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Prioritizing Immunological and Mechanistic Research in Preterm Birth: Microbial-Induced Inflammation and Commonly Occurring Cytokines

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Abstract

Preterm birth, defined as delivery before 37 completed weeks of gestation, poses a critical global health challenge, affecting approximately 13.4 million infants annually and representing a leading cause of early infant mortality. Despite significant global efforts, progress in reducing preterm birth rates has stagnated, particularly in low-to-middle-income countries and vulnerable populations. This stagnation underscores the need for intensified research, investment and innovation to address the complex and incompletely understood pathophysiology underlying spontaneous preterm birth. Intrauterine inflammation, often triggered by microbial infections like chorioamnionitis, is a well-established factor associated with a substantial proportion of preterm births.

Keywords: Preterm birth; Inflammatory markers; Pregnancy; Microbial-induced intrauterine inflammation; STI; HIV

Introduction

The World Health Organization and United Nations agencies reported in 2023 that preterm birth, defined as the delivery of a newborn before 37 completed weeks of gestation, represents a "silent emergency," affecting approximately 13.4 million babies annually [1]. In 2020, this equated to one in ten babies being born too early, translating to one premature birth every two seconds. Preterm birth is the leading cause of mortality in early infancy and remains a significant risk factor up to a child's fifth birthday, accounting for at least 35% of neonatal deaths [1]. The incidence of preterm birth and its complications is notably higher in low-to-middle-income countries, lower-resource settings, and historically vulnerable maternal populations across regions [2]. There is an urgent call to prioritize research, increase investments, drive innovation and accelerate evidence-based implementation to address this global issue in all affected settings.

Despite significant strides over the years to reduce the incidence of preterm birth globally, improvements have begun to stall since the 1990s, more evident in the past decade for all regions [1,3,4]. Complications from preterm birth have remained a topmost predictor of long-term morbidity and chronic illness, resulting in substantial economic losses for society.

Literature Review

While global stakeholders attribute the plateauing global preterm birth rates to some degree of “inaction,” it is worth noting that the unmet prevention needs of preterm birth could also stem from the residual causal unknowns [5]. Spontaneous preterm birth is a highly complex and incompletely understood syndrome from a pathophysiological perspective [6]. Many physiological, demographic and environmental stressors have been linked to preterm birth and contextual interventions have been developed to address those risks. However, modifiable biological risks and underlying causal mechanisms remain poorly understood [5,7,8]. This gap hinders the development of effective and safe biological interventions in pregnant mothers, which holds potential to significantly progress previously achieved reduction of global preterm birth rates.

Despite the limited understanding of these mechanisms, intrauterine inflammation is a well-known underlying factor, where pathological inflammation may disrupt the balance required for adequate placentation and normal labor [6,9]. While it has been challenging to consistently detect genital pathogens in the feto-maternal interface, infection or microbial-induced inflammation of the gestational membranes, such as chorioamnionitis is associated with up to 40% of preterm birth cases, and as high as 80% in spontaneous preterm births occurring before 32 weeks of gestation [10-12]. Systemic infections and bacterial ascension through the vagina/cervix to the amniotic cavity are strongly associated with spontaneous preterm birth, often more so through the ascending genital route [13,14]. Potentially implicated genital pathogens which have demonstrated epidemiological associations with preterm birth include commensal bacteria such as group B *Streptococcus* and Sexually Transmitted Infections (STIs) like *Chlamydia trachomatis, Neisseria gonorrhoeae*, *Mycoplasma genitalium*, *Trichomonas vaginalis and Treponema pallidum* (syphilis) [15-18].

Importantly, antenatal screening for maternal genital infections is limited in many low-resource settings. For instance, outside of syphilis, other STIs are not routinely screened for, due to high costs and unclear evidence of cost-effectiveness [19]. As advocacy for preterm birth prevention increases, addressing neglected infections will be critical, especially in areas with high STI and HIV prevalence [20]. For instance,

in South Africa, antenatal STI and HIV prevalence can be as high as 40% and 30%, respectively [21]. Understanding the biomarkers and host-microbe interactions that trigger pathological inflammation complicating pregnancy and birth is essential [7].

Specific cytokine signals could be relevant for prognostication and developing new therapeutics. Understanding cytokines and chemokine signals related to inflammation and preterm birth is notably challenged by their widespread presence and the dynamic nature of pregnancy immunology as gestation progresses [7,22]. However, machine learning methods hold promise for improving detection of critical immune predictors [23,24]. For preterm birth and related adverse birth outcomes, certain cytokines already merit closer examination as we inch towards the development of new tools for improving prevention. Notables are Interleukin-6 (IL-6), Interleukin-1 (IL-1), Interferon gamma (IFN)-γ, inducible protein (IP-10) and Interleukin-10 (IL-10) important for further research.

Interleukin-6 (IL-6)

IL-6 is instrumental in establishing a pro-inflammatory environment in the uterus necessary for labor [25]. Its levels rise in the myometrium, cervix, choriodecidua and maternal blood as delivery nears, unlike in women who are not in labor [26]. In models of infection-induced preterm birth, placental macrophages produce significant amounts of IL-6. High IL-6 levels are well-documented in cases of microbial colonization or inflammation of the amniotic fluid, often mirrored in cervico-vaginal fluid [25]. Repeatedly, elevated IL-6 in amniotic fluid, cervicovaginal fluid and maternal plasma is shown to be predictive of preterm delivery [27]. Increased IL-6 in plasma has also shown positive associations with preterm birth in pregnant women living with HIV, potentially unmodified by antiretroviral therapy [28]. Treatment with an anti-IL-6 receptor antibody has been shown to reduce inflammation leading to preterm birth and extend gestation in animal models, indicating that targeting IL-6 signaling could be a viable strategy for prevention [29,30].

