ISSN: 3032-3134 (ONLINE)
InaJBCS | Indonesian Journal of Biomedicine and Clinical Sciences

Immune status in pregnant women against *Mycobacterium tuberculosis*: A scoping review

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https://doi.org/10.22146/inajbcs.v58i1.23622

Submitted: 2025-08-05
Accepted : 2025-11-24

ABSTRACT

Tuberculosis (TB) is a major global health concern, especially in vulnerable populations, such as pregnant women. Changes in the immune system in pregnancy may impair the individual's ability to withstand this infection. The objective of this scoping review was to systematically map the available literature regarding alteration of the immune response, specifically cytokines profiles, in pregnant women with or without TB. We conducted a systematic search of four databases (PubMed, EBSCO, ScienceDirect, and Scopus). Studies reporting on cytokine measurements in pregnant women with TB were included. Two reviewers independently screened titles/abstracts and full texts against predefined eligibility criteria. Data were charted on study characteristics, population, and reported cytokine outcomes. From 1.320 records, 14 studies were ultimately included based on the exclusion and inclusion criteria. Pregnant women with TB were shown to have reduction in adaptive proinflammatory response, mainly by the decrease of IFN-γ and IL-2 levels in the latter stage of pregnancy. However, this still remains conflicted due to several studies that state otherwise. Other cytokines, such as IL-6 and IL-17, and TGF-β, show a notable depletion in the concentration suggesting the enhancement of the vulnerability of pregnant individuals. Interestingly, there is a rise in the number and function of innate immune cells, which can be seen from the elevated levels of proinflammatory cytokines, including IP-10, MCP-2, and antiinflammatory cytokine, which is IL-1ra. This scoping review provides an overview of the current evidence landscape. It highlights methodological heterogeneity and inconsistent reporting as major challenges in drawing definitive conclusions. The findings underscore the need for more standardized, longitudinal studies to clarify the immune dynamics in pregnant women with TB. This map can guide future primary research and systematic reviews.

ABSTRAK

Tuberkulosis (TB) adalah sebuah salah satu masalah kesehatan global, terutama pada populasi rentan seperti wanita hamil. Perubahan pada sistem imun selama kehamilan dapat mengganggu individu dalam melawan infeksi ini. Tujuan dari *scoping review* ini untuk memetakan secara sistematis literatur yang tersedia mengenai perubahanrespon imun, khususnya profil sitokin pada wanita hamil dengan atau tanpa tuberkulosis. Pencarian sistematis dilakukan di empat basis data (PubMed, EBSCO, Science Direct, dan Scopus). Studi yang melaporkan pengukuran sitokin pada wanita hamil dengan TB dikutsertakan dalam penelitian ini. Dua penelaah secara independen menyaring judul/abstrak dan teks lengkap berdasarkan kriteria kelayakan yang telah ditetapkan sebelumnya. Data kemudian dicatat dalam bagan berdasarkan karakteristik studi, populasi, dan hasil sitokin yang dilaporkan. Dari 1.320 artikel teridentifikasi kemudian diseleksi dengan menggunakan kriteria inklusi dan eksklusi menjadi 14 studi. Wanita hamil dengan TB ditemukan memiliki penurunan respons imun spesifik yang ditunjukkan utamanya oleh kadar IFNγ dan IL-2 yang menurun, utamanya pada masa akhir kehamilan. Akan tetapi, hal ini masih kontroversi karena beberapa studi melaporkan hal yang berbeda. Sitokin lain, seperti IL-6, IL-17, dan TGF-β, yang menunjukkan peningkatan risiko terjadinya infeksi pada populasi ini. Uniknya, terjadi peningkatan jumlah dan fungsi imun bawaan yang ditunjukkan dengan adanya peningkatan konsentrasi sitokin proinflamasi, IP-10 dan MCP-2, serta sitokin antiinflamasi seperti IL-1ra. *Scoping review* ini memberikan gambaran umum tentang lanskap bukti saat ini. Review ini menyoroti heterogenitas metodologis dan pelaporan yang tidak konsisten sebagai tantangan utama dalam menarik kesimpulan yang definitif. Temuan ini menekankan perlunya studi longitudinal yang lebih terstandarisasi untuk menjelaskan dinamika imun pada wanita hamil dengan TB. Peta bukti ini diharapkan dapat memandu penelitian primer dan *systematic review* di masa depan.

