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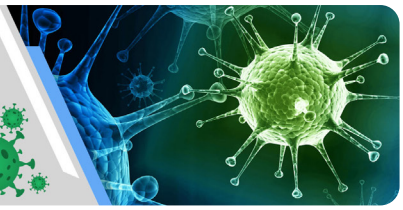

Neutrophils and Pregnancy-Associated Malaria

Moussa Djimde[*,1,2,3,4], Kassoum Kayentao[1], Charles Arama[1], Alassane Dicko[1], Petra F. Mens[2,3] and Henk H.D.F. Schallig[2,3]

Summary

Purpose: Pregnant women living in areas with transmission of *Plasmodium falciparum* are exposed to malaria and its harmful consequences on pregnancy outcomes. Neutrophils are the most abundant white blood cells (WBC) in the bloodstream and are innate immune key effectors against infections. Substantial work has been done to study the role of neutrophils in malaria, but little on pregnancy-associated malaria (PAM). This review focuses on neutrophil responses to malaria during pregnancy that may help us to understand their dynamics and effects on pregnancy outcomes.

Source: A literature review covering the topic of PAM and neutrophils were accessed via PubMed® and Embase® databases. In total, 20 unique publications were found in PubMed while 99 in Embase®. After excluding 114 irrelevant titles and abstracts, 5 original articles full texts were assessed and included in this review.

Results: Due to oestrogen stimulation, the number of neutrophils is higher in pregnant women compared to non-pregnant women. This increase in neutrophil numbers reaches a plateau in the second and third trimesters of pregnancy. However, the number of circulating neutrophils in peripheral blood is lower in pregnant women with *Plasmodium falciparum* malaria than in pregnant women without malaria. The decrease in circulating neutrophils in the context of PAM may reflect the accumulation of neutrophils in the infected placenta. Data showed that the prevalence of children with low birth weight (LBW) was higher in pregnant women with high number of pigmented peripheral neutrophils compared to malaria-infected pregnant women with low number of pigmented peripheral neutrophils.

Conclusions: This review aids our understanding of the dynamics of neutrophils during a malaria infection in in pregnant women by providing scientific evidence that suggests that neutrophil levels decrease in pregnant women with malaria infection. A negative association between the number of pigmented neutrophils in women with malaria and the birth weight of children points towards prioritizing future research in pregnant women with malaria on these cells involved in the first line of innate immunity.

Keywords: neutrophil, pregnancy, malaria, immunity

Abbreviations:

HIV:	Human immunodeficiency virus
IFN-γ	Interferon gamma
IL-	Interleukin

Affiliation:

[1]Malaria Research and Training Center (MRTC), University of Sciences of Techniques and Technologies of Bamako (USTTB), Mali

[2]Amsterdam University Medical Centres, Academic Medical Centre at the University of Amsterdam (AMC), Amsterdam, the Netherlands

[3]Amsterdam Institute for Infection and Immunity, Infectious Diseases Programme, Amsterdam, the Netherlands

[4]Biomedical Research and Training Center (BioMed-RTC), Mali

***Corresponding author:**
Moussa Djimde, Malaria Research and Training Center (MRTC), University of Sciences of Techniques and Technologies of Bamako (USTTB), Mali.

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iRBCs	infected red blood cells
LBW	Low birth weight
MIP-1α	Macrophage inflammatory protein-1α
MMP9	Matrix metalloproteinase
MPO	Myeloperoxidase
NE	Neutrophil elastase
NET	Neutrophil extracellular traps
PAM	Pregnancy-associated malaria
PM	Placental malaria
PRTN3	Proteinase 3
P. falciparum	*Plasmodium falciparum*
P. vivax	*Plasmodium vivax*
ROS	Reactive oxygen species
SSA	Sub-Sahara Africa
TNF-α	Tumor necrosis factor alpha
WBC	White blood cell

