

A Review of Cytokine and C-Reactive Protein Profiles in Pregnant and Non-Pregnant Patients with Malaria

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Abstract: *Malaria remains a major infectious disease associated with significant maternal and fetal complications in endemic regions. Pregnancy increases susceptibility to malaria because physiological and immunological changes can influence host responses to Plasmodium infection. Cytokines and C-reactive protein are important biomarkers for understanding the inflammatory mechanisms involved in malaria pathogenesis. Cytokines, including interleukin-6 (IL-6), interleukin-10 (IL-10), tumor necrosis factor-alpha (TNF-α), interferon-gamma (IFN-γ), and interleukin-1 beta (IL-1β), regulate inflammatory and anti-inflammatory responses during infection. CRP, an acute-phase protein produced primarily by the liver, increases in response to inflammatory stimuli and may reflect the severity of systemic inflammation. However, the patterns of these biomarkers may differ between pregnant and non-pregnant patients because pregnancy modifies immune regulation and placental responses to malaria infection.*

Keywords: Malaria, pregnancy, cytokines, C-reactive protein, IL-6, IL-10, TNF-α, IFN-γ, placental malaria, inflammation

I. INTRODUCTION

Malaria is a mosquito-borne parasitic disease caused by Plasmodium species, particularly Plasmodium falciparum and Plasmodium vivax in humans. The disease continues to impose a substantial burden on public health, especially in tropical and subtropical regions. Pregnant women represent an important risk group because pregnancy-related immunological adaptations and the biological characteristics of placental infection can alter the clinical course of malaria. Malaria during pregnancy may contribute to maternal anemia, placental inflammation, fetal growth restriction, preterm delivery, low birth weight, and, in severe cases, maternal and fetal mortality.

The immune response to malaria involves interactions between innate and adaptive immune mechanisms. When parasites invade red blood cells, parasite-derived molecules and damaged host cells stimulate immune cells to release inflammatory mediators. Pro-inflammatory cytokines, such as TNF-α, IL-6, IL-1β, and IFN-γ, contribute to parasite control and immune activation. However, excessive or prolonged inflammation can also cause tissue injury and interfere with normal physiological processes. Regulatory cytokines, including IL-10, help limit inflammatory damage, although excessive regulatory activity may impair parasite clearance under certain circumstances.

CRP is another important component of the systemic inflammatory response. Its concentration increases following stimulation by inflammatory cytokines, particularly IL-6. Although CRP is not specific to malaria, its measurement may provide information about the degree of inflammation associated with infection. Combining cytokine measurements with CRP, parasite density, and clinical indicators may therefore provide a broader understanding of malaria-associated immune responses.

Pregnancy introduces additional complexity because the maternal immune system must maintain tolerance toward the developing fetus while preserving adequate protection against infections. The placenta also provides a specialized environment in which infected erythrocytes, inflammatory cells, and cytokines may interact. Consequently, pregnant and non-pregnant patients with malaria may demonstrate different inflammatory profiles, even when infected with the same parasite species.

This review evaluates the available scientific understanding of cytokine and CRP profiles in pregnant and non-pregnant patients with malaria, identifies the major factors influencing biomarker variation, and considers their potential relevance to diagnosis, disease severity, maternal health, and pregnancy outcomes.

REVIEW OBJECTIVES AND METHODOLOGICAL APPROACH

The principal objective of this review is to examine differences in inflammatory biomarkers between pregnant and non-pregnant patients with malaria. The review focuses on the following objectives:

To explain the roles of major pro-inflammatory and anti-inflammatory cytokines in malaria infection.

To assess the biological significance of CRP in malaria-associated systemic inflammation.

To compare the expected and reported patterns of inflammatory biomarkers in pregnant and non-pregnant patients.

To evaluate the relationship between inflammatory profiles, parasite burden, disease severity, and pregnancy outcomes.

To identify research gaps and future directions for biomarker-based malaria assessment.

The review adopts a narrative approach to synthesizing established knowledge from malaria immunology, pregnancy-associated malaria, inflammatory biomarkers, and clinical research. The discussion distinguishes well-established biological mechanisms from patterns that require further confirmation in direct comparative studies. It does not claim to be a systematic review or meta-analysis, and the illustrative comparisons below should not be interpreted as pooled clinical measurements.

CYTOKINE PROFILES IN MALARIA INFECTION

Cytokines are signaling proteins that regulate communication among immune cells and coordinate responses to parasitic infection. In malaria, their production is influenced by parasite species, parasite density, infection duration, host immunity, and clinical severity. During pregnancy, placental immune activity and maternal physiological changes further influence cytokine concentrations.

