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REVIEW

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Current update on malaria in pregnancy: a systematic review

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Abstract

Background Malaria during pregnancy poses significant risks to both the mother and the developing fetus. For pregnant women, the infection can result in severe illness and even death. Parasite sequestration in the placenta can cause maternal anemia and increase the risk of mortality both during and after childbirth. Malaria is also a major contributor to stillbirths and preterm births. Infected placental tissue can impede fetal growth, resulting in low birth weight, which is linked to delayed growth and cognitive development in the child. Furthermore, malaria during pregnancy remains a major contributor to perinatal, neonatal, and infant mortality.

Objectives To review the epidemiological patterns of malaria in pregnancy and its impact on maternal and neonatal health, and to analyze the availability and effectiveness of drug treatment options.

Methods Relevant articles published only in English were searched using electronic databases such as PubMed, Web of Science, Scopus, and Pro-Quest. Keywords including "'malaria in pregnancy", "placental malaria", "congenital malaria", "treatment options", and "nutrition intervention and intermittent preventive treatment" were used in combination. Of the total of 4,486 articles identified, 139 articles were ultimately included. Whereas, others were excluded due to duplication, irrelevant abstract, title, and quality assessment.

Results From 139 included studies, 47 focused on epidemiology of malaria in pregnancy, 58 on its impact and 16 on treatment options and 18 on nutrition intervention and intermittent treatment. *Plasmodium falciparum* is the leading cause of complications in pregnant women and is primarily found in Africa, while *P.vivax* is recognized as an emerging global threat, and causing serious consequences. Other species, such as *P.knowlesi*, *P.ovale*, and *P. malariae* are less common. Malaria prevalence in pregnancy can reach 60% in sub-Saharan Africa and 36% globally, with placental malaria affecting up to 28% of cases. The disease causes serious complications such as maternal anemia, premature birth, and low birth weight, severe anemia and increased maternal and infant mortality. Prevention strategies like intermittent preventive treatment (IPTp), insecticide-treated nets (ITNs) and Indoor residual spray (IRS) are essential. Early diagnosis and treatment can reverse adverse effects on placental and congenital function. Artesunate is recommended for severe malaria in all trimesters. Even resistance to chloroquine reported in some areas, it is the drug of choice for uncomplicated *P.vivax* infections.

Conclusions Malaria during pregnancy significantly impacts maternal and fetal health, leading to anemia, growth restriction, preterm birth, and neonatal death. Infants born to mothers with malaria are more likely to contract the disease. Further research and improved treatment strategies are needed to address this issue effectively.

Keywords Malaria, *Plasmodium* species, Malaria in pregnancy, Placenta malaria, Congenital malaria

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Introduction

Malaria continues to be a major public health problem worldwide. According to the 2023 World Health Organization (WHO) malaria report, there were an estimated 249 million malaria cases and over 0.6 million malaria deaths worldwide in 2022. Of these, 95% of malaria cases and 96% of malaria deaths occurred in 29 African countries. In addition, an estimated 35.4 million pregnancies were reported in 2022, of which 12.7 million (36%) were exposed to malaria infection during pregnancy [1].

Malaria in pregnancy can be categorized into three distinct yet interconnected conditions: gestational malaria, placental malaria, and congenital malaria. These involve the infection and/or illness experienced during pregnancy, the infection of the placenta with or without symptoms in the pregnant woman, and the infection and/or disease affecting the neonate up to 28 days of age, excluding infection transmitted through the bite of infected *Anopheles* mosquitoes, respectively [2–4].

Malaria infection during pregnancy remains a significant public health problem, especially in areas where the disease is endemic, such as sub-Saharan Africa, Southeast Asia, and parts of Latin America [5]. The 2023 WHO malaria report shows that the highest rates of malaria exposure during pregnancy were observed in West Africa (39.3%) and Central Africa (40.1%), while the sub-region of East and Southern Africa had a relatively low prevalence of 27.0% [1].

