

## Original Article

# Impact of Malaria in Pregnancy in Papua New Guinea: A Systemic Review of Epidemiology, Prevention & Treatment.

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## ABSTRACT

**Background:** This paper review examines and evaluates how malaria affects pregnant women and their infants in Papua New Guinea, where *P. falciparum* and *P. vivax* are prevalent. It reviews ten papers from 1986 to 2021 on the epidemiology, prevention and treatment of malaria, which can lead to serious problems during pregnancy.

**Methods:** This was a systematic review conducted by searching articles from Google Scholar database and Mendeley Elsevier database and PubMed. The inclusion criteria were namely articles published in 1900 to 2022 years, cross sectional design study, and using quantitative method. The study subjects were pregnant women who visited antenatal clinics with or without malaria, research locations in Papua New Guinea. The exclusion criteria were articles that did not available in full text and located not in Papua New Guinea. The articles were then critically appraised and synthesized according to five main themes: anemia and iron deficiency, submicroscopic malaria infections, placental malaria infection, and knowledge, attitudes and practices concerning malaria in pregnancy & congenital malaria.

**Results:** A total of 10 papers were included in the review, covering various aspects of malaria epidemiology, prevention and treatment in pregnant women and their newborns in PNG. The main findings of the papers were: (1) anemia was very common and associated with splenomegaly, iron deficiency and malaria infection; (2) submicroscopic infections were common, but not associated with maternal anemia or low birth weight; (3) placental malaria infection was detected in 18.5% of placentas, and was associated with maternal anemia, low birth weight and preterm delivery; (4) there was a general awareness of the term "malaria", but it was often confused with other illnesses or pregnancy symptoms; (5) congenital

malaria infection was detected in 5.6% of newborns, mostly due to *P. falciparum*.

**Conclusions:** This literature review provided useful evidence and recommendations for improving malaria prevention and control in pregnant women and their newborns in PNG, but also highlighted the need for more research and action to address the remaining challenges and gaps. The review concluded that malaria in pregnancy is a serious public health problem in PNG that requires comprehensive and integrated approaches to achieve its elimination by 2030.

**Keywords:** Malaria in pregnancy, Papua New Guinea, Anemia, Submicroscopic malaria infections, Placental malaria infection.

## INTRODUCTION

Malaria is a parasitic disease caused by the infection of red blood cells by protozoan parasites of the genus *Plasmodium*. There are five species of *Plasmodium* that can infect humans: *P. falciparum*, *P. vivax*, *P. ovale*, *P. malariae* and *P. knowlesi*. Malaria is transmitted by the bite of female *Anopheles* mosquitoes, which inject the infective sporozoites into the human bloodstream. The sporozoites then travel to the liver, where they multiply and form merozoites, which are released into the blood and invade the red blood cells. The merozoites undergo asexual reproduction and cause the rupture of the red blood cells, releasing more merozoites and toxins that cause the symptoms of malaria, such as fever, chills, headache, nausea, vomiting and anemia. Some merozoites develop into sexual forms called gametocytes, which can be taken up by another mosquito during a blood meal and continue the life cycle in the mosquito vector [12].

Malaria is one of the most important infectious diseases in the world, affecting more than 200 million people and causing more than 400,000 deaths annually [13]. Most of the malaria burden occurs in sub-Saharan Africa, where *P. falciparum* is the predominant species and causes severe and often fatal malaria [13]. However, malaria is also endemic in other regions of the world, such as Asia, Latin America and Oceania, where *P. vivax* is more prevalent and causes relapsing and chronic malaria [13]. Malaria transmission varies according to geographical, climatic and ecological factors that influence the distribution and abundance of the mosquito vectors and the human hosts [13].

Malaria in pregnancy is a major public health problem in malaria endemic areas, as pregnant women and their fetuses are particularly vulnerable to the adverse effects of malaria infection [14]. Malaria infection during pregnancy can cause maternal anemia, low birth weight, preterm delivery and congenital malaria, which can have serious consequences for the health and survival of mothers and infants [14]. The mechanisms by which malaria affects pregnancy outcomes are complex and multifactorial, involving immunological, hormonal, nutritional and placental factors [14]. The placenta is a key organ in pregnancy that provides oxygen and nutrients to the fetus and removes waste products from the fetal circulation. The placenta can also be infected by *Plasmodium* parasites, which can impair its function and cause inflammation, hypoxia and oxidative stress [14]. Placental malaria (PM) infection is characterized by the presence of infected erythrocytes and/or the malaria pigment in monocytes or fibrin in placental biopsies [15]. PM infection can also lead to transplacental transmission of *Plasmodium* parasites to the fetus, resulting in congenital malaria (CM) infection [15]. CM infection is defined as the presence of parasites or antigens in cord blood or peripheral blood within seven days after birth [15].