TUMOR NECROSIS FACTOR-ALPHA (TNF- α)

TNF- α is a major pro-inflammatory cytokine produced by activated monocytes, macrophages, and other immune cells. It contributes to immune activation and parasite control but may also promote endothelial dysfunction, fever, and tissue inflammation when produced excessively. In pregnancy-associated malaria, elevated TNF- α has been associated with placental inflammation and adverse pregnancy outcomes, including low birth weight. Its biological effects depend on concentration, duration of exposure, and the local tissue environment. Excessive TNF- α activity within the placenta may disrupt trophoblast function and interfere with normal fetal development. However, TNF- α concentrations do not consistently predict disease severity in every population, making interpretation alongside other clinical and laboratory findings essential.

INTERLEUKIN-6 (IL-6)

IL-6 participates in the acute inflammatory response, stimulates hepatic production of CRP, and influences immune-cell differentiation. During malaria infection, increased IL-6 may reflect systemic inflammation and activation of innate immune mechanisms. Pregnant patients with malaria may exhibit elevated IL-6 because of both infection-related inflammation and interactions between maternal and placental immune responses. Nevertheless, IL-6 levels can vary according to gestational age, parasite burden, sampling time, and the presence of additional infections. Its relationship

with CRP is particularly important because CRP may provide a more accessible measure of downstream inflammatory activity, although it cannot identify the specific cytokine or infection responsible.

INTERLEUKIN-10 (IL-10)

IL-10 is an important anti-inflammatory and immunoregulatory cytokine that limits excessive immune activation. It helps regulate macrophage activity and can reduce the production of pro-inflammatory mediators. During malaria, IL-10 may rise as a compensatory response to inflammatory stimulation. In pregnancy-associated malaria, elevated peripheral IL-10 has been associated with placental infection and inflammatory changes in some studies. However, its interpretation is complex: sufficient regulatory activity may protect maternal and placental tissues from excessive inflammation, whereas excessive suppression of inflammatory responses may weaken parasite control. Research involving placental malaria has therefore emphasized the balance between IL-10 and pro-inflammatory mediators rather than treating IL-10 as an exclusively protective or harmful marker.

INTERFERON-GAMMA (IFN- γ)

IFN- γ is a cytokine involved in cellular immunity and activation of macrophages. It contributes to the host response against intracellular pathogens, including malaria parasites. During pregnancy, IFN- γ concentrations may differ between peripheral maternal blood and placental tissue because immune cells can accumulate in or migrate toward the placenta. This distinction is important when comparing studies that use different biological specimens. An elevated local IFN- γ response may contribute to parasite control, but excessive inflammatory activity may also affect placental function. Conversely, insufficient responses may impair effective immunity. Consequently, the relationship between IFN- γ and pregnancy outcomes depends on the site, timing, and intensity of immune activation.

INTERLEUKIN-1 BETA (IL-1 β)

IL-1 β is a pro-inflammatory cytokine associated with inflammasome activation and the amplification of inflammatory responses. It may contribute to fever, leukocyte recruitment, and local tissue inflammation during malaria. In placental malaria, inflammatory pathways involving IL-1 β may affect trophoblast function and placental nutrient transport. Nevertheless, differences in measurement techniques and sample collection can influence reported concentrations. IL-1 β should therefore be investigated together with other inflammatory markers and indicators of placental function rather than interpreted independently.

C-REACTIVE PROTEIN (CRP) IN MALARIA

CRP is an acute-phase protein synthesized predominantly by hepatocytes in response to inflammatory signaling, particularly IL-6. Its circulating concentration can increase during infections, tissue injury, and other inflammatory conditions. In malaria, CRP may reflect the systemic inflammatory response associated with parasite infection and the resulting immune activation.

CRP measurement has practical advantages because it is widely available in clinical laboratories, relatively straightforward to perform, and generally less technically demanding than multiplex cytokine analysis. It may help characterize the inflammatory burden when interpreted alongside fever, hemoglobin concentration, parasite density, and other clinical findings.

However, CRP is a nonspecific biomarker. Increased concentrations can result from bacterial coinfection, respiratory infections, urinary tract infections, obstetric complications, and other inflammatory conditions. Pregnancy itself may also influence baseline inflammatory measurements, although the magnitude varies among individuals and clinical circumstances. Consequently, a raised CRP concentration cannot establish a malaria diagnosis or distinguish malaria from other infections.