Pregnant women are particularly susceptible to malaria due to the immunological changes they experience and the presence of a new organ, the placenta, which provides a favorable environment for the most dangerous malaria parasites, *P.falciparum* and *P.vivax* [6–8]. The prevalence and impact of malaria in pregnancy vary according to the intensity of malaria transmission, the number of previous pregnancies, and the availability of preventive measures. The African region accounts for approximately 90% of global malaria cases, and pregnant women, especially those in their first pregnancy (primigravidae), are at a higher risk of severe malaria and its complications [8–11]. This burden is the highest in sub-Saharan Africa, where approximately 25% of all pregnancies are affected by malaria, mainly due to the highly virulent *P.falciparum* strain [1]. The burden of malaria during pregnancy is considerable and has a significant impact on maternal and neonatal health [12].

In pregnancy-associated malaria, *P.falciparum* is the main causative agent, attaching to the placenta and causing placental malaria. The infected red blood cells attach to chondroitin sulfate A (CSA) and other placental receptors, leading to inflammation, fibrosis in the intervillous space, and impaired placental function. This sequestration in the placenta disrupts the exchange of nutrients and oxygen between mother and fetus, contributing to adverse pregnancy outcomes such as low birth weight, premature birth, and increased infant mortality [13].

Malaria in pregnancy can present with a wide spectrum of clinical symptoms, ranging from asymptomatic parasitemia to severe disease [14]. Asymptomatic infections show no obvious symptoms but can still pose a significant risk to fetal development [15]. These severe complications include cerebral malaria, severe anemia, hypoglycemia, and acute pulmonary edema [14]. The physiological changes that accompany pregnancy, such as immunomodulation, reduce the effectiveness of the immune response to malaria and make pregnant women more susceptible to severe forms of the disease [15].

Malaria in pregnancy is associated with several adverse outcomes for both the mother and the baby. Maternal complications include severe anemia, increased susceptibility to other infections, and a higher mortality rate. The fetus and newborn are at risk of intrauterine growth retardation, low birth weight, premature birth, and increased neonatal mortality. Moreover, infants born to mothers with malaria have a higher risk of malaria infection and morbidity in early life [16–18].

In the absence of an effective vaccine, malaria during pregnancy remains a significant public health problem [19]. Therefore, the management of malaria in pregnancy encompasses a multifaceted approach that includes preventive and therapeutic strategies [20]. Preventive measures include IPTp with sulfadoxine-pyrimethamine and the use of ITNs to mitigate mosquito bites [21]. Effective case management includes timely diagnosis and treatment with antimalarial drugs that are considered safe for use during pregnancy, taking into account the potential development of drug resistance and the special needs of pregnant women [22].

Recent studies have aimed to clarify the pathophysiological mechanisms of pregnancy-associated malaria, improve diagnostic methods, and develop new preventive and therapeutic strategies [10, 19, 20]. Researchers are exploring the molecular underpinnings of placental malaria, the influence of host and parasite genetic factors, and the development of malaria vaccines tailored for pregnant women [10, 20, 23]. Moreover, studies are continually assessing drug resistance trends and the safety of emerging antimalarial drugs in pregnant women [10, 19].

Questions of this systematic review

1. What have been the global and regional trends in malaria during pregnancy, especially in Africa, since 2000?
2. How does malaria in pregnancy impact maternal and neonatal health outcomes: particularly concerning

anemia, premature birth, and low birth weight, congenital malaria, neonatal death, and infant mortality?
3. How effective are current drug treatments for malaria during pregnancy, such as artesunate, chloroquine, and other antimalarial drugs, and what are the implications of drug resistance in different regions?
4. How effective are preventive interventions, such as intermittent preventive treatment, insecticide-treated nets, and indoor residual spraying, in reducing malaria prevalence during pregnancy and improving maternal and neonatal outcomes?
5. How do nutrition interventions and intermittent preventive treatment affect the health outcomes of pregnant women and neonates in malaria-endemic areas?
6. What challenges do emerging *Plasmodium* species, such as *P. falciparum*, *P. vivax*, *P.ovalae*, *P.malarae*, and *P. knowles*i, pose in the context of malaria during pregnancy, and how do these species impact maternal and neonatal health?
7. What are the main gaps in current research on malaria in pregnancy, and what are the recommendations for future research to address these gaps?