Introduction

Despite ongoing efforts, malaria continues to be a major public health problem. The number of malaria deaths per 100,000 population at risk has been estimated at 14.8 in 2021 [1]. Malaria in pregnancy can occur in any country in which transmission of Plasmodium falciparum occurs. It is a refractory disease that can affect the blood, placenta, brain and other internal organs. These are distinctive features of *P. falciparum* malaria [2]. The World Health Organization's (WHO) reported in 2021 [3] that among the estimated 33.8 million pregnancies that occur worldwide annually, 34% (11.6 million) were exposed to malaria infection in sSA alone. Although pregnant women are more vulnerable to malaria than non-pregnant women, this vulnerability is greater in women who are in their first or second pregnancy and who have not yet developed adequate pregnancy-specific immune responses against the parasite strains that sequester into the placenta microvasculature [4]. Pregnancy-associated malaria (PAM) is responsible for maternal anaemia and low birth weight (LBW) [5], both increasing the risk of maternal and infant mortality.

Neutrophils (also known as polymorphonuclear cells) are the most abundant white blood cells in the human bloodstream [6]. They are involved in innate immune defence and play a crucial role against bacterial and fungal pathogens, and also participate in the development of inflammatory reactions [7]. They are key effectors of innate immunity by eliminating pathogens through phagocytosis, by generating reactive oxygen species (ROS) and antimicrobial peptides, or by forming neutrophil extracellular traps (NET) [8]. In addition, they also play a role in the activation and regulation of the immune response, through the secretion of cytokines and chemokines [9].

During PAM, *P. falciparum*-infected erythrocytes sequester in the placenta, often resulting in monocyte infiltration [10] with increased production of pro- and anti-inflammatory mediators [11,12]. Given the abundance of neutrophils in the white blood cell count and their role in innate immunity, it is essential to understand their role in PAM. This will contribute to the management of this disease during pregnancy. However, little is known about the dynamics of neutrophils during PAM and their contribution to control malaria infection. Therefore, this review synthesized the available data on how neutrophils respond to malaria infection in pregnant women. It aims to get an insight into the behaviour of neutrophils during PAM and how they can affect the pregnancy outcome. This review also examined the role of PAM in immune system activation.

Methods

Search Strategy

Original peer-reviewed publications in English, French, or Spanish covering the topic of "pregnancy-associated malaria and neutrophil" were accessed via PubMed® and Embase® databases. From 8th June 2022 to 13th June 2022, bibliographic research was conducted for this review. The database search has been updated on 5th April 2023. The literature search involved the articles indexed in PubMed® (from 1928 to April 2023) or in Embase® (from 1947 to April 2023). In PubMed®, the database search was done using the topic of malaria, pregnancy and neutrophils. Searching for publications on ***malaria***, the search term used was: "malar*"[All Fields] OR "palud*"[All Fields]. About publications on ***pregnancy***, the search term used was: "gravid*" OR "grossess*"[All Fields] OR "embaraz*"[All Fields] OR "pregnan*"[All Fields]. About ***neutrophils***, the search term used was "neutro*"[All Fields]. Then, looking for publications on ***malaria and pregnancy***, the search term used was: ("malar*"[All Fields] OR "palud*"[All Fields]) AND ("gravid*" OR "grossess*"[All Fields] OR "embaraz*"[All Fields] OR "pregnan*"[All Fields]).

Malaria and neutrophil publications search required the use of search term: ("malar*"[All Fields] OR "palud*"[All Fields]) AND ("neutro*"[All Fields]).

Neutrophil and pregnancy publications search was done using the term: ("gravid*" OR "grossess*"[All Fields] OR "embaraz*"[All Fields] OR "pregnan*"[All Fields]) AND "neutro*"[All Fields]. Finally, for the publications investigating ***malaria in pregnancy and neutrophils*** the following search term was used: "malar*"[All Fields] OR "palud*"[All Fields]) AND ("gravid*" OR "grossess*"[All

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Fields] OR "embaraz*"[All Fields] OR "pregnan*"[All Fields]) AND ("neutro*"[All Fields]).