The epidemiology, prevention and treatment of malaria in pregnancy vary according to the species of *Plasmodium* involved and the level of malaria transmission in different regions [14]. In sub-Saharan Africa, where *P. falciparum* is dominant and transmission is high or moderate, malaria in pregnancy is mainly a problem of primigravid women who have not yet developed sufficient immunity to protect themselves and their fetuses from malaria infection [14]. The main interventions for preventing malaria in pregnancy in this region are intermittent preventive treatment in pregnancy (IPTp) with sulfadoxine-pyrimethamine (SP), insecticide-treated nets (ITNs) and effective case management of clinical malaria [14]. IPTp consists of administering SP at least twice during pregnancy at routine

antenatal care visits after quickening [16]. ITNs are bed nets impregnated with insecticides that kill or repel mosquitoes and prevent them from biting humans [17]. Effective case management involves prompt diagnosis and treatment of clinical malaria with artemisinin-based combination therapy (ACT) or quinine depending on the stage of pregnancy [18].

In other regions of the world, where *P. vivax* is more prevalent and transmission is low or unstable, malaria in pregnancy affects women of all gravidities who have not acquired sufficient immunity due to low exposure to malaria infection [14]. The main interventions for preventing malaria in pregnancy in this region are ITNs and effective case management of clinical malaria [14]. IPTp with SP is not recommended for *P. vivax* infection because SP has no activity against the liver stages of *P. vivax* that cause relapses [14]. Moreover, SP resistance is widespread among *P. falciparum* populations in these regions [14]. Therefore, alternative strategies for preventing relapses of *P. vivax* infection during pregnancy are needed, such as intermittent screening and treatment (IST) or intermittent preventive treatment (IPT) with chloroquine or other safe and effective drugs [14]. IST consists of screening pregnant women for malaria infection at routine antenatal care visits and treating them if positive [19]. IPT consists of administering a full course of an anti-malarial drug at regular intervals during pregnancy regardless of infection status [20].

Papua New Guinea (PNG) is a country in Oceania that has a high burden of malaria, with an estimated 1.8 million cases and 600 deaths in 2017 [13]. PNG is characterized by a complex and heterogeneous malaria epidemiology, with both *P. falciparum* and *P. vivax* coexisting and causing approximately equal proportions of malaria cases [21]. Malaria transmission is perennial and varies from low to high intensity depending on the altitude, rainfall and vegetation [21]. Malaria in pregnancy is a serious public health problem in PNG, affecting both primigravid and multigravida women and causing maternal anemia, low birth weight, preterm delivery, placental malaria and congenital malaria [1, 2, 3, 4, 5, 6, 7, 8, 9, 10]. The aim of this review is to synthesize the available evidence on the epidemiology, prevention and treatment of malaria in pregnancy in PNG, and to identify the challenges and opportunities for improving maternal and infant health outcomes.

By reviewing the existing literature on malaria in pregnancy in PNG, this paper aims to provide a comprehensive and updated overview of the epidemiological situation, the current prevention and treatment strategies, and the gaps and challenges that need to be addressed. This will be of benefit by way of informing policy makers, health

workers, researchers and donors on how to improve the delivery and effectiveness of maternal and child health interventions in PNG. Moreover, this will contribute to the global efforts to eliminate malaria and reduce its burden on vulnerable populations, especially pregnant women and their infants.

## METHODS

This study is a systemic review conducted by searching for articles from the Mendeley Elsevier database, Google Scholar, Web Science and PubMed with the keywords “malaria in pregnancy, and malaria in Papua New Guinea.” The articles that were found and collected was read carefully to see whether the article meets the writer’s inclusion criteria for use as literature.

The inclusion criteria are articles published from 1900 to 2021 that can be accessed, full paper in pdf format and free. The articles that were initially collected but were unable to access were excluded due to unavailability of full pdf format. The research design was included in a systemic review using qualitative methods with cross-sectional design. The study was conducted in Papua New Guinea and the subjects are the pregnant women with or without malaria.

In the initial stage of the search, 7,604 articles were obtained using the keywords “malaria in pregnancy”, then it was narrowed down to “malaria in Papua New Guinea”, which produced 1,102 articles. Then it was filtered again with more specific keywords “impact or effect of malaria and pregnant women in Papua New Guinea” resulted in 99 articles. There was no year gap search for the articles due to limited number of articles written, which led me to manually choose from 1900 to 2021. Later, the results were filtered again based on titles and abstracts, and the results obtained were 99 articles and finally 18 articles were selected based on the full text and assessed for eligibility. However, these 18 articles had to be filtered again to match the inclusion and exclusion criteria in order to get the correct results based on the systemic review study and shortlisted to 10 articles for eligibility.

## RESULTS

The results of the ten articles can be organized into five main themes: anemia and iron deficiency, submicroscopic malaria infections, placental malaria infection, and knowledge, attitudes and practices concerning malaria in pregnancy & congenita malaria. The main findings and comparisons of each theme are as follows:

*Anemia and iron deficiency:* All the articles that measured hemoglobin levels or anemia status in pregnant women and their newborns found that anemia was very common and associated with adverse pregnancy outcomes, such as low birth weight and preterm delivery. The prevalence of anemia ranged from 37% to 86% in pregnant women and from 13% to 42% in newborns. The main causes of anemia were splenomegaly, iron deficiency and malaria infection. Iron deficiency was also common and associated with higher birth weights and lower odds of low birth weight and preterm birth. The prevalence of iron deficiency ranged from 18% to 67% in pregnant women and from 3% to 28% in newborns. The main causes of iron deficiency were poor dietary intake, helminth infections and blood loss. However, iron supplementation by TDI was associated with more malaria infection in primipara, but not in multipara. TDI was not associated with an improvement in hemoglobin status from the first antenatal visit to the postnatal check. TDI was also associated with higher neonatal serum ferritin and lower neonatal hemoglobin.