Objectives of the study

The objective of this systematic review was to examine the epidemiology of malaria in pregnancy, its impact and strategies for managing it. By analyzing the latest empirical evidence and current guidelines, the review aims to provide health professionals, policymakers, and researchers with insights into optimal treatment approaches and new strategies to mitigate the adverse effects of malaria on pregnant women and their infants. By advancing research and refining public health policy, we can improve health outcomes for pregnant women and their children while contributing to the global reduction of malaria in pregnancy.

Specific objective of the review

1. To assess the prevalence, distribution, and their changes in malaria during pregnancy over time.
2. To review the maternal health outcomes directly associated with malaria during pregnancy.
3. To explore the effects of malaria on the neonate and how it contributes to mortality and morbidity in newborns.
4. To evaluate the treatment effectiveness, safety, and challenges related to drug resistance in different regions.
5. To assess preventive measures and their role in minimizing malaria-related risks during pregnancy.
6. To explore the potential role of nutritional support in managing the health effects of malaria during pregnancy.
7. To point out on the emerging threats of different malaria species and their impact on pregnancy outcomes.
8. To highlight areas where further investigation is needed, particularly in treatment, prevention, and understanding of malaria's effects on maternal and neonatal health.

Methodology

This systematic review on malaria in pregnancy focused on the epidemiological aspects, the impacts on maternal and neonatal health, and drug treatment options. It was performed based on Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (additional file 1:Table S1).

Search strategy

To find relevant articles for this study, we used global electronic databases: PubMed, Web of Science, Scopus, and Pro-Quest. The search keywords used in the literature search included both MeSH terms and test words: "malaria in pregnancy," "placental malaria," "congenital malaria," "impacts of malaria in pregnancy," "treatment options for malaria in pregnancy," "nutrition interventions," and "intermittent preventive treatment." These terms were used either separately or in combination. We applied filters: English, Humans, female, from 2000/1/1—2024/12/12. We conducted the search in two phases: from May 15 to June 12, 2024, and from November 15 to November 21, 2024 (additional file 2: Table S2).

Study selection and eligibility criteria

The eligibility criteria for this systematic review were designed to encompass significant original research on the epidemiology of malaria in pregnancy, its associated impacts, and available management strategies. Articles published in English since January 2000 were considered for inclusion. This timeframe was selected due to the increasing global emphasis on maternal and neonatal health outcomes in public health research. Additionally, this period coincides with key advancements in malaria diagnostics, the introduction of novel antimalarial therapies such as artemisinin-based combination treatments (ACTs), and the emergence of new malaria strains. The growing concern over drug resistance, as well as the rising global focus on malaria control and prevention exemplified by initiatives like the Roll Back Malaria Partnership and the WHO Global Malaria Programme also began in this era.

Only peer-reviewed articles, along with randomized controlled trials, observational studies, and laboratory-based experimental studies, were considered based on population intervention comparison outcome (PICOS), length of follow-up and report characteristics. Articles were included if they addressed the objective comprehensively and contained relevant data on epidemiology, clinical outcomes, or treatment strategies. Articles were excluded if they focused on non-pregnant populations or non-malaria conditions, lacked full-text access, were not published in peer-reviewed journals, or did not contain sufficient data on prevalence, interventions, or outcomes related to malaria in pregnancy.

Data extraction

Two authors (AM and GA) independently collected all necessary data using a standardized extraction form that was modified from the JBI format designed for systematic reviews. They collected information from various sources within the articles, including text, figures, and tables. Any inconsistencies between these authors regarding the data to be extracted were addressed and resolved through discussion with the other coauthors of this study.

Assessment of methodological quality

The quality and potential for bias were assessed before inclusion in the review through critical appraisal, which was incorporated into the review process. Two authors (AM and GA) independently evaluated the quality of each article using a standardized assessment tool, adapted from the JBI critical appraisal checklist for studies reporting prevalence data [24]. The quality assessment tools consisted of nine criteria designed to evaluate the quality of the primary studies considered for inclusion in our review. These criteria focused on aspects such as sample size, sampling frame, methods for identifying outcomes, study setting, response outcomes, and statistical analysis. Studies qualities scoring above 50% were included, while those scoring 50% or below were excluded. Consequently, 139 articles were included in the review, and 892 were excluded. To simplify the table, only the selected articles were included in the supporting file (additional file 3: Table S3). The 50% cut-off point was determined after reviewing relevant literature.