In pregnant patients, the clinical interpretation of CRP requires particular caution because an elevated value may reflect systemic malaria, placental inflammation, or an unrelated condition. Similarly, a low CRP concentration does not

reliably exclude malaria, especially when infection is asymptomatic, low-density, or sampled early. Serial CRP measurements may be useful in selected clinical investigations, but their value for predicting placental malaria or adverse birth outcomes requires further validation.

COMPARISON OF PREGNANT AND NON-PREGNANT PATIENTS WITH MALARIA

The comparison between pregnant and non-pregnant patients must account for differences in immune regulation, parasite exposure, placental sequestration, age, previous pregnancies, and disease severity. Non-pregnant patients provide a useful reference for systemic malaria-associated inflammation, whereas pregnant patients may demonstrate additional inflammatory processes associated with placental infection.

Studies comparing peripheral and placental blood have reported differences in cytokine concentrations, indicating that circulating measurements may not accurately represent the placental immune environment. Research also suggests that IL-10 and TNF- α may be elevated in placental malaria, although the direction and magnitude of differences vary across populations and study designs.

Table 1. Major inflammatory biomarkers and their potential differences in pregnant and non-pregnant patients with malaria

Biomarker	Principal function	Potential profile in pregnant patients with malaria	Potential profile in non-pregnant patients with malaria
TNF- α	Pro-inflammatory signaling and immune activation	May increase with placental inflammation and parasite sequestration	May increase with systemic inflammation and disease severity
IL-6	Inflammation and stimulation of CRP production	May increase with systemic or placental inflammatory activity	May increase during acute infection and inflammatory responses
IL-10	Regulation of excessive inflammation	May be elevated as a regulatory response to placental or systemic inflammation	May increase to regulate malaria-associated inflammation
IFN- γ	Cellular immunity and macrophage activation	May vary between maternal peripheral blood and placental tissue	Reflects systemic cellular immune activation
IL-1 β	Amplification of inflammation and inflammasome activity	May contribute to placental inflammatory changes	May contribute to systemic inflammatory responses
CRP	Acute-phase response protein	May rise because of malaria or other maternal inflammatory conditions	May rise because of malaria or other concurrent inflammatory conditions

Source note: This table summarizes established biological functions and qualitative patterns reported in the literature. It is not a dataset of direct measurements, and it does not imply that every biomarker is consistently higher in pregnant than in non-pregnant patients.

Table 2. Important considerations when interpreting inflammatory profiles

Comparison factor	Why it matters	Recommended approach
Pregnancy status	Pregnancy changes immune regulation	Include pregnant and non-pregnant comparison groups
Gestational age	Inflammatory physiology changes during pregnancy	Record trimester and gestational week
Placental infection	Peripheral blood may not reflect placental inflammation	Use placental assessment where clinically and ethically appropriate

Parasite density	Inflammatory responses may vary with parasite burden	Quantify parasitemia using standardized methods
Malaria species	Different species may produce different clinical and immune patterns	Confirm species using microscopy or an appropriate diagnostic assay
Parity	Previous pregnancies can influence immunity to placental malaria	Record gravidity and parity
Coinfection	Other infections may elevate CRP and cytokines	Screen for relevant coinfections
Sampling time	Cytokines and CRP can change during infection and treatment	Standardize sampling relative to symptom onset and therapy

RELATIONSHIP BETWEEN INFLAMMATORY BIOMARKERS AND PREGNANCY OUTCOMES

The clinical significance of cytokines in malaria extends beyond the identification of inflammation. Their balance may influence placental development, nutrient transport, maternal health, and fetal growth. Placental malaria is particularly associated with the sequestration of infected erythrocytes in the placental intervillous space, where immune-cell recruitment and inflammatory responses can interfere with normal placental function.

Maternal anemia: Malaria contributes to anemia through the destruction of infected and uninfected erythrocytes, splenic clearance, and impaired erythropoiesis. Inflammatory mediators may further affect iron regulation and red blood cell production. CRP and cytokine concentrations can help characterize the inflammatory environment but cannot independently establish the cause of anemia.

Low birth weight and fetal growth restriction: Persistent placental infection and inflammation may compromise the transfer of oxygen and nutrients to the fetus. Elevated inflammatory activity has been associated with adverse birth outcomes in some studies, although the strength of these associations varies by population, gestational timing, and parasite burden.

Preterm delivery and pregnancy loss: Severe or sustained inflammatory responses may contribute to placental dysfunction and adverse pregnancy outcomes. However, cytokine concentrations are not deterministic predictors of these events, and their clinical value requires validation in appropriately designed longitudinal studies.