Interleukin-1 (IL-1)

Both alpha (IL-1α) and beta forms (IL-1β) of Interleukin-1 are potentially as important as IL-6 in the mechanisms underlying infection-induced preterm birth [25,31,32]. Approximately 30% of placental macrophages produce IL-1β under baseline inflammatory conditions, compared to less than 5% that synthesize IL-6. However, when stimulated by bacterial lipopolysaccharide, the number of cells secreting IL-6 increases to 30%-40%, while IL-1β increases by only about 20% [33]. This suggests that the production of IL-6 by placental macrophages may be more inducible during an acute infection, while both cytokines are involved in infection that is associated with early delivery [25,33]. IL-1α and IL-1β have been validated as pro-inflammatory cytokines that could predict, with a sensitivity of about 77%, the likelihood an STI (any of *Chlamydia trachomatis*, *Neisseria gonorrhoeae*, *Mycoplasma genitalium* and *Trichomonas vaginalis*) in non-pregnant women of reproductive age who have or are at risk of HIV in sub-Saharan Africa [34].

Interferon gamma inducible protein (IP-10)

Interferon gamma (IFN)-γ inducible protein, also known as IP-10 or CXCL10, requires further study for its potential role in predicting or treating preterm birth [35]. Elevated levels of IP-10 have been observed in the plasma and genital tracts of pregnant women, as well as non-pregnant women with HIV or those at risk of HIV in sub-Saharan Africa [34,36]. CXCL10/IP-10 has also been associated with pre-eclampsia, a gestational syndrome linked to spontaneous preterm births [37]. This chemokine, which has pro-inflammatory and anti-angiogenic properties, is also associated with small-for-gestational-age births, often occurring alongside preterm births [35]. Important to note, maternal infections, including STIs, have been epidemiologically linked with hypertensive disorders of pregnancy, especially pre-eclampsia [38].

Interleukin10(IL-10)

Pregnancy is a complex dynamic process that requires a balance between pro- and anti-inflammatory immune responses until labor. In this context, the IL-10 family of cytokines deserves attention. While a relatively transient player in pregnancy immunomodulation, the role of IL-10 is notable due to its pleiotropic effects-primarily acting as an immunosuppressive or anti-inflammatory agent against common pro-inflammatory markers such as IL-1, IL-6 and tumor necrosis factor [39]. Increased concentrations of IL-10 have been observed in the endocervical secretions of women with Chlamydia, Gonorrhea, or bacterial vaginosis, likely as a response to the pro-inflammatory markers produced in response to these infections [40]. Dysregulation of IL-10 is linked to preterm birth, fetal loss, fetal growth restriction and pre-eclampsia [31,39].

Evolvingtreatmentsandtherapeutics

Understanding pathogen-biomarker pathways that lead to preterm birth is increasingly important to developing treatments that can prolong pregnancy in at-risk women. Effective, safe, and timely interventions to reverse intrauterine inflammation are essential. Focusing on infections prevalent in specific regions, the role of targeted and presumptive antibiotic or antiviral treatments in preventing early delivery has remained largely inconclusive [41,42]. In areas with high rates of STIs and HIV, it is important to study how such routine treatments might modify inflammatory markers and to what extent reverse or influence inflammatory pathways to adverse birth outcomes.

Discussion

One example of a preventive intervention is low-dose aspirin, a Non-Steroidal Anti-Inflammatory Drug (NSAID). It has historically shown effectiveness in preventing preeclampsia and recently shown efficacy in reducing preterm birth risks among nulliparous women in low- and middle-income countries [43]. However, the precise mechanisms by which low-dose aspirin works during pregnancy are still unclear. In low-resource settings with unique health risks and a high prevalence of STIs and HIV, investigating how these factors influence the immune pathways involved in aspirin's effects on preterm birth prevention is vital to delineate populations that will benefit the most.

Emerging treatments targeting specific cytokine pathways are also promising. Cytokine-Suppressive Anti-Inflammatory Drugs (CSAIDs) that target specific pathways could be future candidates for preterm birth prevention. For example, evolving IL-1 receptor antagonists, by inhibiting pathways to NF-κB activation, for instance, have been shown to prolong gestation in several inflammation models, including

preterm birth, without documented adverse maternal or neonatal effects [25,44]. Hence, CSAIDs could offer a targeted approach for select markers.

Conclusion

As progress in preterm birth prevention continues to threaten to plateau, prioritizing immunological and mechanistic research in preterm birth is essential for delineating modifiable pathways leading to adverse outcomes, towards the potential development of novel effective interventions. Microbial-induced inflammation is a significant mechanism warranting closer examination. Key cytokines like IL-6, IL-1, IL-10 and IP-10 may be particularly relevant in this research, especially for settings with high STI and HIV prevalence. Continued investigations into innovative therapeutic approaches are necessary to address the complexities of preventing preterm birth, small newborns and improve outcomes for mothers and infants globally.

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