This search identified 7,109 publications addressing PAM, but only 20 publications addressing PAM in which there was an investigation of the neutrophils.

A database search was also done in Embase® (a biomedical research database) for all publications using the topic of ***malaria***: (search term: (malar* OR palud*)); ***pregnancy*** (search term: (pregnan* OR gravid* OR grossess* OR embaraz*)); ***neutrophil*** (search term: (neutro*)), ***malaria and pregnancy*** (search term: (malar* OR palud*) AND (pregnan* OR gravid* OR grossess* OR embaraz*)), ***malaria and neutrophil*** (search term: (malar* OR palud*) AND (neutro*)), ***neutrophil and pregnancy*** (search term: (pregnan* OR gravid* OR grossess* OR embaraz*) AND (neutro*)) and ***PAM and neutrophils*** (search term: (malar* OR palud*) AND (pregnan* OR gravid* OR grossess* OR embaraz*) AND (neutro*)). It identified 9,546 publications addressing PAM, but only 99 publications addressing PAM in which there was an investigation of the neutrophils.

Eligibility Criteria

This review included originals articles reporting on malaria in pregnancy that assessed the dynamics and / or activity of neutrophils, including in vitro studies. Excluded from this review were review papers, editorials, case reports, conference abstracts and commentaries. Animal studies were also not included in this systematic review.

Results

Of the 119 articles that met the search criteria, 114 were excluded on the basis of title and abstract (Fig. 1). An additional 47 papers, identified from the references of the 5 original papers, contributed to this review. In total 52 manuscripts were used for this review and are listed as references 4, 5 and from 11 to 61 in the reference list.

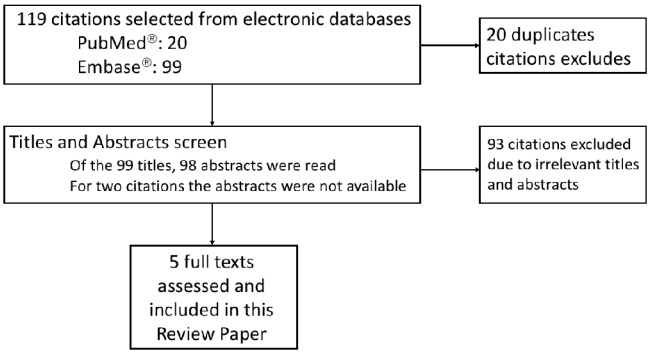

Figure 1: Flow chart for the selection of papers assessed in this review. The diagram shows the procedure for selecting articles for this review. First, duplicate articles were eliminated and then articles not suitable for this review paper were eliminated based on the titles and abstracts.

Leukocytes and neutrophils variations during pregnancy

The total white blood cell (WBC) count was found to be higher in pregnant women than in non-pregnant women due to an increase in neutrophils[13]. The number of neutrophils increases at the time of the oestrogen peak of a normal menstrual cycle and, if fertilization has occurred, neutrophils continue to increase[14]. Subsequently, there is an increase in neutrophils from day 45 of pregnancy, reaching a plateau during the second and third trimesters[12]. Breastfeeding may prolong the rise in neutrophil counts (*reviewed by* Cruickshank *et al.*[14]). Increases in neutrophil count and metabolic activity are apparently the result of oestrogen stimulation [15–17].