Result

Study selection and characteristics

An initial search yielded 4,269 publications from various international databases. Of these, 1,027 were removed due to duplication. A further 2,211 articles were excluded based on deficiencies in their titles and abstracts. After additional screening for studies with insufficient data, unclear methodologies, or a focus on specific demographic groups, 892 articles were removed. Ultimately, 139 articles were selected and retrieved for this review (see Fig. 1).

Epidemiology of malaria in pregnancy: a global perspective

Of the 139 original studies retrieved, 47 dealt with the epidemiology of malaria during pregnancy, 58 investigated its effects, and 16 discussed its treatment options and its prevention using 18 nutrition interventions and IPTp. *P.falciparum* is the main cause of malaria complications during pregnancy, but it is mainly restricted to Africa. *P.vivax* is widespread and is currently considered a significant global threat to pregnancy. Other *Plasmodium* species, such as *P.knowlesi*, *P.ovale,* and *P.malariae*, have also caused malaria in pregnancy in various countries, although less frequently [25–29] (Fig. 2).

The figure indicates malaria during pregnancy is mainly caused worldwide by *P.falciparum* and *P.vivax* [6, 28–56]. Although *P.falciparum* is the main cause of severe morbidity and mortality associated with malaria in pregnancy, the global threat from *P.vivax* is increasing [57–59]. In addition to these two dominant species, other *Plasmodium* species such as *P.malariae*, *P.knowlesi* and *P.ovalae* have been reported in various regions of Asia and Africa, which also contribute to the burden of malaria in pregnancy [25–27].

On the other hand, malaria in pregnancy remains a significant global health issue due to its substantial disease burden. A brief timeline illustrating the prevalence of malaria in pregnancy, based on WHO malaria reports from 2000 to 2023, along with additional findings from references [8, 60] is shown in Fig. 3. The most important epidemiological data on malaria in pregnancy are summarized in Tables 1, 2, and 3.

Malaria in pregnancy remains a significant public health issue, with the burden being much higher in the African region. The figure illustrates the trends in malaria during pregnancy from 2000 to 2011, with more than 98% of the data coming from the African region. For example, the prevalence of malaria in pregnancy in Eastern and Southern Africa was 29.5%, while in west and Central Africa it was 35.1% [60]. While the number cases of malaria in pregnancies was decreased globally between 2007 and 2020, the number of cases of malaria in pregnancies in Africa increased by 25.4% [8]. This increase is mainly due to rapid population growth in malaria-endemic areas, which led to rise in pregnancies. In general, the data indicate a decline in malaria in pregnancy over time, reflecting the impact of improved prevention measures and treatment strategies. From 2000 to 2023, the global trend shows an overall increase in the prevalence and burden of malaria in pregnancy but decline in

