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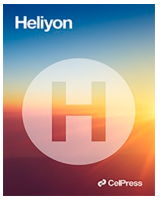

Review article

Preterm birth, a consequence of immune deviation mediated hyperinflammation

Juan Wei [a,c,1], LiYuan Zhang [a,c], Heng Xu [b], Qiong Luo [a,c,*]

[a] Department of Obstetrics, Women's Hospital, of Zhejiang University School of Medicine, Hangzhou, 310006, China
[b] Zhejiang University School of Medicine, Hangzhou, 310058, China
[c] Key Laboratory of Reproductive Genetics, Ministry of Education, China

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ABSTRACT

Preterm birth represents a multifaceted syndrome with intricacies still present in our comprehension of its etiology. In the context of a semi-allograft, the prosperity from implantation to pregnancy to delivery hinges on the establishment of a favorable maternal-fetal immune microenvironment and a successful trilogy of immune activation, immune tolerance and then immune activation transitions. The occurrence of spontaneous preterm birth could be related to abnormalities within the immune trilogy, stemming from deviation in maternal and fetal immunity. These immune deviations, characterized by insufficient immune tolerance and early immune activation, ultimately culminated in an unsustainable pregnancy. In this review, we accentuated the role of both innate and adaptive immune reason in promoting spontaneous preterm birth, reviewed the risk of preterm birth from vaginal microbiome mediated by immune changes and the potential of vaginal microbiomes and metabolites as a new predictive marker, and discuss the changes in the role of progesterone and its interaction with immune cells in a preterm birth population. Our objective was to contribute to the growing body of knowledge in the field, shedding light on the immunologic reason of spontaneous preterm birth and effective biomarkers for early prediction, providing a roadmap for forthcoming investigations.

1. Introduction

Preterm birth stands as a prevalent anomaly within the pregnancy timeline, marked by delivery occurring prior to 37 weeks of gestation [1,2]. The definition of the lower limit of preterm labor varies across countries, with developed nations often referencing 20 weeks [2], certain regions opting for 22 weeks or 24 weeks [3], and many developing countries aligning with the World Health Organization's benchmark of 28 weeks [4]. Globally, the World Health Organization (WHO) reported 13.4 million premature births annually and percentage varies from 4% to 16% across countries [5]. This serious issue is notably concentrated in Asia and sub-Saharan Africa, bearing the brunt of 80% of the global burden of preterm birth [5,6].

Compared to full-term newborns, preterm infants exhibited a markedly higher mortality rate and were prone to multiple complications [6,7], with the severity often correlated with gestational age at delivery [7]. Notable complications include respiratory

* Corresponding author. Department of Obstetrics, Women's Hospital, Zhejiang University School of Medicine, 1st Xueshi Road, Hangzhou, 310006, China.
E-mail address: luoq@zju.edu.cn (Q. Luo).
[1] First author: Juan Wei.

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distress syndrome, intraventricular hemorrhage, and necrotizing enterocolitis and so on. Moreover, preterm infants would encounter long-term challenges such as cerebral palsy, cognitive deficits, impaired sensory function, and chronic conditions like hypertension and heart failure and so on [8–11].

Preterm deliveries fall into two principal categories: spontaneous preterm labor and Iatrogenic preterm birth [2,12]. Existing research posits that spontaneous preterm deliveries may contribute to as much as 50% of all preterm deliveries [2,12]. Nevertheless, despite the frequent presence of multiple risk factors in the spontaneous preterm birth population, such as advanced age, obesity, black race, infections, cervical insufficiency and environmental stress [2,4,13–17], the intricate mechanisms governing spontaneous preterm birth remain elusive, impeding a comprehensive understanding of its causative factors [18]. This knowledge gap, in turn, constrains the development of effective strategies for the prevention and prediction of preterm labor in clinical settings [2,19]. Consequently, there exists a lag in the clinical management of populations at heightened risk for spontaneous preterm labor [2,19]. In other words, once the myometrium begins to contract regularly, preterm labor inevitably arrived. Recognizing and identifying potential preterm birth population emerge as important components in the proactive prevention and management of this complex phenomenon.