Neutrophils and cytokine variations in PAM

In response to stress, such as inflammation or infection, neutrophils are released into the blood circulation. This is a fast-early response to stimuli, together with early release. Normally, neutrophils are released in large numbers, more than any other leukocytes. In case of PAM, recently, Okezie Caleb Okamgba *et al* showed that the number and type of WBC lineages that may be preferentially increased against the pathogenic malaria parasite in peripheral and placental blood [18]. Comparison of the mean of the neutrophil counts between malaria-infected peripheral and placental blood, showed that the number of neutrophils is higher in placental blood [18]. Bostrom S *et al.* showed that the number of neutrophils in the peripheral blood stream was reduced in pregnant women with *P. falciparum* infection compared to pregnant women without malaria infection (Fig. 2 A) [19]. In contrast, other studies reported an increase in neutrophil counts in African children with uncomplicated malaria [20,21]. In contrast to African children, a significant reduction of neutrophil counts in Thailand adults with *P. falciparum* malaria was described [22]. This difference in immune response may reflect different inflammatory responses and differences in neutrophils functions. Age difference and hormonal status could also play a role in immune response.

Although undetectable in the peripheral blood, the malaria parasite may be present in the placenta and induce an immune response detectable in the peripheral blood. It has been investigated that the number of maternal peripheral granulocytes decreases with placental malaria (PM) in the presence and absence of pre-existing human immunodeficiency virus (HIV) infection [23]. Even though the study did not perform a differential analysis targeting the number of neutrophils among granulocytes, these results are consistent with previous publications that have reported reduced numbers of neutrophils in malaria-infected pregnant women compared with uninfected women [19,24]. This reduction in the number of neutrophils in the peripheral

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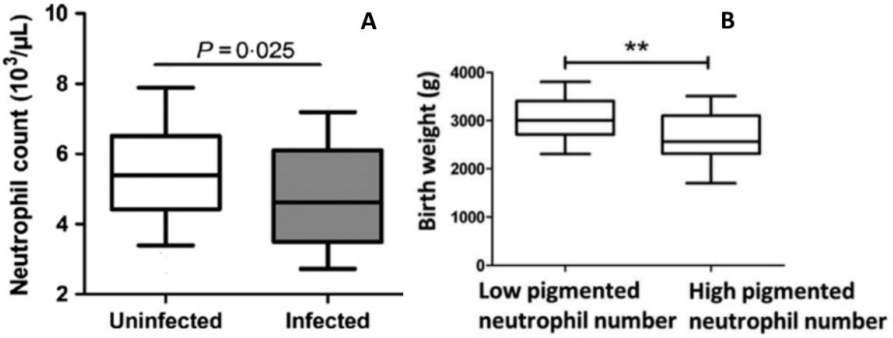

Figure 2: Neutrophils count according malaria infection and Birth weight according pigmented neutrophil number. In pregnant women, the neutrophil count drops when infected with malaria parasites (Fig. 2 A). The birth weight of babies is lower when the number of pigmented neutrophils in the peripheral blood is high during pregnancy (Fig. 2 B). Adapted from Boström *et al.*, 2017 [19] (Fig. 2 A, Reprinted with permission of Wiley Parasite Immunology) and Chua *et al.*, 2015 [23] (Fig. 2 B; Reprinted with permission of International Journal for Parasitology).

blood may be explained by their accumulation in the placenta infected with malaria parasites. Other publications confirmed an important accumulation of neutrophils in the placenta during PM [18,25].

The decreased neutrophil counts observed in peripheral blood might partially reflect the accumulation of neutrophils in the infected placenta as part of immune response. Neutrophils, eosinophils, basophils and mast cells have in fact often been observed in histological studies of placental biopsies from pregnant women with malaria infection [26,27]. Moreover, cytokine levels such as interferon gamma (IFN-γ), tumor necrosis factor alpha (TNF-α), interleukin-4 (IL-4), IL-6, and IL-10 were elevated in pregnant women with malaria compared to those uninfected by malaria parasites [14]. Other studies reported that IFN-γ and IL-6 were significantly higher in malaria-infected pregnant women than in non-pregnant uninfected women [15,16] . Additional finding (Torre et *al.,* 2002) [30], showed that a significantly higher levels of IFN-γ, TNF-α, and IL-10 were found in malaria-infected pregnant women than in their control counterparts. Data from East Africa, published by Bayoumi *et al* [31] and Boström *et al* [32], show a significant increase in IL-10 in malaria infected pregnant women compared to uninfected pregnant women. However, data from Nigeria [18] described that IFN-γ, IL-4 and IL-10 were higher in peripheral blood not infected with malaria parasites than in infected peripheral blood. The authors believe that this may be due to regional differences, as Nigeria is a region where malaria is very prevalent. From these findings, it can be speculated that the intensity of malaria prevalence can modulate cytokine levels.