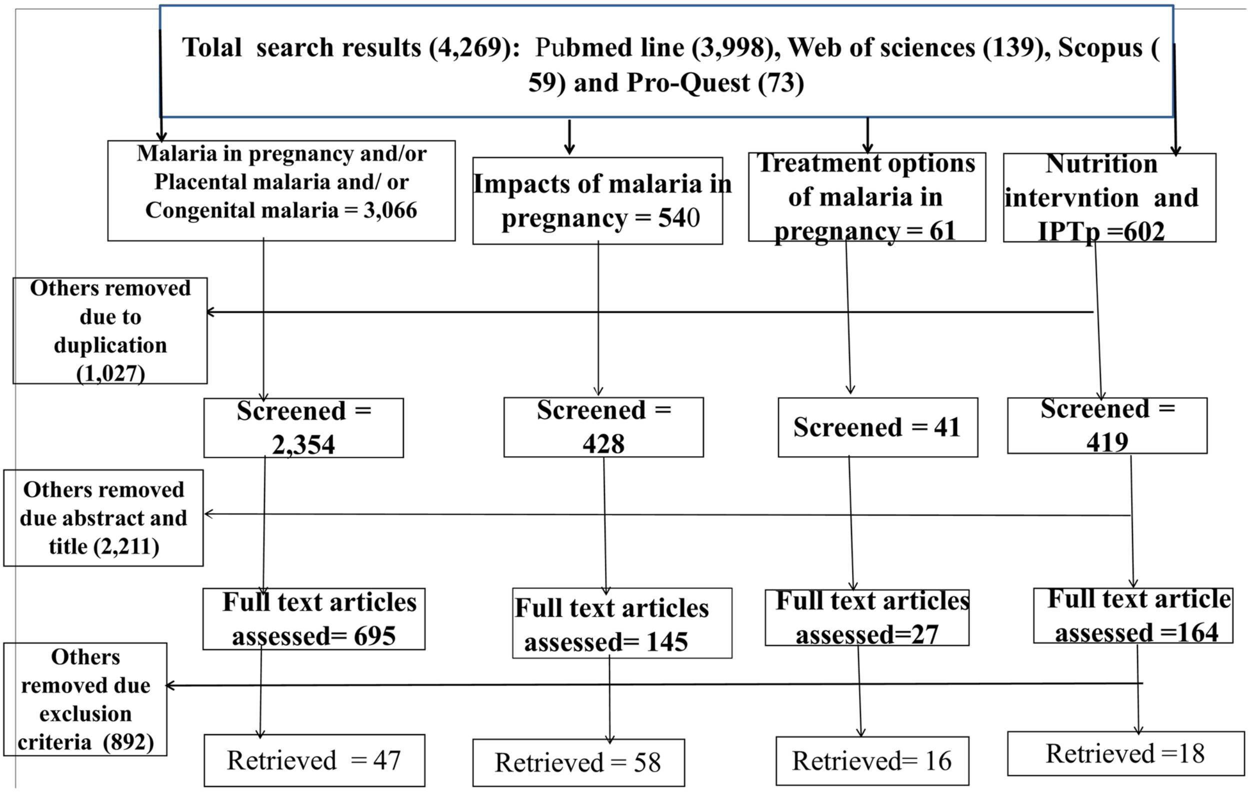

Fig. 1 The flowchart of search and selection of articles for review of current update on malaria in pregnancy: A Systematic review