The fetus represented a hemizygous graft, emphasizing the significance of maternal and fetal immune harmony for the maintenance of pregnancy [20]. However, this harmonious immunity may be constantly challenged by various maternal as well as fetal factors [2,4,13–17], thus posing a potential threat to pregnancy maintenance [21]. The inflammatory cascade, a tangible manifestation of immune disharmony in maternal and fetal body, could lead regular contractions of the myometrium to promote preterm labor [21,22]. In light of the close association between inflammatory cascade and the dysregulation of immune cells in the maternal and fetal body, we endeavored to shed light on the role of aberrant innate and adaptive immunity in spontaneous preterm birth, to discuss the potential predictive value of vaginal microbial-mediated immune disorder, and to unravel the effects of progesterone on uterine myocytes and immune cells. In summary, this review sought to elucidate the potential causes driving spontaneous preterm labor within an immunological lens and propose avenues for its early prediction.

2. Immune trilogy during pregnancy

A healthy full-term pregnancy represents a notably feat, as it presents a formidable challenge to the maternal immune system. Extensive reviews have underscored that the maternal immune response commences as early as sperm entry into the vagina [21,23–25], marking the onset of an intricate journey characterized by immune activation, tolerance, and subsequent reactivation (Fig. 1). This transition unfolds from the embryo's implantation in the endometrium, spans throughout pregnancy maintenance, and culminates in the initiation of labor (Fig. 1). The successful completion of this great process hinges upon the orchestrated symphony of immune cells and inflammatory responses. However, deviations from this delicate balance, marked by failures in transitioning from immune tolerance or premature immune activation, frequently manifest in pregnancy complications such as miscarriage and preterm labor [21,25,26].

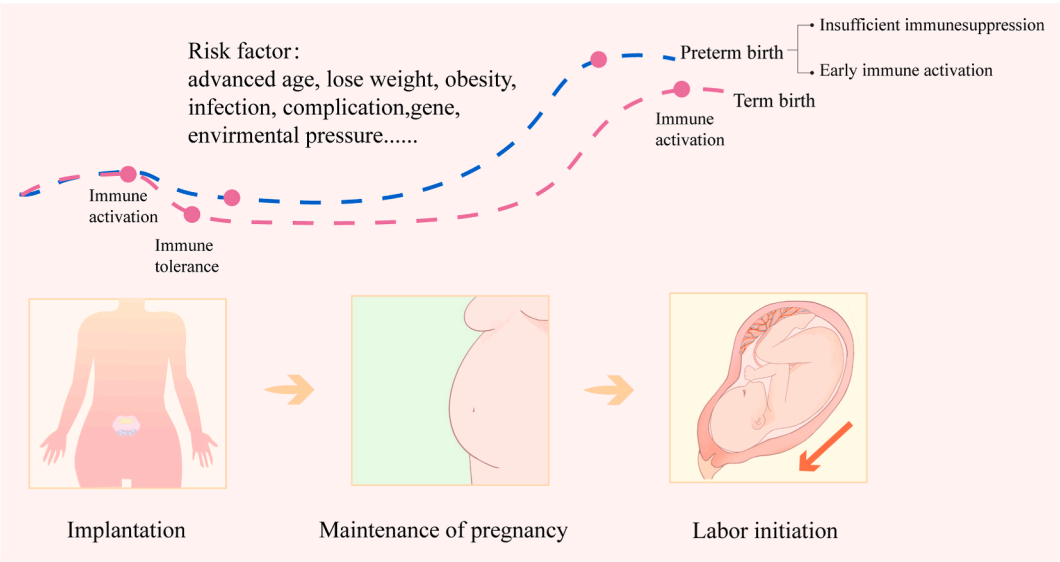

Fig. 1. Immune trilogy in pregnancy. During implantation, a state of mild maternal immune activation fosters embryo implantation. Throughout the maintenance of pregnancy, immunosuppression predominates in the body to prevent fetal rejection. However, during labor, maternal immunity is reactivated. Inadequate immunosuppression and early immune activation during pregnancy may be correlated with preterm birth. Advanced age, lose weight, infection and other risk factors promote the immune deviation.

3. Pathophysiology of preterm birth

Adequate oxygen and nutrient supply are imperative for healthy fetal development, and the ischemic and hypoxic environment at the maternal-fetal interface is often associated with pregnancy complications. Previous studies have highlighted there were failure of spiral artery conversion, decidual vasculopathy and decidua aging that existed at maternal-fetal interface in preterm compared to term birth [18,27,28], suggesting dysfunction of trophoblast and stromal cells in the preterm population. The maternal-fetal interface serves as a site of multicellular convergence and mutual regulation [29,30]. Thus, there is a possibility here that hyperinflammation stemming from immune deviation mediated by maternal risk factors may serve as an aggressor to cause those cell dysfunction. On one hand, trophoblast and stromal cells undergo apoptosis under the persistent assault of inflammatory factors and further release inflammatory mediators that exacerbate inflammation. On the other hand, inflammatory stimuli cause vasculature constriction, and thus increase vascular resistance or permeability, resulting in subsequent ischemic and hypoxic environment and then also in turn exacerbate inflammation. Ultimately, the heightened levels of inflammatory factors and proinflammatory immune cells together contribute to the activation of the labor pathway in advance (Fig. 2).