In addition to *in vivo* studies, *in vitro* models have also been used to observe the activation of immunological parameters including neutrophils. *In vitro* studies showed that stimulation of human placental cells line that originates from a choriocarcinoma (BeWo cells) [33] with malaria infected red blood cells (iRBCs) resulted in a pronounced release of interleukin 8 (IL-8) and strongly induced neutrophil migration in a transwell assay. This is in the same line with other co-culture studies where iRBCs incubated with whole blood [34] or brain endothelial [35] cells also led to IL-8 production. In addition to this, IL-8 as well as macrophage inflammatory protein-1 alpha (MIP-1α) were elevated in placenta plasma of pregnant women with malaria [11]. This suggests that the PM associated with choriocarcinoma promote neutrophil migration and activities.

Neutrophil levels in the peripheral bloodstream and poor birth outcome during PAM

It has been reported based on data collected in Papua New Guinea that women in the second or third trimester of pregnancy with increased numbers in pigmented neutrophils gave birth to babies with lower weights (Fig. 2 B) [36]. Furthermore, the prevalence of children with low birth weight (LBW) was higher in pregnant women with high number of pigmented peripheral neutrophils than in PAM women with low numbers [36]. When the women were grouped into primigravidae, secundigravidae and multigravidae, the study found no significant difference in either birth weight or pigmented neutrophil count among the different groups [36]. The role of neutrophils in the pathogenesis of PAM needs to be further explored, but the available data are consistent with the role of neutrophil activation in the pathogenesis of idiopathic intrauterine growth restriction and preeclampsia [37,38]. Evidence suggests that abnormally pigmented neutrophils clearance in malaria-infected women may be delayed in the peripheral circulation, leading to chronic inflammation and thus impacting fetal growth [39]. Furthermore, pigmented

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neutrophil counts were positively correlated with levels of TNF-α [40], a pro-inflammatory cytokine steady associated with LBW [4,41]. Similarly, sequestration of maternal monocytes in placental intervillous blood has been linked to LBW in placental malaria [5,42]. It could be that their excessive cytokine production impairs placental nutrient transport [43] and placental trophoblast invasion [44], thereby contributing to poor fetal growth. Circulating pigmented neutrophils counts can be used to predict malaria fatality with more accuracy compared to peripheral parasitemia [45] but remains speculative regarding poor delivery outcome.

Neutrophil activation markers and malaria or malaria and HIV coinfection in pregnant women

Neutrophil activation results in massive production of its markers such as myeloperoxidase (MPO), matrix metalloproteinase (MMP9), neutrophil elastase (NE) and proteinase 3 (PRTN3). MPO is involved in the oxidative burst of neutrophils and macrophages. Interestingly, the placental blood MPO and PRTN3 levels are increased with PM in both HIV negative and HIV positive pauci-gravidae women relative to women negative to both PM and HIV [23]. In addition, MPO was found in placental tissue sections, suggesting that this factor may be produced by both neutrophils and intervillous macrophages. However, most MPO-expressing cells observed by immunofluorescence also stain for NE, identifying them as neutrophils. Furthermore, it has been found that placental levels of MPO, MMP9, and PRTN3 correlated positively with placental malaria parasite density [23].

