized Experimental	40	During pregnancy, there is an induction of extramedullary hematopoiesis (EMH) to accommodate the swift escalation in the mother's blood volume. This process necessitates the expansion and mobilization of hematopoietic stem cells (HSCs), a mechanism reliant on the estrogen receptor alpha (ER $\alpha$ ) within these cells.
He, Suhai et al.,	2023	Elsevier Journal	Experimental design	24	To facilitate myeloid cell differentiation, the culture system was augmented with the addition of granulocyte/macrophage colony-stimulating factor.
Natascha and Christian	2020	Frontiers in immunology	Case control	83	The immune systems of both the mother and the fetus face significant challenges during pregnancy due to their proximity, necessitating a delicate balance between tolerance and rejection. Post-delivery, the neonate must maintain this equilibrium with its new surroundings, accepting commensal organisms while warding off pathogens, and in its tissue development to prevent inflammatory harm despite prevailing immunosuppressive conditions.
Nkemeh, Christine et al.,	2023	American Journal of obstetric and gynecology	Observational prospective	54	Enhanced mobilization of hematopoietic stem cells (HSCs) during pregnancy exhibits a positive correlation with the progression of gestational age. It is hypothesized that this response may be attributed to the activation of signaling pathways that expand as pregnancy advances. Our research aims to explore the underlying mechanisms responsible for initiating HSC mobilization during pregnancy and to investigate the potential links between HSC mobilization and adverse pregnancy outcomes.
Pessach et al.,	2013	Human Reproduction Update	Cohort study	46	Administration of progesterone to women during the second and third trimesters appears to be safe according to the available data, although clinical experience in this regard is relatively limited.
Chen et al.,	2018	Nature communication Journal	Observational dan experimental design	40	This findings highlight Med23 as a critical regulator of myeloid potential in hematopoietic stem cells (HSCs) and offer valuable insights into the interplay between Med23-mediated transcriptional control, HSC myeloid potential, and HSC activation.
Shardina et al.,	2022	Cell and tissue biology journal		71	Myeloid-Derived Suppressor Cells (MDSCs) play a significant role in regulating crucial immunological processes during both pregnancy and the neonatal period. The quest for novel targets capable of modulating MDSCs and establishing tolerance between the mother and child holds significant potential for addressing pregnancy-related pathologies.



**Fig. 2.** Immune Tolerance in Pregnancy.

including tempering potentially harmful immune responses and being exploited by some parasites to induce immunotolerance. The placenta permits the transfer of maternal IgG antibodies to the fetus for infection protection, and foreign fetal cells can persist in the maternal circulation. Abnormal immune responses toward the placenta are a known cause of preeclampsia (PE). There is significant evidence suggesting that exposure to a partner's semen, which contains immune-modulating factors in seminal fluid, may help prevent PE [20] (Figure 2).

#### 4.2. Hematopoietic stem cells in pregnancy immunological tolerance

Cell therapy involves administering living cells to patients to repair or replace damaged tissues or organs. These cells can be sourced from the patient (autologous) or from a matched or mismatched donor (allogeneic). The therapeutic cells vary in their capabilities and may be undifferentiated or pre-differentiated in vitro. Administration methods include intravenous injection or direct application to affected areas. Recent research, as highlighted by Ekblad-Nordberg et al. [21], shows that stem cell therapy primarily functions through transplantation, differentiation, and tissue replacement, or via trophic effects through the release of factors like cytokines and growth factors.

Hematopoietic stem cells (HSCs), a type of multipotent primitive cell, are capable of developing into all blood cell types, including both myeloid and lymphoid lineages. They are located in various organs like peripheral blood, bone marrow, and umbilical cord blood. These cells are crucial as they are the source of all blood cell lineages through self-renewal and differentiation. Understanding the molecular mechanisms that govern their self-renewal and cell fate is vital for clinical applications tailored to specific diseases and conditions. A small subset of HSCs is sufficient to initiate the entire hematopoietic process [22].

#### 4.3. Strength of the study

This review was methodically conducted with specific criteria for including and excluding studies regarding patient populations, interventions, comparators, outcomes, and study designs.

#### 4.4. Limitation of research

Our study acknowledges certain limitations, notably the constrained sample size due to strict inclusion criteria, which could introduce a risk of bias.

## 5. Conclusion

There is substantial research focusing on the role of myeloid differentiation of hematopoietic stem cells in immune tolerance during pregnancy, particularly in pathological conditions. Myeloid differentiation is also recognized for its significant role in regulating crucial immunological processes during pregnancy. The myeloid differentiation pathway of hematopoietic stem cells is pivotal in modulating the immune environment during pregnancy, supporting the sustenance of a healthy gestational period. Future research in this domain is expected to advance our understanding of the immunological processes occurring at the maternal-fetal boundary.

### Conflict of Interests

The author has no conflicts with any step of the article preparation.

### Consent for publications

The author read and approved the final manuscript for publication.

### Ethics approval and consent to participate

No human or animals were used in the present research.

### Informed Consent

The authors declare that no patients were used in this study.

### Availability of data and material

The data that support the findings of this study are available from the corresponding author upon reasonable request.

### Author contributions

Jingxin Yao and Tingsong Weng designed the study and performed the experiments, Zheng Zheng collected the data, Xiaodan Di analyzed the data, Jingxin Yao and Tingsong Weng prepared the manuscript. All authors read and approved the final manuscript.

### Acknowledgement

The authors express their gratitude for the support from the Delivery Room, Department of Obstetrics and Gynecology at Guangzhou Women and Children's Medical Center, affiliated with Guangzhou Medical University, located in Guangzhou, China.

### Funding

This study did not receive any funding in any form.

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