However, Inflammation does not solely originate at the maternal-fetal interface; rather, it represents a holistic event from both the mother and fetus. This proinflammatory phenomenon extends beyond the maternal-fetal interface and can be observed in various compartments including the peripheral blood, umbilical cord blood, amniotic fluid and even the vagina (Fig. 2).

In addition, vigorous and regular contractions of uterine myocytes are the most crucial step in labor to facilitate the delivery of the fetus. Previous studies have underscored inflammation as a significant contributor to the transition of term uterine myocytes from a quiescent to an active state [22,31]. Immune cells emerge as key sources of inflammatory factors, with reports from human single-cell

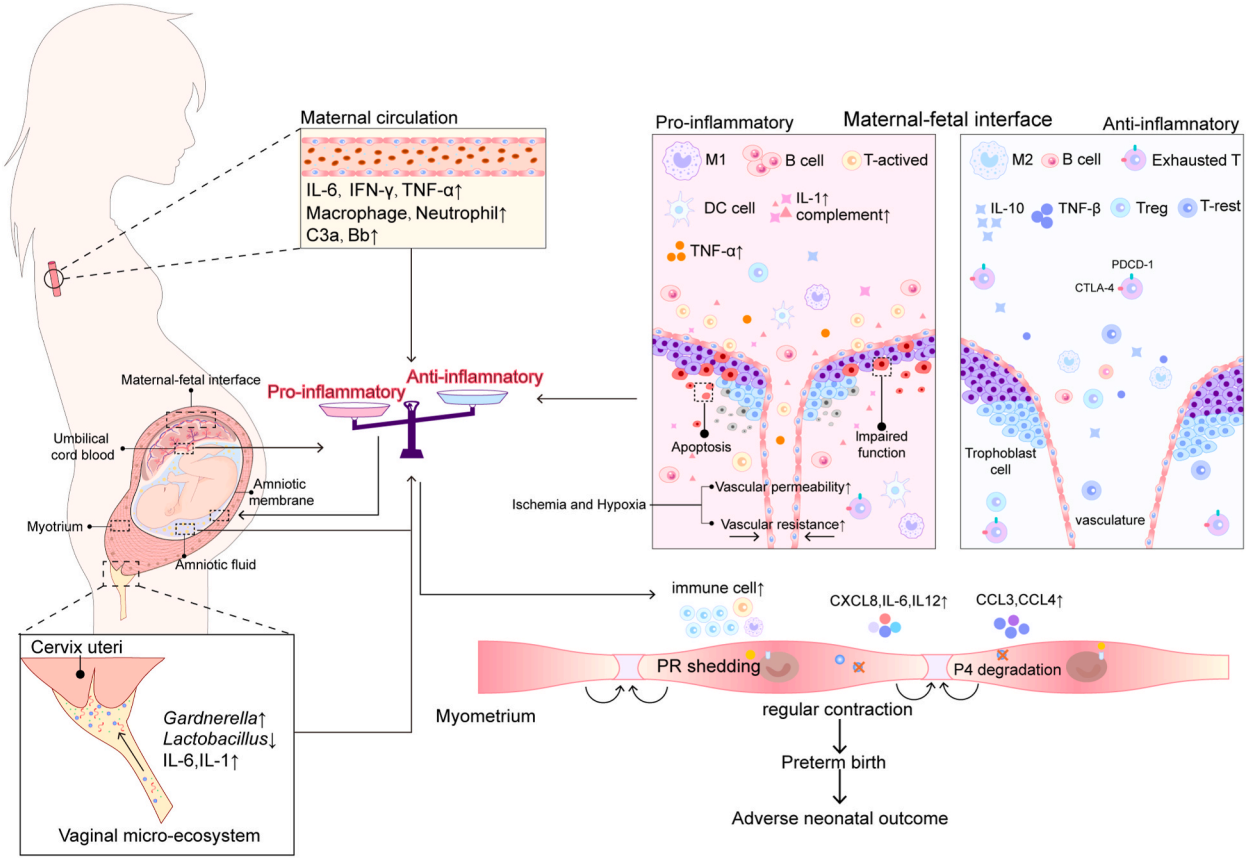

Fig. 2. Maternal and fetal pro-inflammatory changes in body. Compared with term birth, pro-inflammatory alterations could be found in preterm birth spanning maternal peripheral blood, the maternal-fetal interface, vagina, umbilical cord blood and amniotic fluid. This was characterized by increased levels of inflammatory factors(IL-1, IL-6, TNF-α and so on), increased numbers of inflammatory immune cells (M1, T-activated and Neutrophil), and decreased numbers of tolerance immune cells(M2, Tregs and Exhausted T cells). In addition, there was also an increase of *Gardnerella* and a decrease of *Lactobacillus* in the vagina. In the maternal-fetal interface, these changes may precipitate escalated trophoblast dysfunction and apoptosis, alongside heightened vascular resistance and permeability, culminating in an ischemic and hypoxic milieu. Moreover, they have the potential to activate myometrium, fostering the shedding of progesterone receptors(PR) and degradation of progesterone(P4), thereby engendering regular contractions. Meanwhile, rupture of membranes and shortening of the cervix may also occur. This cascade of events eventually leads to preterm birth and to adverse neonatal outcomes.

studies indicating the presence of immune cell infiltrates, including macrophages, monocytes, and T cells, within the myometrium during labor [22,31]. Notably, preterm labor often coincided with increased levels of immune cells and inflammatory factors [21, 32–35]. In vitro experiments have demonstrated a notable increase in myometrial cell contraction amplitude upon stimulation by inflammatory cytokines such as TNF-α and IFN-γ [33]. Animals experiments utilizing immunohistochemistry has further highlighted a significant elevation in leukocyte presence within the myometrium of preterm mice [36]. Collectively, these findings suggested that fierce inflammation mediated by immune activation plays an important role in augmenting myometrium contraction, thereby increasing the possibility of delivery and then initiating preterm labor.

4. Innate immunity

4.1. Complement