Keywords:
cytokine;
immune response;
pregnancy;
tuberculosis;
Mycobacterium

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INTRODUCTION

Tuberculosis (TB) is a significant global health challenge. The disease is caused by *Mycobacterium tuberculosis* (*M. tb*) and most commonly presents as a pulmonary disease.[1] In 2022, 7.5 million people were diagnosed with TB, 46% of them in Southeast Asia, 23% in Africa, and 18% in the Western Pacific. These figures represent the highest numbers since global TB monitoring began in 1995. Currently, an estimated 10.6 million people around the world live with active TB, including 5.8 million men, 3.5 million women, and 1.3 million children. Approximately 90% of those infected with TB have latent infections, with about 5% progressing to active TB within the first two years after infection, while another 5% develop the disease later.[2,3] Tuberculosis remains one of the world's most fatal infectious diseases, ranking second in infectious disease-related deaths and claiming about 1.4 million lives in 2021.[4] In the following year, TB caused 1.3 million deaths worldwide and was the leading cause of death among individuals with HIV, accounting for 167,000 deaths.[2,3] The burden of this disease increases particularly in certain populations, such as pregnant women.[5]

Pregnant women and their fetuses are a vulnerable population often overlooked in TB control efforts.[6] During pregnancy, the maternal immune system undergoes major adaptations to protect both the mother and the fetus. A decrease in adaptive immune cells, especially T helper 1 cells (Th1), is found due to high levels of progesterone.[7] This immunological shift is essential to prevent maternal immune rejection of the fetus. At the same time, these changes also increase the individual's susceptibility to TB, leading to an escalation of the risk of maternal morbidity, miscarriage, preterm birth, low birthweight, and perinatal death.[5] Although the exact burden of TB during pregnancy is still unclear, it is estimated to occur at an incidence of approximately 1 in 10.000 pregnancies per year.[8] In such cases, there are notable differences in immune function between pregnant women with TB and those without.[9]

There is a complex immunological interplay in pregnant women who are also infected with TB. The maternal immune system, which leans toward an anti-inflammatory profile during pregnancy, must still mount an effective defense against *M. tb*.[9] This results in alterations in various components and functions of immune cells.[10] However, studies specifically examining this condition remain limited. Therefore, this literature aimed to describe the immune status of pregnant women in response to tuberculosis.

MATERIAL AND METHODS

This study was conducted as a scoping review. The objective of this review was to map the existing literature on alterations in immune responses among pregnant woman with tuberculosis. The review considered studies based on the following criteria, which were guided by PCC (Population, Concept, Context) framework, a standard for scoping review. search was guided by a predetermined PCC framework, as follows: 1) Population: pregnant women with active or latent TB, regardless of the presence of comorbidities or coinfections; 2) Concept: the key concept under review is the immune status and response, as defined by laboratory assessment such as cytokines profiles (e.g., IFN-γ, IL-2, IL-6), Interferon Gamma Release Assays (IGRA), tuberculin skin tests (TST), or flow cytometry; 3) Context: the comparison groups, where available, included healthy pregnant women and/or postpartum conditions with active or latent tuberculosis, with or without comorbidities and co-infections.

A systematic search was performed across four electronic databases PubMed, EBSCO, ScienceDirect, and Scopus. The

search strategy utilized a combination of keywords and Medical Subject Headings (MeSH) terms were identified using Boolean operators and then used to search for articles in the databases. The keywords used were: ("pregnancy" OR "gestation" OR "parturition") AND ("tuberculosis" OR "tb") AND ("immune" OR "innate" OR "adaptive").