Maternal disease severity: Systemic inflammatory markers may contribute to the assessment of disease severity when interpreted with clinical signs, organ-function measurements, and parasitological findings. Neither CRP nor an individual cytokine should replace established malaria diagnostic procedures or severity assessments.

Although research has improved understanding of malaria-associated immune responses, several important gaps remain.

First, many studies examine cytokines in isolation rather than assessing coordinated inflammatory and regulatory pathways. A combined analysis of TNF- α , IL-6, IL-10, IFN- γ , IL-1 β , and CRP may offer a more comprehensive representation of the host response.

Second, direct comparisons between pregnant and non-pregnant patients remain challenging when studies differ in parasite species, geographical setting, gestational stage, age, previous malaria exposure, and clinical severity. Future research should use standardized recruitment criteria and comparable laboratory procedures.

Third, cross-sectional investigations cannot reliably establish whether biomarker changes precede placental complications or merely reflect existing infection. Longitudinal studies involving repeated measurements during pregnancy and follow-up of birth outcomes are needed. A systematic review of placental malaria biomarkers similarly identified the need for longitudinal research to establish whether biomarkers can predict placental infection before delivery.

Fourth, CRP requires additional evaluation as part of a combined biomarker panel. Studies should assess its diagnostic performance, sensitivity, specificity, and incremental clinical value relative to parasite testing and routine clinical measurements.

Finally, future investigations should evaluate whether biomarker patterns differ between *P. falciparum* and *P. vivax* infections, between symptomatic and asymptomatic cases, and across different levels of parasitemia. Such research could help determine whether inflammatory profiles are suitable for risk stratification in specific clinical settings.

II. CONCLUSION

Cytokines and C-reactive protein are important components of the inflammatory response to malaria, but their interpretation becomes more complex during pregnancy. TNF- α , IL-6, IFN- γ , and IL-1 β contribute to inflammatory and cellular immune responses, whereas IL-10 helps regulate excessive inflammation. CRP provides an accessible indicator of systemic inflammatory activity but lacks specificity for malaria. Pregnancy-associated malaria may produce distinct inflammatory patterns because of maternal immune adaptation, placental sequestration, and localized immune-cell activity. These mechanisms may contribute to maternal anemia, placental dysfunction, low birth weight, and other adverse pregnancy outcomes.

The available evidence supports investigating cytokines and CRP together rather than relying on a single biomarker. Nevertheless, the direction and magnitude of biomarker differences between pregnant and non-pregnant patients cannot be generalized across all populations. Standardized comparative studies, longitudinal sampling, parasite-density measurements, and careful assessment of pregnancy outcomes are necessary to clarify their diagnostic and prognostic value. Ultimately, inflammatory biomarkers may complement established malaria diagnostic methods and clinical assessments, but their routine use for predicting disease severity or pregnancy outcomes should depend on evidence of validated clinical benefit.

REFERENCES

1. Chua, C. L. L., Hasang, W., Rogerson, S. J., & Teo, A. (2018). Variations in the leukocyte and cytokine profiles between placental and maternal circulation in pregnancy-associated malaria. *Research and Reports in Tropical Medicine*.
2. Conroy, A. L., et al. (2017). Systemic inflammatory response to malaria during pregnancy is associated with pregnancy loss and preterm delivery. *Clinical Infectious Diseases*, 65(10), 1729–1736.
3. Fried, M., & Duffy, P. E. (2002). Maternal malaria: A challenge for the placenta. *American Journal of Tropical Medicine and Hygiene*, 66(6), 7–12.
4. Muehlenbachs, A., et al. (2010). Maternal interferon gamma, tumor necrosis factor, and interleukin-10 responses to placental malaria and their association with birth outcomes. Related evidence on inflammatory responses in placental malaria can be explored through.
5. Obeagu, E. I., & Nwankwo, O. B. (2026). Malaria in pregnancy induces a pro-inflammatory cytokine milieu: Comparative analysis with non-infected pregnant and non-pregnant women. *Asian Journal of Immunology*, 9(1), 88–94.
6. Peripheral and placental biomarkers in women with placental malaria: A systematic review. (2015).
7. Placental malaria: A new insight into the pathophysiology. (2017).
8. Pregnancy-associated malaria: Effects of cytokine and chemokine expression. (2022). *Travel Medicine and Infectious Disease*, 47, 102282.
9. Submicroscopic infections with *Plasmodium falciparum* during pregnancy and their association with circulating cytokine, chemokine, and cellular profiles. (2014). *Clinical and Vaccine Immunology*.
10. World Health Organization. (2017). Meeting report of the Evidence Review Group on malaria in pregnancy.