The complement system, a key component of the innate immune response, emerges as a important regulator in placental immunity, influencing the development and sustenance of pregnancy [37]. Experimental evidence from animal studies underscored the significance of complement in embryonic survival, as demonstrated by intrauterine death and fetal resorption in Cr1-related protein Y (Crry) or C3 knockout mice [38,39]. In addition, C1q-deficient mice displayed placental insufficiency, and administering anti-C1q antibodies to pregnant mice resulted in elevated miscarriage rates and heightened complement activation [40,41]. Interestingly, anti-C1q antibodies were detectable in women with systemic lupus erythematosus (SLE), a demographic at an elevated risk for spontaneous preterm delivery [42] that the relative risk (RR) was 2.05 (95% CI: 1.72–3.32) [43].

Clinical trials in humans have illuminated the association between increased serum levels of complement factors C3a and Bb in early pregnancy and the occurrence of preterm labor before 34 weeks, signifying potential indicators of adverse pregnancy outcomes [44–47]. Transcriptome sequencing of placental tissues in the context of spontaneous preterm birth further underscored the significant activation of the complement pathway at the maternal-fetal interface [35,46]. Collectively, findings from animal and clinical experiments bolstered the premise that the complement system played a important role in initiating labor and contributing to spontaneous preterm birth and is expected to be a predictive biomarker in the future.

4.2. Macrophages

Macrophages, constituting the second most abundant leukocyte population in human decidua basalis (approximately 20% of total leukocytes), exhibit a stable presence and stand out as natural contributors to tissue remodeling at the maternal-fetal interface [30]. Previous investigations have substantiated that during labor, macrophages could release substantial quantities of inflammatory mediators, including MMP, IL-1β, IL-6, TNF-α, and nitric oxide (NO), actively to participate in the cervical ripening process [48]. Moreover, macrophages identified in the amniotic membrane were suggested to play a role in mediating the secretion of MMP-9, facilitating the rupture of fetal membranes [49].

Recent flow cytometry results indicated a significant increase in the M1/M2 ratio in the decidua of preterm labor compared to term labor [50], while single-cell sequencing reports highlighted the heightened expression of NFKB1 in decidua macrophages, implicated in initiating the inflammatory process [30]. Transcriptomic analyses of peripheral blood in pregnant women further revealed an upswing in macrophage numbers during mid-pregnancy in those experiencing spontaneous preterm labor [51]. And following upregulation of ADAMTS2 [51], a disintegrin and metalloproteinase with thrombospondin motifs, along with inflammatory genes such as CXCL3, CXCL8, IL1β and so on [51]. In summation, these observations collectively suggested the active involvement of macrophages in the proinflammatory alterations associated with spontaneous preterm birth.