The retrieved articles were processed using Zotero to remove duplicates and screened using the Rayyan website. Titles and abstracts were screened for relevance. Subsequently, the full texts of potentially eligible studies were assessed. Studies were then selected based on the inclusion and exclusion criteria. The inclusion criteria were: 1) study population of pregnant women with either latent or active TB through bacteriological examination, IGRA, TST, or PCR regarless of comorbidities or co-infections; 2) reporting of immune response outcomes (e.g., cytokine levels); 3) original articles publish in English; The exclusion criteria were: 1) review articles, commentaries, or reference abstracts; 2) studies lacking one or more of the following keywords—immunity, pregnancy, and tuberculosis, and articles that had been published before 2014. Two individual reviewers did the screening process from November 30th to December 4th, 2024. Any disagreements between the reviewers were resolved through consulting a third reviewer. The results of the study selection process are presented in a PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews) flow diagram.[11]

RESULTS

Study identification

The database search yielded 1.320 articles, which were reduced to 1,098 after duplicates were removed. These articles were then screened based on their titles and abstracts, resulting in the exclusion of 1.063 articles for various reasons. Subsequently, 35 full-text articles were screened based on the inclusion and exclusion criteria, and all 14 articles met the eligibility criteria. This process followed the PRISMA-ScR guidelines and is illustrated in FIGURE 1.[11]

Study characteristics and patient demographics

The characteristics of the fourteen studies presented in TABLE 1 highlight a research focus on immune responses in pregnant women with or without latent tuberculosis infection (LTBI) across various high TB burden countries, such as India, Ethiopia, Kenya, and Indonesia. The total number of participants across all studies exceeded 3.000, with a combined sample size of 3.742 individuals. The average age of the women studied ranged from 23 to 30 yr, and most were pregnant women without severe comorbidities such as HIV or diabetes, although some studies specifically recruited pregnant women with HIV.[10,12,13]

The majority of studies employed prospective cohort and longitudinal designs, with a few using cross-sectional or case-control approaches. Data collection was conducted at various stages of pregnancy, including the first to third trimesters, during delivery, and postpartum, to assess immunological dynamics, particularly with regard to interferon-gamma (IFN-γ), interleukin (IL)-2, IL-10, IP-10, and MCP-2. Diagnostic methods for LTBI varied and included IGRA, QGIT, and TST, with some studies also comparing the reliability of these different methods.[13,14,15]

Synthesis of immunology findings

The synthesis of the 14 studies revealed distinct patterns in innate and adaptive immune response, though not

without contradictions, particularly concerning IFN-γ.

Adaptive immunity: A predominant suppression

A majority of studies (8/14) reported a suppression of Th1-type adaptive immunity during pregnancy. This was most consistently observed as a significant decrease in IFN-γ levels during the second and third trimesters compared to postpartum periods.[10, 13-17] This suppression was also noted in IL-2 and other proinflammatory cytokines like IL-1β and IL-6.[16,18] This pattern was observed in both HIV-negative and HIV-positive cohorts.[11,15] Contradicting this trend, two studies reported higher IFN-γ levels in pregnant women with LTBI compared to non-infected controls or during the third trimester compared to earlier pregnancy and postpartum.[19,20]

Innate immunity and chemokine responses: A contrasting elevation

In contrast to the adaptive response, markers of innate immunity were frequently elevated. Multiple studies reported increased levels of the chemokines IP-10 and MCP-2 in pregnant women with TB infection compared to healthy controls.[21,22] An increase in the anti-inflammatory cytokine IL-1ra was also documented.[21]

Dynamic changes across pregnancy and postpartum

The data clearly illustrate that immune responses are not static. Several longitudinal studies tracked the evolution of responses, typically finding that the lowest levels of IFN-γ occurred in late pregnancy, with a rebound-though not always to fully protective levels-in the postpartum period.[9,12,14]