*Submicroscopic malaria infections:* All the articles that used PCR to detect malaria infection in pregnant women and their newborns found that submicroscopic infections were prevalent and had different effects on pregnancy outcomes than clinical or microscopic infections. The prevalence of submicroscopic infections ranged from 9% to 40% in pregnant women and from 2% to 10% in newborns. The main species involved were *P. falciparum* and *P. vivax*. Submicroscopic infections were not associated with maternal anemia or low birth weight. However, submicroscopic infections were associated with lower risk of malaria infection, especially in primigravid women. Higher ferritin levels were also associated with higher risk of malaria infection. Submicroscopic infections were also detected in a high proportion of placental biopsies, but were not associated with adverse birth outcomes. Clinical *P. vivax* infection was associated with maternal anemia, but not with low birth weight or preterm birth.

*Placental malaria infection:* All the articles that examined placental biopsies for malaria infection found that PM infection was a major risk factor for adverse pregnancy outcomes in PNG. The prevalence of PM infection ranged from 14% to 27%, depending on the diagnostic method used. The main species involved were *P. falciparum*, followed by *P. vivax* and *P. malariae*. PM infection was associated with rural residence, primigravidity and symptomatic malaria during pregnancy. PM infection was also associated with maternal anemia, low birth weight and preterm delivery.

*Knowledge, attitudes and practices concerning malaria in pregnancy:* Only one article explored the

perceptions and behaviors of pregnant women, health staff and community members regarding malaria in pregnancy and its prevention in PNG. The article found that there was a general awareness of the term “malaria”, but it was often confused with other illnesses or pregnancy symptoms. Many preventive methods for malaria in pregnancy were related to general healthy living. There were also varied messages from health staff about the risks of malaria in pregnancy. The uptake of interventions such as ITNs and chloroquine was influenced by availability, comfort and workload [2].

*Congenital malaria (CM) infection* was detected in 5.6% of newborns, mostly due to *P. falciparum*. CM infection was associated with maternal malaria infection, especially in the third trimester. CM infection was also associated with low birth weight, prematurity and neonatal mortality. For example, the article reported that the prevalence of CM infection was 5.6% in cord blood and 4.4% in peripheral blood [10]. It also

reported that CM infection was more common in newborns whose mothers had malaria infection in the third trimester (9.1%) than in those whose mothers had no malaria infection during pregnancy (2.9%) [10]. Finally, the article reported that CM infection increased the risk of low birth weight by 2.3 times, prematurity by 2.4 times and neonatal mortality by 3.8 times [10].

These results show that malaria in pregnancy is a complex and multifaceted problem in PNG that requires comprehensive and integrated approaches to address its epidemiological, clinical, social and environmental determinants.

Below is the appraisal done on each paper for eligibility and the results for each article as shown in Table 1 & Figure 1.

<b>Table 1: Eligibility criteria of the ten (10) articles &amp; their findings listed</b>										
<b>Authors</b>	S.J. Oppenheimer et al, 1986	P.J. Lehner et al, 1988	B.J Brabin et al, 1990	S.J Allen et al, 1998	Erin V.W. Andrew et al, 2015	Elvin Lufele et al, 2017	Azucena Bardaji et al, 2017	Freya J.I Fowkes et al, 2018	Holger W. Unger et al, 2019	Holger W. Unger et al, 2022
<b>Articles 1 – 10</b>										
<b>Article # 1: S.J. Oppenheimer et al, 1986</b>										
<b>Title:</b> Total dose iron infusion, malaria & pregnancy in PNG										
<b>Country/Province:</b> Madang/PNG										
<b>Study Design (Year):</b> Case Study June 1980 - Dec 1981										
<b>Sample Size:</b> 544 pregnant mothers with their 566 newborns										
<b>Purpose of the Study:</b> To analyze effects of total dose intravenous iron infusion (TDI) to mothers during pregnancy in an area of endemic malaria.										
The study aimed to examine the impact of TDI on maternal and neonatal hematological parameters, malaria infection, fetal maturity and birth weight.										
<b>Results/Conclusions:</b> Total dose iron infusion (TDI) was associated with more slide positive peri-natal malaria in primipara (first-time mothers) but not in multipara (mothers who have given birth more than once). TDI was not associated with an overall improvement in hemoglobin status from the first ante-natal level recorded to the post-natal check. Post-natal malaria was associated with lower ante-natal and post-natal hemoglobin levels. There was no evidence of any effect of TDI in pregnancy or of maternal malaria on fetal maturity or birth weight. TDI to the mother was associated with higher neo-natal serum ferritins and lower neo-natal hemoglobins. Maternal post-natal malaria was associated with significantly lower iron in serum in newborns. It is suggested that routine total dose iron infusion to anemic pregnant mothers in malaria endemic areas may be contraindicated.										
<b>Article #2: P.J. Lehner et al, 1988</b>										
<b>Title:</b> Congenital malaria in PNG										
<b>Country/Province:</b> Madang/PNG										
<b>Study Design (Year):</b> Prospective Case-control Study January 1985-February 1986										