Nevertheless, the protective role of macrophages also equally deserving of attention [52]. For instance, decidual macrophages may play a vital role in removing apoptotic cells through cytotaxis, promoting trophoblast invasion via the secretion of vascular endothelial growth factor(VEGF) and the proinflammatory factor interleukin-1β(IL-1β), and contributing to helical arterial vascular remodeling [53]. Moreover, there exist multiple subtypes of macrophages, and a detailed exploration by Gomez-Lopez et al. into the functions of CD11b macrophages revealed that depleting maternal CD11b macrophages using diphtheria toxin resulted in preterm labor, neonatal death, and postnatal developmental deficits [54]. Uterine tissues displayed elevated levels of proinflammatory factors, while which were partially counteracted by the transfer of macrophages [54]. In fact, macrophages are multifaceted and our current comprehension for its function is insufficient, and a more meticulous categorization of macrophages is sufficiently reasoned to delineate the distinct roles of each subtype in the initiation of labor and idiopathic preterm delivery.

5. Adaptive immunity

5.1. T cells

The fetus and placenta stand as notably successful organs for transplantation, with T cells emerging as a pivotal cell population vital for the establishment of immune tolerance [55]. T cells can be broadly classified into activated and tolerant subsets, and the activation of T cells plays a significant role in the maintenance of pregnancy. Animal studies have reported that administering CD3 antibodies to induce T cell activation in mice led to a substantial reduction in gestation time [56]. Recent findings from flow cytometry and single-cell transcriptome analyses have corroborated increased activation of T cells at the maternal-fetal interface in preterm women [30,57], also applied to amniotic fluid [58]. A recent study delving into T cells in detail within the context of spontaneous preterm birth

has uncovered a significantly surge in the number of CD4 Tcm cells at the maternal-fetal interface among individuals experiencing preterm birth [34]. This finding underscores an augmented activation of CD4 T cells within this population. The key question arises: how do T cells orchestrate the onset of spontaneous preterm labor? Is their involvement linked to heightened uterine contractions? A study has indeed suggested their relevance in this regard. Through in vitro experiments, uterine myocytes co-cultured with activated T cells exhibited an increase in contraction amplitude [33]. Moreover, in mouse models, transfer of activated T cells resulted in a significant shortening of the gestation period [33]. Collectively, these findings strongly indicate that activated T cells play a contributory role in augmenting uterine myocyte contractions, thereby implicating their involvement in the onset of spontaneous preterm labor.

Regulatory T cells (Tregs), a crucial subset of immune-tolerant T cells renowned for their ability to suppress inflammation [59,60]. Clinical evidence has consistently shown diminished numbers of $CD4^{+}CD25+$Tregs in individuals with complication of pregnancy [61,62]. In a recent study utilizing flow cytometry to isolate the decidua basilaris of term and preterm, a significantly decrease in Treg cells was observed in the decidua basilaris of the preterm group, accompanied by an elevated Tc17/Treg ratio [50,63]. Further supporting the vital role of Tregs, a study by Gomez-Lopez et al. employed diphtheria toxin to deplete all Foxp3+ Tregs in mouse. This depletion markedly increased the rate of preterm birth (15%), resulting in adverse neonatal outcomes [63]. Subsequent analysis revealed heightened expression of inflammatory factors, including IFN-γ, IL-22, and CCL7 within the serum of Foxp3+DTR mouse [63]. Transcriptome results hinted at dysregulation in placental development and cellular metabolism processes [63]. Although these studies emphasize the role of Tregs in the development of preterm labor, the role of Tregs in the development of spontaneous preterm labor may still be weak [63], and further elucidation of the pathways regulated by Tregs and other immune cells may be necessary as it may be a lever to pry other immune cells into activation [63].

Compared to $CD4^{+}$ T cells, $CD8^{+}$ T cells were relatively more abundant at the maternal-fetal interface [34], but their role remains relatively elusive. Recent findings shed light on the emergence of tolerogenic $CD8^{+}CD122+$ T cells at the maternal-fetal interface, showcasing their active contribution to maternal-fetal tolerance and the facilitation of fetal development [64,65]. However, another recent report using flow cytometry to look at maternal-fetal T cells suggested that $CD8^{+}$ T cells was increased in the amniotic membranes of pregnant women with spontaneous preterm labor [34]. This paradoxical result underscored the importance of scrutinizing its subgroups and examining whether it is correlated with premature rupture of membranes.