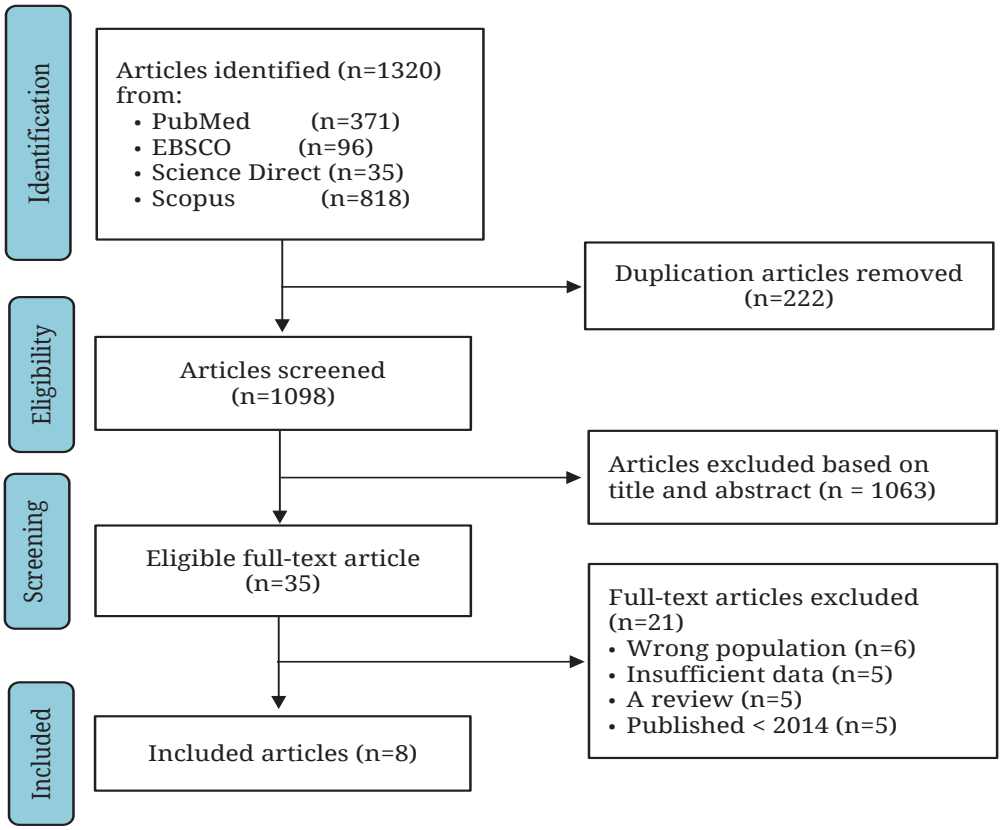

FIGURE 1. Article Screening Process Using PRISMA-ScR Chart

TABLE 1. Characteristics and key immunological findings of included studies (n=14)