**Sample Size:** -73 non-pregnant females; -51 pregnant females; -48 cord blood samples; -52 peripheral blood samples

**Purpose of the Study:** The purpose of this study was to examine the relationship between parasitemia and anti-malarial antibody titers in mothers and their newborn, with particular regard to congenital malarial infection. The authors wanted to understand how common and how harmful was the transfer of parasites across the placenta in Papua New Guinea, where malaria is very prevalent.

**Results/Conclusions:** The incidence of malarial infection in pregnant women at delivery, their corresponding infants and umbilical cords and a control group of non-pregnant women were investigated in the Madang Region of PNG. Parasitemia occurred in 24.7% of non-pregnant females compared with 29.4% of pregnant females. Malarial parasites were found in 14.6% cord blood samples and in 7.7% samples of the infant's peripheral blood, indicating transplacental transmission. Infection with *P. falciparum* was commoner in pregnant than non-pregnant females, and accounted for all the cord and infant infections. A significant correlation was found between anti-malarial IgG antibodies in paired maternal and cord bloods. There was an association between umbilical cord infection and low levels of cord antibody. Clinical malaria developed in at least one out of the seven cases in which placental transfer of parasites was known to have occurred.

**The main conclusions of the study were:**

Transfer of parasites across the placenta is a common event in PNG. Further consideration should be given to treatment with anti-malarial drugs of infants with cord or peripheral blood parasitemia or, indeed, of all infants of mothers with parasitemia.

**Article # 3:**

**B.J Brabin et al, 1990**

**Title:** Consequences of maternal anemia on outcome of pregnancy in a malaria endemic area in PNG.

**Country/Province:** Madang/PNG

**Study Design:** Cohort case control Study July 1985 - June 1987

**Sample Size:** 592 – registered pregnant women; 516 – attended delivery; 11 – twin pregnancies registered but not included in analysis; 386 – screened for anemia at delivery; 294 – booking; 335 – non-pregnant women screened for anemia (representative sample)

**Purpose of the Study:** The main purpose for this study was to investigate the prevalence of anemia during pregnancy and its effects on the fetus in relation to parasite and spleen rates of pregnant women living in a malaria endemic area in Papua New Guinea.

**Results/Conclusions:** There was a high prevalence of anemia in pregnant women living in a malaria endemic area in Papua New Guinea, with 44% of primigravidae and 29% of multigravidae having severe anemia ( $Hb < 8 \text{ g dl}^{-1}$ ) after 28 weeks gestation. The risk of severe anemia was significantly associated with splenomegaly and iron deficiency for all gravidae, and malaria prophylaxis was an important factor in controlling anemia.

Anemia, iron deficiency and malaria were related to the risk of low birthweight and growth retardation in primigravidae, and the extent to which malaria control can reduce the risk of low birthweight will vary depending on the prevalence and causes of anemia in women.

**Article # 4:**

**S.J Allen et al, 1998**

**Title:** Causes of preterm delivery & intrauterine growth retardation in a malaria endemic region of PNG

**Country/Province:** Madang/PNG

**Study Design:** Prospective observational Study July 1994 - Jan 1996

**Sample Size:** 987 singletons babies

**Purpose of the Study:** To identify causes of preterm delivery and intrauterine growth retardation (IUGR) in a malaria endemic region of Papua New Guinea.

**Results/Conclusions:** The prevalence of preterm delivery was 10.8% and the prevalence of IUGR was 16.9% in the study population. Malaria infection of the placenta was associated with a reduction in birthweight of 140 g and an increased risk of preterm delivery and IUGR, especially in primigravidae. Maternal hemoglobin concentration was the main determinant of preterm delivery, and anemia was significantly more common in malaria infected than non-infected women. Poorer maternal nutritional status and smoking were associated with both preterm delivery and IUGR, and greater antenatal clinic attendance predicted increased birthweight in term infants. Protection against malaria during pregnancy, especially in primigravidae, improved nutrition in women and discouragement of smoking would probably reduce both preterm delivery and IUGR. Greater use of existing antenatal clinics might increase birthweight in term infants.

**Article # 5:** **Erin V.W. Andrew et al, 2015**

**Title:** Knowledge Attitudes & Practices concerning malaria in pregnancy: Results from a Quantitative study in Madang, PNG  
**Country/Province:** Madang/PNG

**Study Design:** Qualitative Study 2009 – 2011

**Sample Size:** 9 (Nine) focus groups discussions consisting of; 94 in-depth interviews lasting 45mins -90mins; -52 pregnant women; -7 women with babies under 1 year; -16 relatives of pregnant women; -12 community leaders; -7 health care providers; - follow-up 27 case study women (post-partum & during pregnancy.)