This further confirms that MPO is derived from neutrophils whose activation is proportional to the parasite density. MPO levels in placental blood were significantly increased in chronic, inflammatory PM in primigravida. MPO is associated with vascular dysfunction [46], which underlies the pathophysiology of many vascular inflammatory diseases, including arteriosclerosis and coronary artery disease [47,48]. High neutrophil activation, proved by higher plasma concentrations of not only MPO but also PRTN3 and NE, is correlated with severe pediatric malaria [49]. Relatedly, MMP9, an endopeptidase discharged by neutrophils and monocytes, is incriminated in the pathogenesis of severe malaria [50–52]. A polymorphism in MMP9 protects against PM, implying an important role for this enzyme in *P. falciparum* infection [53]. High concentrations of neutrophil-derived antimicrobial compounds can render these cells harmful to the host [54–56]. Neutrophils can rapidly be recruited to sites of infection and tissue injury [8], generate ROS which can exacerbate preeclampsia [57–60].These findings suggest that malaria during pregnancy associated with HIV infection perturb granulocyte activation. Further exploration is needed to better understand neutrophil function in pregnant women co-infected with malaria and HIV.

Conclusions

This review highlighted that in case of malaria infection, in contrast to the increase observed in children, neutrophil levels decrease in pregnant women. Data gathered in this review suggest a negative association between the number of pigmented neutrophils in women with malaria and the birth weight of the child, pigmented neutrophils being predictive of disease severity. On the other hand, gravidity does not have an effect on birth weight or the number of pigmented neutrophils. In addition, PM and PM/HIV co-infection disrupt granulocyte levels, and soluble signatures of neutrophil activation are associated with indicators of PM infection and associated symptoms. This paper showed that PAM has the ability to induce immune activation with the release of cytokines but also that this activation could be exacerbated when choriocarcinoma is associated.

Future Investigations

Neutrophils and their potential role(s) in PAM remain understudied. We have listed below future research priorities that will greatly help us to understand the role of neutrophils during malaria in pregnancy and reduce the burden of this disease in pregnant women:

1. Determine whether pigmented neutrophils became pigmented in the peripheral circulation after schizogony or whether they became pigmented in the intervillous space of the placenta and were recirculated.

   Approach: PM is a special forthcoming of PAM. Pigmented neutrophil levels are known to be negatively correlated with birth weight [19]. If pigmented in the placenta, pigmented neutrophils may be absent in the peripheral blood while colonising the placenta intervillous space. This can be an additional hidden threat because during pregnancy, microscopy will not detect these pigmented neutrophils.

2. Assessment of the effect of neutrophil levels variation in artemisinin-based combination therapies (ACTs) effectiveness in pregnant women with malaria.

   Approach: Decreased neutrophil counts in children have been shown to decrease the effectiveness of ACTs (Moussa Djimde *et al.*, in press at the Journal of Infection in Developing Countries (JIDC)). The same study showed that the rate of reappearance of malaria parasites after treatment in neutropenic patients was higher among those treated with artemether lumefantrine. Many phenomena occur during pregnancy including hormonal and immunological changes and could affect ACTs effectiveness, with a general shift from cell-mediated immunity toward humoral immunity [62]. If pregnant women based on their neutrophil count respond

as children to ACTs (Moussa Djimde *et al.,* in press at JIDC), a drug with longer prophylactic coverage may be advised.

Ethics approval and consent to participate

The various original studies have been approved by the ethics committees in the respective countries.

Consent for publication

Not applicable

Availability of data and Material

Not applicable

Competing interests

None of the authors declare a conflict of interests.

Author's Contributions

MD did the database search and wrote the first draft of the paper. KK, CA, AD, PFM and HDFHS have made a substantial intellectual contribution to the work. All authors approved this paper for publication.

Authors' Information

Moussa Djimde: mdjimde@icermali.org

Kassoum Kayentao: kayentao@icermali.org

Charles Arama: charama@icermali.org

Alassane Dicko: adicko@icermali.org

Petra F. Mens: p.f.mens@amsterdamumc.nl

Henk H.D.F. Schallig: h.d.schallig@amsterdamumc.nl

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