Author, year	Title	Key findings	Immune profile pattern
Naik *et al.*[18]	Systemic inflammation in pregnant women with latent TB infection	Significantly lower levels of IL-1b, IL-6, IL-17A, and AGP but higher levels IFN-**γ** in women infected with *M. tb* women than in the comparison group.	Mixed profile
La Course *et al.*[10]	Effect of pregnancy on interferon gamma release-assay and tuberculin skin test detection of latent TB infection among HIV-infected women in a high burden setting	IFN-**γ** responses were significantly lower in pregnancy compared to postpartum.	Th1 suppression
Tesfaye *et al.*[9]	Dynamics of *M. tb*-specific and nonspecific immune responses in women with TB infection during pregnancy	Higher IL-2 and IP-10 expression and lower TGF-**β**1 secretion in late pregnancy and postpartum compared to earlier stages of pregnancy. In addition, nonspecific IL-2, IP-10, and MCP-2 levels were elevated postpartum in women with active TB.	Innate/elevated chemokines
Saha *et al.*[16]	*M. tb*-specific T-cell responses are impaired during late pregnancy with elevated biomarkers of TB risk postpartum	IFN-**γ** and IL-2 have significant decreases in the third trimester compared to before pregnancy, the second trimester, and postpartum.	Th1 suppression
Meirina *et al.*[19]	Comprehension of calcitriol levels in pregnant women with latent TB and immune function in their newborns	LTBI pregnant women had greater mean IFN-**γ** levels than their noninfected counterparts.	Conflicting IFN-**γ** (increase)
Ranaivomanana *et al.*[17]	Longitudinal variations of *M. tb*-induced IFN-**γ** responses in HIV-negative pregnant women exposed to TB	Lower median concentration of IFN-**γ** in pregnant women compared to their counterparts, especially in pregnant women with *M. tb* infection and even lower in active TB women. The decrease in IFN-**γ** levels was found in pregnant women after 6 mo	Th1 suppression
Birku *et al.*[15]	Effect of pregnancy and HIV infection on detection of latent TB infection by Tuberculin Skin Test and QuantiFERON-TB Gold In-Tube assay among women living in a high TB and HIV burden setting	Active TB pregnant and non-pregnant HIV-infected women have insignificant median CD4+ T-cell count differences.	Unclear
Weinberg *et al.*[11]	Effects of pregnancy and isoniazid preventive therapy on *M. tb* IFN-**γ** response assays in Women with HIV	Decreased IFN-**γ** responses in pregnancy reduced QGIT positivity.	Th1 suppression
Tesfaye *et al.*[21]	Alternative biomarkers for classification of latent TB infection status in pregnant women with borderline Quantiferon plus results	Higher MCP-2, IP-10, and IL-1ra in infected pregnant women than in healthy pregnant women and controls	Innate/ elevated chemokines
Tesfaye *et al.*[22]	Longitudinal *M. tb*-specific IFN-**γ** responses in Ethiopian HIV-negative women during pregnancy and postpartum	Higher IFN-**γ** responses during the 3rd trimester than in earlier pregnancy and postpartum. No significant difference between 1st/2nd trimester and postpartum IFN-**γ** levels.	Conflicting IFN-**γ**

TABLE 1. Cont.

Author, year	Title	Key findings	Immune profile pattern
Bhosale *et al.*[12]	Stages of pregnancy and HIV affect diagnosis of TB infection and *M. tb*-induced immune response: Findings from PRACHITi, a cohort study in Pune, India. Stages of pregnancy and HIV status influence TB diagnostic accuracy	There was a significant decrease in IFN- **γ** before labour. The level of IFN-**γ** increased 6 mo postpartum but still not enough to protect the mother from TB.	Th1 suppression
Mathad *et al.*[13]	Pregnancy differentially impacts performance of latent TB diagnostics in a high-burden setting	Lower QGIT and TST positive results were found among antepartum and at delivery than among postpartum women. TST positive results were found to be the lowest in delivery.	Th1 suppression

DISCUSSION

Summary of evidence and overall interpretation

This scoping review systematically mapped the evidence on immunological alterations in pregnant women with *M. tb* infection. Our synthesis reveals a complex and seemingly paradoxical immune state characterized by concurrent suppression of adaptive immunity and activation of innate inflammatory pathways.[9,12–16.] This dissonant immune activation suggests a immunological dysregulation rather than a simple, system-wide suppression, which may underpin the unique susceptibility of pregnant women to TB progression.

The paradox of suppressed adaptive immunity

Immune changes in pregnant women are primarily found in the adaptive immune system, where there is a shift from Th1 cell dominance to Th2.[9] This is reflected in decreased IFN-γ levels in pregnant women with TB compared to both healthy pregnant women and non-pregnant women with TB. This condition is more severe in cases of active TB than latent TB.[15,17,19,21] The decline becomes particularly evident by the 6 mo of pregnancy and continues into the third trimester, reaching its lowest point near labor.[17] IFN-γ plays a crucial part in fetal implantation, but this cytokine can also induce apoptosis and disrupt fetal growth; thus, there is a decline in this cytokine in pregnancy.[7,23] This makes pregnant women more vulnerable to *M. tb* infection. Interestingly, another study shows that IFN-γ responses are stronger in the third trimester compared to early pregnancy and postpartum. In the third trimester, it has been speculated that there is an increase in bacterial exposure and a decrease in bacterial replication control, which results in a surge of IFN-γ levels.[20] During the postpartum period, IFN-γ levels increase rapidly. However, by the sixth postpartum month, they have not yet reached protective levels against *M. tb*.[17] Progesterone, one of the hormones produced during pregnancy, alters the immune system towards an anti-inflammatory state. This hormone decreases during the third trimester, increasing proinflammatory cytokines.[10]