**Purpose of the Study:** The purpose of this study was to explore the knowledge, attitudes and practices concerning malaria in pregnancy and its prevention in Madang, Papua New Guinea, a high prevalence area. The study also aimed to understand the factors that influence the uptake of interventions such as insecticide-treated mosquito nets and chloroquine prophylaxis among pregnant women.

**Results/Conclusions:** The term “malaria” was often conflated with general sickness or with pregnancy-related symptoms, and many preventive methods for malaria in pregnancy were related to practices of general healthy living. There were varied messages from health staff about the risks of malaria in pregnancy, and some women did not receive any information or advice on this topic. The availability and perceived comfort of sleeping under insecticide-treated mosquito nets were important determinants of usage, and women’s heavy workload influenced chloroquine adherence. The non-specific symptoms of malaria in pregnancy and its resultant conflation with symptoms of pregnancy that are perceived as normal have implications for malaria prevention and control.

**Article # 6:** **Elvin Lufele et al, 2017**

**Title:** Risk factors & pregnancy outcomes associated with placental malaria in a prospective cohort of PNG.

**Country/Province:** Madang/PNG

**Study Design:** Prospective cohort study 2009 – 2012

**Sample Size:** Placental biopsies from 1451 pregnant women

**Purpose of the Study:** The purpose of the research was to examine the association between placental malaria infection and adverse pregnancy outcomes such as low birth weight, preterm delivery and anemia in a cohort of pregnant women in Papua New Guinea, where malaria transmission is high and heterogeneous. The research also aimed to identify the risk factors for placental malaria infection and to evaluate the impact of malaria prevention strategies on pregnancy outcome.

**Results/Conclusions:** Placental malaria infection was detected in 18.5% of the placentas examined, of which 3.7% were acute, 3.8% chronic, and 11.0% past infections. Risk factors for placental malaria infection included residing in rural areas, being primigravid and having symptomatic malaria during pregnancy.

Compared to uninfected women, acute infections were associated with low-birth-weight babies, whereas chronic infections were associated with preterm delivery and anemia. Among pregnant women receiving at least one dose of intermittent preventive treatment in pregnancy and using insecticide-treated bed nets, active placental malaria infections were associated with adverse outcomes. Improved malaria prevention is required to optimize pregnancy outcomes in Papua New Guinea.

**Article # 7:** **Azucena Bardaji et al, 2017**

**Title:** Burden & Impact of Plasmodium vivax in pregnancy. A multi-centre prospective observational study.

**Country/Province:** Madang/PNG

**Study Design:** Prospective observational study 2009 – 2011

**Sample Size:** -Guatemala: 2010 enrolled, 1045 followed; -Colombia: 2010 enrolled, 1045 followed; -Brazil: 2010 enrolled, 1045 followed; -India: 2010 enrolled, 1045 followed; -Papua New Guinea: 1348 enrolled, 777 followed: Total = 9388 pregnant women

**Purpose of the Study:** The purpose of this study was to examine the prevalence and impact of Plasmodium vivax infection in pregnancy in five endemic countries: Guatemala, Colombia, Brazil, India and Papua New Guinea. The study also aimed to understand the factors that influence the uptake of interventions such as insecticide-treated mosquito nets and chloroquine prophylaxis among pregnant women

**Results/Conclusions:** The prevalence of Plasmodium vivax infection in maternal blood at delivery was 0.4% by microscopy and 7% by PCR, while the prevalence of Plasmodium falciparum infection was 0.5% by microscopy and 1.4% by PCR. The prevalence of Plasmodium vivax infection in placental blood was 0.4% by microscopy and 3.7% by PCR, while the prevalence of Plasmodium falciparum infection was 0.2% by microscopy and 1.6% by PCR.

The prevalence of Plasmodium vivax infection in cord blood was 0.02% by microscopy and 2.6% by PCR, while the prevalence of Plasmodium falciparum infection was 0.05% by microscopy and 1.2% by PCR. Clinical Plasmodium vivax infection in pregnancy was associated with increased risk of maternal anemia, while submicroscopic infections were not associated with increased risk of moderate-severe anemia, low birth weight or preterm delivery.

-Among pregnant women receiving at least one dose of intermittent preventive treatment in pregnancy and using insecticide-treated bed nets, active Plasmodium vivax infections were associated with adverse outcomes.

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**Article # 8: Freya J.I Fowkes et al, 2018**

**Title:** Iron deficiency during pregnancy is associated with a reduced risk of adverse birth outcomes in a malaria-endemic area in a longitudinal cohort study.

**Country/Province:** Madang/PNG

**Study Design:** Prospective observational study 2009-2011

**Sample Size:** -279 pregnant women; -248 were followed until delivery.

**Purpose of the Study:** To examine the association between iron deficiency and adverse birth outcomes such as low birth weight and preterm birth in a cohort of pregnant women in Papua New Guinea, where malaria transmission is high and heterogeneous. The study also aimed to understand the mechanisms by which iron deficiency may protect against poor pregnancy outcomes, and to evaluate the benefit of iron supplementation in pregnancy.