The presence of exhausted T cells different from chronic inflammatory during pregnancy emerges as a positive factor in sustaining gestation [66]. Within the decidua, a population of Tim-3+PD-1+$CD8^{+}$ T cells has been identified, and impairment of Tim-3+PD-1+$CD8^{+}$ T cells in decidua basilaris has been observed in women who experienced miscarriage [67]. In vivo studies utilizing animal models have demonstrated that blocking PD-1 or TIM-3 led to increased rates of fetal loss [67]. This outcome coincided with a decrease in the number of Th2-type cells and an increase in the trophoblast-killing and IFN-γ-producing capacities of $CD8^{+}$ T cells [67]. An investigation focused on exhausted T cells at the maternal-fetal interface revealed an increase in exhausted T cells with advancing gestational age [66]. Notably, there was a decrease in exhausted CD4 and CD8 T cells in the decidua at the onset of physiological labor, and a significant down-regulation of the number of exhausted T cells in the decidua basilaris of women with preterm labor [55,68]. In summary, these studies posit that exhausted T cells play a vital role in the preservation of pregnancy, acting as essential regulators that restrain excessive inflammatory responses to maintain a balanced immune microenvironment. Interestingly, the features of exhausted T cells observed during pregnancy distinguish them from those present in tumors and chronic inflammatory conditions [66]. These exhausted T cells during pregnancy were largely dependent on FAT pathway [66], so could this suggest that the abnormal expression of gene in the NFAT pathway in preterm labor populations as a cause to result in altered numbers of those cells?

Fetal T cells were noted for their activation in response to maternal inflammation [69], a phenomenon potentially linked to the dynamic presence of immune cell mobility at the maternal-fetal interface [30,70]. Previous research has unveiled a significantl surge in memory T cells in the umbilical cord blood of preterm infants compared to term infants [33], particularly in cases associated with brain damage [71]. Clinical reports scrutinizing inflammatory factors in umbilical cord blood from preterm and term deliveries have indicated significant increases in IL-6 and MMP levels among preterm infants [33]. Further insights from animal experiments affirmed that activated fetal T cells could release IFN-γ and TNF-α, orchestrating heightened myometrial contractions and then fostering the progression of spontaneous preterm labor [33]. In short, these findings collectively underscored the key role of fetal T cells as key contributors to the inflammatory response. However, the precise triggers initiating the intricate crosstalk between maternal and fetal immune systems remain unclear. Certain reports have suggested a potential correlation between elevated levels of maternal microchimerism in umbilical cord blood and the initiation of a fetal immune response [33]. This finding hinted at the possibility of immune interplay between maternal and fetal systems. May it raises the prospect of new biomarkers to early predict preterm infants complications to anticipate potential challenges and enhance the prognosis of those infants.

5.2. B cells

Recently, B cells have observed as key players in the intricate dynamics of gestation [72–74]. In a large European population cohort, variants within the EBF1 locus, a gene governing B cell development, were identified in preterm population [75]. Recent clinical studies have also confirmed the association of EBF1 with spontaneous preterm birth [76,77]. Additionally, functional studies on decidual B cells underscored the significance of B cells in maintaining gestational integrity. B-cell-deficient mice exhibited vulnerable susceptibility to LPS-induced infectious preterm labor, leading to significantly shorter gestation times [73]. Conversely, pregnant B-cell-deficient mice with B cell transfers demonstrated increased resilience against preterm labor [73]. Further analysis pinpointed reduced levels of progesterone immunomodulatory binding factor 1(PIBF1) and augmented proinflammatory mediators NK cell and neutrophil activity in organisms with B-cell defects [73].

Moreover, a distinct subset of B cells, known as regulatory B cells (Bregs) which have demonstrated the capacity for interleukin-10 (IL-10) secretion, has garnered attention for its role in placental and fetal growth, implicated in the occurrence of preterm labor [78,79]. Animal studies involving BIL10 deficient mice further support the idea that these mice were more susceptible to preterm labor, accompanied by increased uterine artery resistance [80]. In conclusion, these findings posited that decreased decidual B cells significantly contribute to the development of spontaneous preterm labor. However, the current understanding of B cells subtype in immune tolerance and pregnancy maintenance is limited, necessitating further elucidation, particularly through advanced techniques such as single-cell atlas in future research.