In addition to IFN-γ, CD4+ and CD8+ cells can also produce other cytokines such as IL-2, a pleiotropic cytokine involved

in the differentiation and hemostasis of both pro- and anti-inflammatory immune responses. High doses of IL-2 promote proinflammatory immune activity, while low doses enhance Treg cell differentiation and inhibit Th17 cells.[24] According to Tesfaye *et al.*, IL-2 levels increased during the third trimester and postpartum compared to the first and second trimesters in pregnant women with active TB.[9] However, in patients with TB infection, some studies reported decreased IL-2 production by CD4+ cells in the third trimester compared to before pregnancy, the second trimester, and postpartum.[12,16] The increase of IL-2 may reflect heightened *M. tb* activity within granulomas during active TB, triggering stronger proinflammatory responses.[9]

Other cytokines, such as IL-6, IL-17, and TGF-β, decrease during late pregnancy in infected pregnant women. IL-6 and IL-17 play a huge part in inhibiting TB progression.[25,26] The IL-6 level reaches the highest point during labor, while IL-17 increases during the second and third trimesters. Abnormalities of these cytokines can lead to complications in pregnancy.[27,28] In infected pregnant women, the increase of neutrophils as a sequela to the infection diminished the production of these cytokines.[18] As for TGF-β, this cytokine has a significant role in fetal protective effect and inhibits the activity of macrophages due to TB. The low concentration of this cytokine in this study may stem from the migration of the immune cells that produce this cytokine to the lungs; thus, only a certain amount of this cytokine is found in the blood.[9] These decreases are associated with an increased risk of developing active TB during the postpartum period.[18]

Concurrent activation of innate immunity

In pregnant women, the levels and function of innate immune cells such as neutrophils and NK cells decrease in the first trimester and begin to rise again in the second trimester.[29,30] With *M. tb* infection, proinflammatory immune activity increases further. This is demonstrated by elevated levels of IP-10 and MCP-2 in pregnant women with active TB compared to healthy pregnant women.[9,21] These chemokines are released by monocytes, endothelial cells, and fibroblasts in response to IFN-γ or direct pathogen stimulation.[31] Their levels are even higher postpartum than during pregnancy.[9] Interestingly, IFN-γ elevation can negatively affect other proinflammatory functions. For instance, IL-1β and IL-6 in pregnant women with latent TB compared to healthy pregnant women.[18] Furthermore, *M. tb* also stimulates macrophages to produce more IL-1ra, which can impede the function of IL-1β, thus enhancing susceptibility towards this bacterium.[32]

Limitations and inconsistencies

The primary limitation lies in the scarcity and inconsistency of the available data. While several studies have attempted to characterize immune responses in pregnant women with active TB, findings remain inconsistent, both in terms of measured immunological parameters and reported outcomes. The conflicting data also due to several factors: 1) Methodological variations, 2) Populations heterogeneity and 3) Disease spectrum (e.g., differing immune response in latent vs active TB during pregnancy). The small number of studies focusing specifically on this population further limits the generalizability of the findings. Despite these limitations, the collective evidence strongly suggests that the immune landscape in this vulnerable group is not one of simple suppression but significant immunological dysregulation.

CONCLUSION

In conclusion, the available evidence suggests a dynamic increase in the activation of the proinflammatory immune cells throughout pregnancy and into the postpartum period in women with TB infection. To solidify these findings, future research should prioritize longitudinal studies with standardized laboratory methods and well-characterized, homogeneous cohorts to dissect this complex host-pathogen interaction and clarify the timeline of immune changes throughout pregnancy and postpartum.

ACKNOWLEDGMENT

There is no conflict of interest in this study.

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