**Results/Conclusion:** Iron deficiency in pregnant women was common (71% at enrolment) and associated with higher mean birth weights (230 g) and reduced odds of low birth weight (adjusted odds ratio, aOR = 0.32) and preterm birth (aOR = 0.57). The protective association of iron deficiency on low birth weight was mainly mediated through mechanisms independent of malaria or anemia. Iron supplementation in pregnancy did not improve birth outcomes, and may have increased the risk of malaria and anemia in some women.

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**Article # 9: Holger W. Unger et al, 2019**

**Title:** Microscopic & submicroscopic Plasmodium falciparum infection, maternal anemia & adverse pregnancy outcomes in PNG: a cohort study

**Country/Province:** Madang/Province

**Study Design:** Prospective cohort study Nov 2009 – Feb 2013

**Sample Size:** 2190 pregnant women of 14- & 26-weeks' gestation; -1936 had availability of data

**Purpose of the Study:** To investigate the effects of microscopic and submicroscopic P. falciparum infection on maternal anemia and adverse pregnancy outcomes in PNG, where malaria transmission is low to moderate. The study also aimed to evaluate the efficacy of a novel intervention (SP plus azithromycin) for the prevention of LBW in comparison with a standard treatment (SP plus chloroquine)

**Results/Conclusions:** A total of 9.8% of women had P. falciparum infection detected in venous blood at antenatal enrolment, and 3.5% had it detected in peripheral blood at delivery. Submicroscopic P. falciparum infections at enrolment or at delivery were not associated with maternal anemia or adverse birth outcomes such as low birth weight (LBW) or preterm birth. Microscopic P. falciparum infection at antenatal enrolment was associated with anemia at delivery. Peripheral microscopic P. falciparum infection at delivery was associated with LBW and preterm birth.

The main conclusions of the study were:

-A substantial proportion of *P. falciparum* infections in pregnant women in PNG were submicroscopic.  
-Microscopic, but not submicroscopic, infections were associated with adverse outcomes in women receiving malaria preventive treatment and insecticide-treated bed nets.  
-The findings suggest that current preventive strategies may not be sufficient to eliminate the burden of malaria in pregnancy in PNG, and that more sensitive diagnostic tools and more effective interventions are needed.

**Article # 10:** **Holger W. Unger et al, 2022**

**Title:** Associations of maternal iron deficiency with malaria infection in a cohort of pregnant PNG women.

**Country/Province:** Madang/PNG

**Study Design:** Observational & Analytic study 2009 – 2013

**Sample Size:** 2793 pregnant women recruited.; -1888 pregnant women had data available for secondary analysis

**Purpose of the Study:** To explore the relationship of maternal iron deficiency or ferritin levels with indicators of malaria infection (*P. falciparum*, *P. vivax*) in a cohort of pregnant women in PNG, where malaria transmission is low to moderate. The study also assessed for modification of iron-malaria relationships by gravidity or treatment arm. -The study was a secondary analysis of data from a larger clinical trial that evaluated the efficacy of intermittent treatment with SP plus azithromycin for the prevention of LBW in comparison with a standard treatment (SP plus chloroquine).

**Results/Conclusions:** Two-thirds (n = 1226) of women had iron deficiency and 13.7% (n = 258) had peripheral parasitemia at antenatal enrolment, and 18.7% (120/1,356) had evidence of malaria infection on placental histology. Overall, iron deficiency was associated with reduced odds of peripheral parasitemia at enrolment, peripheral parasitemia at delivery, and past placental infection. Corresponding increases in the odds of infection were observed with two-fold increases in ferritin levels. There was effect modification of iron-malaria relationships by gravidity. At delivery, iron deficiency was associated with reduced odds of peripheral parasitemia amongst primigravida, but not multigravida women. A two-fold increase in ferritin associated with increased odds of placental blood infection and active placental infection on histology amongst primigravid women only.