6. Vaginal microbes

Huge alterations in the vaginal microbiota were observed during normal pregnancy [81]. This process of microbial rearrangement and remodeling commences early in pregnancy, leading to a reduction and stabilization in the rate and variability of flora compared to non-pregnant states [81]. Notably, there is a pronounced expansion in the dominance of *Lactobacillus* [81], whose abundance exhibits a strong correlation with gestational age [82,83]. Some studies have shown that dysbiosis of the gestational microbiota was associated with an increased risk of preterm birth [84–86], with black women being particularly vulnerable, influenced by environmental, genetic, and social status factors [81,86]. Recent studies highlighted a significant rise in the abundance of vaginal bacteria such as *Gardnerella*, *Mycoplasma Urealyticum*, *Prevotella*, *Peptoniphilus*, *Streptococcus*, and *Dialister*, coupled with a notable decrease in *Lactobacillus* levels at the woman with preterm labor [84–88], and may associated with short cervix, premature rupture of membranes, failure of emergency cervical cerclage and adverse neonatal prognostic outcomes, such as sepsis [89–91]. Concurrent cytokine profiling revealed increasing levels of inflammatory factors, including eosinophil, interleukin-1β, interleukin-6, and MIP-1β in the vaginas of preterm pregnant women [84,85,92,93]. Meanwhile, recent microbial metabolomic studies have corroborated these findings [94–97], identifying elevated levels of specific metabolites, such as diethanolamine, ethylglucose, and tyramine, in vaginal fluids during preterm births [95]. Of particular interest was diethanolamine, a substance derived from immune-stimulation, indicative of a potential inflammatory state within the host organism [95–97].

However, exploring the role of vaginal microbes in the mechanisms underlying preterm labor presents several challenges. Firstly, the intricate interplay between changes in vaginal microbial composition and inflammatory factors remains largely understudied. This complexity is compounded by the predominance of fibrous connective tissue in the cervix, which suggests a limited presence of cervical immune cells, thereby complicating investigations into the mechanisms linking vaginal microbes to immune responses [18]. Secondly, inflammation was recognized as a key initiator of cervical remodeling [48], but the area of research is made even more challenging given the difficulty in replicating animal models of cervical shortening remodeling in mice, further impeding progress in understanding the underlying mechanisms of preterm labor.

Redirecting focus towards early prediction in populations at risk of preterm labor could yield valuable results. An article highlighted the potential of vaginal metabolites in predicting preterm labor, demonstrating an area under the receiver operating characteristic curve (auROC) of 0.78 and an area under the precision-recall curve (auPR) of 0.61 [95]. Furthermore, when combining individual characteristics of pregnant women with vaginal metabolites and microbial profiles, the predictive power for preterm labor at 34 weeks gestation soared to an ROC of 0.835 [94]. These findings underscore the potential of delving into the changes in vaginal microflora during pregnancy and identifying specific microbial strains, which may offer novel insights into the early prediction of spontaneous preterm labor. Such endeavors hold promise for improving clinical practice by enabling timely interventions to mitigate the risk of preterm birth and improve maternal and neonatal outcomes.

7. Progesterone and preterm birth

During pregnancy, progesterone(P4) is primarily secreted by the corpus luteum until approximately 8 weeks gestation. Subsequently, its production shifts primarily to the trophoblast layer of the placenta, where it remains at elevated levels to sustain pregnancy. Contrary to the expectation of a decline in progesterone levels at the onset of labor, studies have shown that progesterone levels remain stable, with functional progesterone withdrawal attributed to altered progesterone receptor activity [22]. For individuals at high risk of preterm birth, progesterone serves as an exceedingly vital tocolytic drug during pregnancy [2,19]. If progesterone supplementation could facilitate the maintenance of pregnancy, does it suggest that there is a relative deficiency of progesterone during pregnancy in the bodies of pregnant women with spontaneous preterm birth? Some studies proposed an increase in progesterone levels in preterm labor compared to full-term births [98], while others suggested a decrease evidence [32]. Understanding this contradiction necessitates further investigation to determine whether it is influenced by gestational age, experimental design, or population variability.