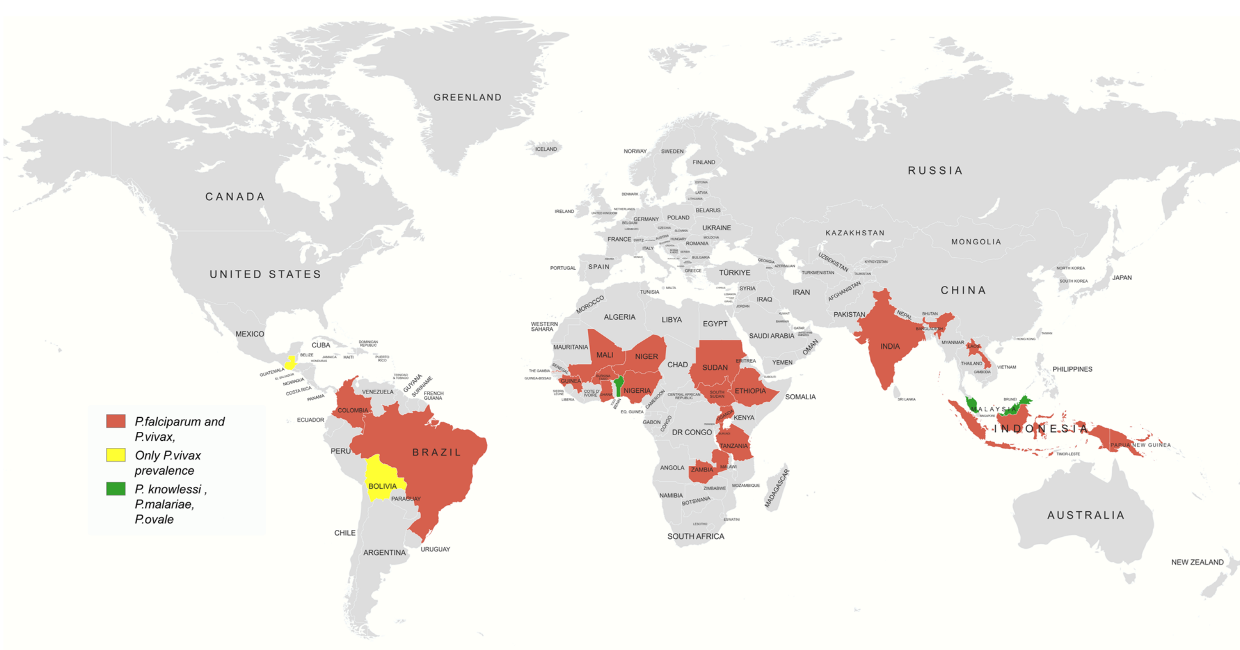

Fig. 2 Global epidemiology of malaria in pregnancy by *Plasmodium* species

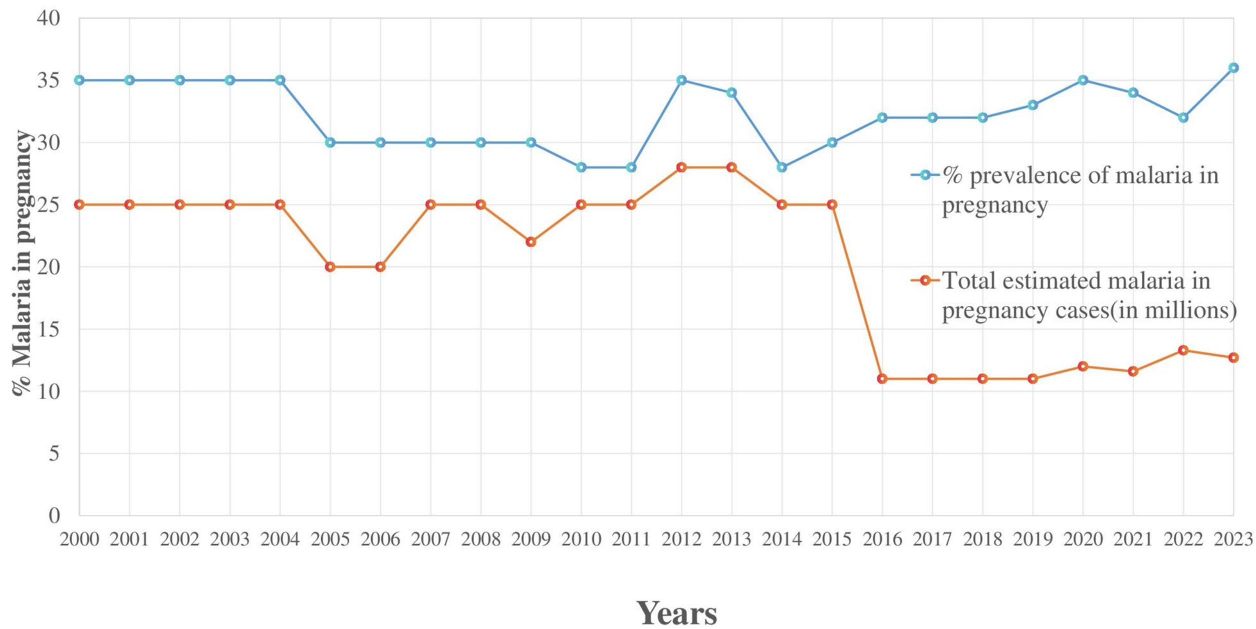

Fig. 3 Prevalence of malaria in pregnancy based on WHO reports from 2000 to 2023

estimation of malaria in pregnancy cases, due to interventions such as IPTp, ITNs, and better treatment protocols. However, regional disparities remain, and challenges such as drug resistance and gaps in health systems have slowed progress in some areas. The COVID-19 pandemic also caused setbacks that further impacted progress in the regions most affected by malaria [1].