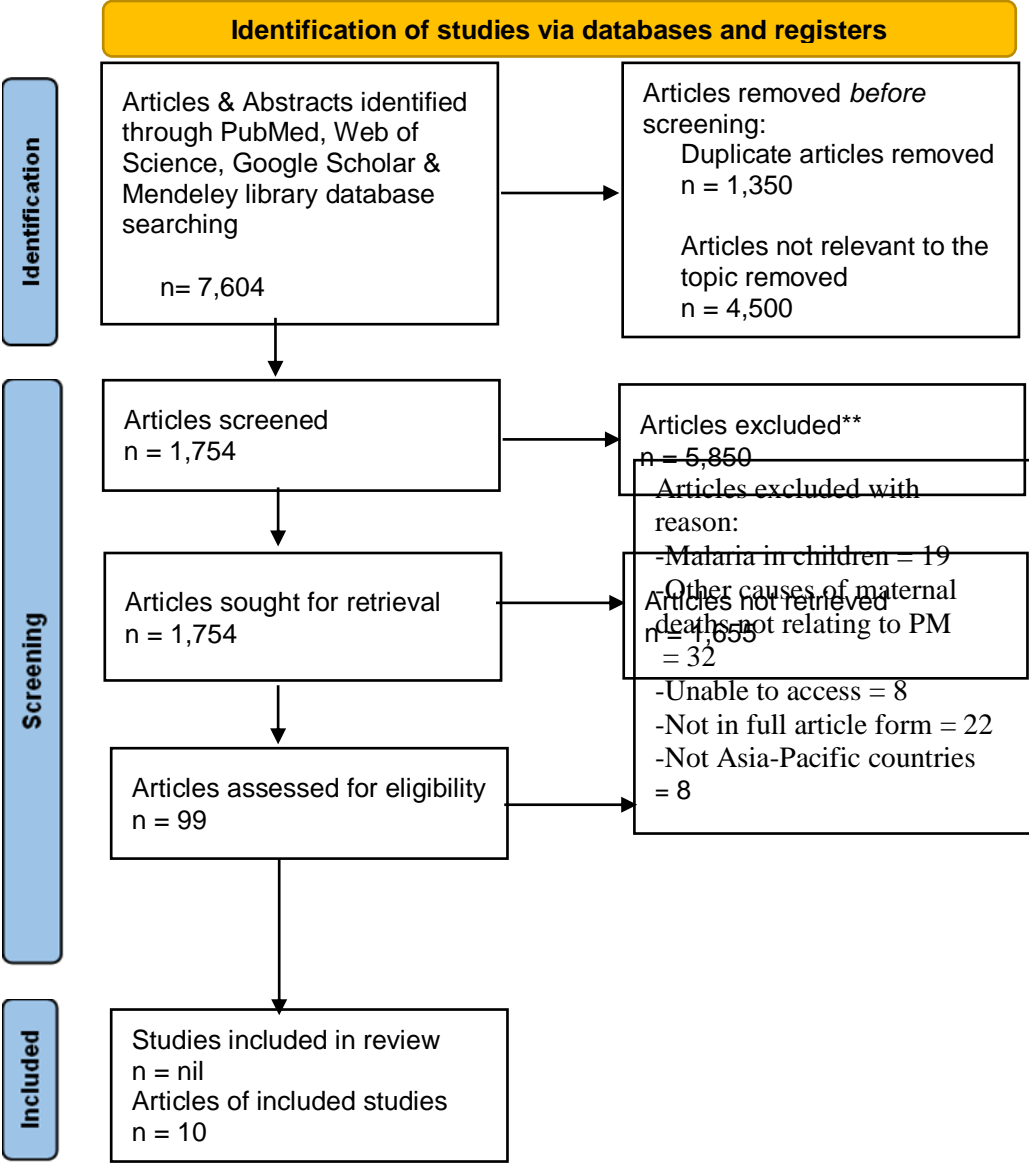
The main conclusions of the study were:

Low maternal ferritin at first antenatal visit was associated with a lower risk of malaria infection during pregnancy, most notably in primigravid women.

The mechanisms by which maternal iron stores influence susceptibility to infection with *Plasmodium* species require further investigation



Figure 1: The Criteria for Quality of the Paper Appraisal.



## Flowchart of PRISMA Methods (2020)



## DISCUSSION

Malaria in pregnancy is a major public health problem in Papua New Guinea (PNG), where both *Plasmodium falciparum* and *P. vivax* are endemic. Malaria infection during pregnancy can cause maternal anemia, low birth weight, preterm delivery and congenital malaria, which can have serious consequences for the health and survival of mothers and infants. The papers reviewed in this topic explored various aspects of malaria epidemiology, prevention and treatment in pregnant women and their newborns in PNG.

One of the common themes that emerged from the papers was the high prevalence and impact of anemia in pregnant women and their babies. Anemia was found to be very common and associated with splenomegaly, iron deficiency and malaria infection [1, 2, 3, 4]. Anemia also increased the risk of low birth weight, especially for first-time mothers [1, 2]. Iron deficiency was common and associated with higher birth weights and lower odds of low birth weight and preterm birth [4]. The protective effect of iron deficiency was mainly mediated by mechanisms independent of malaria or anemia [4]. However, iron supplementation by total dose intravenous iron infusion (TDI) was associated with more malaria infection in primipara, but not in multipara [8]. TDI was not associated with an improvement in hemoglobin status from the first antenatal visit to the postnatal check [8]. TDI was also associated with higher neonatal serum ferritin and lower neonatal hemoglobin [8]. These findings suggest that routine TDI to anemic pregnant mothers in malaria endemic areas may be contraindicated, and that alternative strategies to prevent and treat anemia during pregnancy are needed [8].

Another theme that emerged from the papers was the role of submicroscopic malaria infections in pregnancy outcomes. Submicroscopic infections were defined as infections that are detectable by PCR but not by microscopy or rapid diagnostic tests. Submicroscopic infections were common, but not associated with maternal anemia or low birth weight [3]. However, submicroscopic infections were associated with lower risk of malaria infection, especially in primigravid women [3]. Higher ferritin levels were associated with higher risk of malaria infection [3]. The mechanisms by which maternal iron stores influence susceptibility to infection with *Plasmodium* species require further investigation [3]. Submicroscopic infections were also detected in a high proportion of placental biopsies, but were not associated with

adverse birth outcomes [9]. Clinical *P. vivax* infection was associated with maternal anemia, but not with low birth weight or preterm birth [6]. These findings suggest that submicroscopic infections may have different effects on pregnancy outcomes than clinical or microscopic infections, and that more sensitive diagnostic tools are needed to detect and treat these infections [3, 6].