Here, we try to review the potential reason through which progesterone exerts its effects [22,99]. Progesterone have capability to control of myometrial contractility. The action of progesterone hinges on two nuclear progesterone receptors: PR-A and PR-B, which originate from the same gene and are co-expressed throughout pregnancy [22,99]. PR-B is typically acknowledged as a transcriptional activator of genes downstream of progesterone, while PR-A exerts an inhibitory effect on PR-B [99]. Previous research indicated that a high PR-A/PR-B ratio in the myometrium could hamper P4/PR-B-mediated transcriptional responses affected by the local immune environment [31,99]. In other words, under conditions of hyperinflammation, NF-κB/AP-1 pathways mediate an increase in the expression of 20α-Hydroxysteroid Dehydrogenase (20αHSD), an enzyme involved in P4 metabolism. This leads to enhanced intracellular metabolism of P4 and shedding of PR-B, culminating in functional progesterone withdrawal [99]. This may provide an explaination for understanding how inflammatory factors, such as TNF-α and IFN-γ, could stimulate myometrial contractions [33],

which may be related with possibility to induce alterations in PR isoforms, thereby undermining the role of P4 in preserving the quiescent of myometrium. Hence, it holds significance to unravel the intricate interactions among inflammation, progesterone signaling and uterine contractility through future experiments. Such endeavors will not only enhance our comprehension of the underlying mechanisms of preterm labor but also yield novel insights into its prevention and treatment.

In addition, much evidence also converged on its anti-inflammatory and immunomodulatory mechanisms [100–102]. In in vitro experiments, progesterone has demonstrated effectiveness in inhibiting the LPS-induced released of inflammatory factors such as tumor necrosis factor-α, interleukin-1β, IL-6, and matrix metalloproteinase-9 from morula cells [100]. In in vivo experiments employing LPS-induced preterm animal models, progesterone application proves beneficial by counteracting COX2 expression, inhibiting NF-κB activation, and reducing inflammation at the myometrium, decidua basilaris, and placenta [101,103].

The interesting immunosuppressive effects of progesterone have been a subject of interest [104]. Animal studies have illustrated that progesterone possesses the capability to inhibit the activation of dendritic cells, macrophages, and natural killer cells [104]. In terms of adaptive immunity, recent research has demonstrated that progesterone exerts an inhibitory effect on effector T cells [57,105]. But the effect of progesterone on Tregs remains unclear, some studies suggested that progesterone could induce Tregs production, fostering endometrial tolerance to facilitate fetal development [106], while there was a studies suggested that Tregs differentiation was inhibited after progesterone supplementation in in vitro [107], which discrepancy could stem from variations in the regulatory environments between in vivo and in vitro conditions, there is room for further exploration in this regard.

Moreover, progesterone played a key role in promoting the expression of PIBF1, which has been observed to be deficient in early pregnancy in human studies involving the miscarriage population [108,109]. And animal evidence has showed increased natural killer (NK) and Th1 cell activity and reduced numbers of mature B cells at the maternal-fetal interface in the mice of blockade of PIBF1, ultimately embryo implantation was failure [110]. All these studies suggested that progesterone and PIBF1 maintain pregnancy by suppressing the maternal immune response. But the relationship between progesterone and and B cells appears to be unique. Previous studies have reported that PIBF1 can be secreted by decidual B cells to protect pregnancy [73,74], so is there a synergistic effect between progesterone, PIBF1 and B cells? Perhaps it can be further explored.

8. Conclusion

A trilogy of dynamic immune events unfolds throughout pregnancy. While full-term pregnancy embodies the harmonious resolution of this trilogy, preterm labor often presents with multiple abnormalities in innate and adaptive immune cells, including complement, macrophages, T-cells, and B-cells. These cells can serve as sources of inflammation, triggering a cascade of inflammatory responses in the maternal and fetal body and then activating uterine myoblasts, ultimately leading to regular contractions of myometrium. A comprehensive investigation into the inter-regulatory relationship between immune cells and uterine myoblasts holds promise for elucidating the mechanisms underlying spontaneous preterm labor. In addition, vaginal microorganisms possess the capacity to influence the balance between innate and adaptive immunity. Identifying specific microbial flora and metabolites could judge prognosis for emergency cervical cerclage populations and aid in developing biomarkers for early prediction of spontaneous preterm labor. Moreover, progesterone severed as a pivotal clinical agent for preventing preterm labor. A combined assessment of maternal characteristics, peripheral blood inflammation levels, and vaginal microbial abundance may offer valuable insights for determining the appropriate population for progesterone intervention and optimizing the timing of its initiation and termination.

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Consent for publication

All authors consent to publication.

Data availability

No data was used for the research described in the article.

CRediT authorship contribution statement

Juan Wei: Writing – review & editing, Writing – original draft, Data curation. **LiYuan Zhang:** Writing – review & editing, Visualization. **Heng Xu:** Visualization. **Qiong Luo:** Writing – review & editing, Supervision, Funding acquisition.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:Qiong Luo reports financial support was provided by National Key Research and Development Program of China. Qiong Luo reports a relationship with Women's Hospital School of Medicine Zhejiang University that includes: employment. Juan Wei reports a

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