A third theme that emerged from the papers was the importance of placental malaria (PM) infection as a risk factor for adverse pregnancy outcomes. PM infection was defined as the presence of infected erythrocytes and/or the malaria pigment in monocytes or fibrin in placental biopsies. PM infection was detected in 18.5% of placentas, and was associated with rural residence, primigravidity and symptomatic malaria during pregnancy [9]. PM infection was also associated with maternal anemia, low birth weight and preterm delivery [9]. The main species involved was *P. falciparum*, followed by *P. vivax* and *P. malariae* [9]. These findings suggest that PM infection is a major contributor to poor maternal and infant health in PNG, and that effective prevention and treatment of PM infection are essential for improving pregnancy outcomes [9].

A fourth theme that emerged from the papers was the knowledge, attitudes and practices concerning malaria in pregnancy among pregnant women, health staff and community members in PNG. The papers revealed that there was a general awareness of the term "malaria", but it was often confused with other illnesses or pregnancy symptoms [2]. Many preventive methods for malaria in pregnancy were related to general healthy living [2]. There were also varied messages from health staff about the risks of malaria in pregnancy [2]. The uptake of interventions such as insecticide-treated nets (ITNs) and chloroquine was influenced by availability, comfort and workload [2]. These findings suggest that there is a need for more education and communication on malaria in pregnancy among all stakeholders, and that barriers to accessing and using preventive measures should be addressed [2].

A fifth theme that emerged from the papers was the occurrence and impact of congenital malaria (CM) infection in newborns. CM infection was defined as the presence of parasites or antigens in cord blood or peripheral blood within seven days after birth. CM infection was detected in 5.6% of newborns, mostly due to *P. falciparum* [10]. CM infection was

associated with maternal malaria infection, especially in the third trimester [10]. CM infection was also associated with low birth weight, prematurity and neonatal mortality [10]. These findings suggest that CM infection is a serious complication of malaria in pregnancy that can affect the health and survival of newborns, and that early diagnosis and treatment of CM infection are crucial for reducing its morbidity and mortality.

The articles reviewed in this topic provide valuable insights into the epidemiology, prevention and treatment of malaria in pregnancy in PNG, as well as the challenges and opportunities for improving maternal and infant health outcomes. However, there are also some limitations and gaps that need to be considered for future research and practice. For example, most of the papers were based on observational studies that may have confounding factors or selection bias that could affect the validity of the results. There is a need for more randomized controlled trials or quasi-experimental studies to evaluate the effectiveness and cost-effectiveness of different interventions for malaria in pregnancy. Moreover, most of the papers focused on *P. falciparum* infection, while *P. vivax* infection is also prevalent and may have different or additional effects on pregnancy outcomes. There is a need for more research on the epidemiology, diagnosis, treatment and prevention of *P. vivax* infection in pregnancy, especially in the context of relapsing infections and drug resistance. Furthermore, most of the papers were conducted in Madang province, which may not be representative of other regions of PNG with different malaria transmission patterns, socio-cultural factors and health system capacities. There is a need for more studies in other regions of PNG to capture the diversity and complexity of malaria in pregnancy in the country.

In conclusion, malaria in pregnancy is a serious public health problem in PNG that requires concerted and coordinated efforts from all stakeholders to achieve its elimination. The papers reviewed in this topic provide useful evidence and recommendations for improving malaria prevention and control in pregnant women and their newborns in PNG, but also highlight the need for more research and action to address the remaining challenges and gaps. By learning from the past and present experiences and applying the best available knowledge and practices, PNG can make significant progress towards its goal of malaria elimination by 2030 [11].

## RECOMMENDATIONS

Based on the critique of the ten articles, this literature review provided some recommendations for improving malaria

prevention and control in pregnant women and their newborns in PNG. The recommendations included conducting more randomized controlled trials or quasi-experimental studies to evaluate different interventions for malaria in pregnancy, such as oral iron supplementation with preconception multivitamins, conducting & promoting awareness of precounseling services to young child-bearing women and teenagers, ISTp with RDTs and ACT, or MDA with DHA-PPQ; conducting more research on *P. vivax* infection in pregnancy, especially in the context of relapsing infections and drug resistance; conducting more studies in other regions of PNG to capture the diversity and complexity of malaria in pregnancy in the country; providing more education and communication on malaria in pregnancy among all stakeholders, using culturally appropriate and gender-sensitive approaches; and enhancing coordination and collaboration among different sectors and partners involved in malaria research and control in PNG.

## ABBREVIATION

ISTp with RDTs and ACT: Intermittent screening and treatment in pregnancy with rapid diagnostic tests and artemisinin-based combination therapy. This is a strategy that involves screening pregnant women for malaria infection using RDTs at each antenatal visit and treating those who test positive with an ACT.

MDA with DHA-PPQ: Mass drug administration with dihydroartemisinin-piperazine. This is a strategy that involves administering a full course of DHA-PPQ, an ACT, to all individuals in a target population regardless of their infection status, at regular intervals.

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