The epidemiological results of this study assessed the varying prevalence of gestational malaria in different countries, showed substantial regional differences. In Africa, where malaria transmission is the highest, the gestational malaria ranges from 10% to 56.3%. The highest gestational malaria was observed in West Africa, where high prevalence rates were found, such as in Burkina Faso (54.5%) and Ghana (56.3%). While, up to 37.8% (Sudan) gestational malaria was reported in East Africa. However, lower rates are observed in Southeast Asia and the Western Pacific. Both *P.falciparum* and *P.vivax* are widespread in various parts of Africa and in certain regions of the Amazon, India and Southeast Asia. In addition, *P.ovale*, *P.malariae* and *P.knowlesi* have been reported from Africa, Southeast Asia and the Western Pacific, and the review also discusses the two main diagnostic methods: Polymerase chain reaction (PCR) tends to detect a higher prevalence than thick blood smear (TBS), as seen in countries like Southern Laos, where TBS reported 1.5%, compared to PCR's 5.9%. The review underscores the importance of early diagnosis by microscopy and prompt treatment of malaria during pregnancy to reduce the risk of placental and congenital malaria (Table 1).

Placental malaria

The review emphasizes that placental malaria is more common in regions with high malaria transmission, particularly in sub-Saharan Africa. There is considerable geographic variation in the prevalence of placental malaria. Countries like Ghana, Burkina Faso, and Sudan report high prevalence rates, while India and some other regions show negligible or no prevalence. Higher prevalence rates of placental malaria were reported in epidemiological studies of *Plasmodium*-infected mothers in Uganda (44.3%) and Burkina Faso (87%). However, relatively low prevalence out of Africa such as India and Bolivia In regions outside of Africa, placental malaria caused by *P.vivax* was generally more prevalent than other species. Nevertheless, the high prevalence of placental malaria in Africa underscores the ongoing challenges in malaria control, particularly in areas where both *P.vivax* and *P.falciparum* are endemic. The lower intensity of microscopy findings suggests that submicroscopic infections may serve as the main reservoir for malaria transmission (Table 2).

Congenital malaria

This systematic review addressing the impact of malaria during pregnancy underscores the significant issue of congenital malaria, as a serious outcome linked to maternal malaria. The incidence of congenital malaria varies significantly across different nations. In various African countries, high prevalence rates have been documented; for example, Niger recorded a prevalence of 26.5% for

Table 1 Prevalence of gestational malaria by country and diagnostic techniques (TBS or PCR)

Authors	Countries	% (Prevalence of gestational malaria)						References
		P.falciparum		*P.vivax*		Mixed		
		TBS	PCR	TBS	PCR	TBS	PCR	
Martínez-Espinosa et al. (2004)	Brazil	3.5	NA	7.9	NA	0.3	NA	[30]
Bôtto-Menezes et al.(2016)	Brazil	27.6	NA	16.8	NA	3.1	NA	[61]
Pincelli et al. (2018)	Brazil	1.6	15.7	4.9	13.1	0.1	1.1	[29]
Dombrowski et al. (2018)	Brazil	2.4	NA	5.7	NA	0.8	NA	[62]
Bardají et al. (2017)	Brazil	0	2	0.3	8.4	0.3	10	[58]
Mean	Brazil	7.02	8.8	7.1	10.7	0.9	-	
Brutus et al. (2013)	Bolivia	NA	NA	7.9	NA	NA	NA	[57]
Agudelo et al. (2013)	Colombia	2.5	4.9	5.8	9.1	0.8	0	[63]
Agudelo-Garc´ıa et al. (2017)	Colombia	8	18.9	0	4.4	0	0.7	[34]
Va´squez1 et al. (2018)	Colombia	3.7	4.8	0	0	0	0	[64]
Cardona-Arias and Carmona-Fonseca (2024)	Colombia	1.1	10.3	3.2	10.8	0.2	0.9	[6]
Bardají et al. (2017)	Colombia	0.6	3	0.6	6	2.1	15.6	[58]
Mean	Colombia	3.2	8.4	1.9	6.1	0.6	3.4	
Bardají et al. (2017)	Papua New Guinea	6.7	11.6	1.7	13.9	8.3	23.7	[58]
Poespoprodjo et al. (2008)	Papua, Indonesia	9.6	NA	5.6	NA	0.6	NA	[28]
Bardají et al. (2017)	Guatemala	0	14	1.1	11.6	0.1	21	[58]
Bardají et al. (2017)	India	0.05	NA	1.2	1	0	NA	[58]
Hamer et al. (2009)	India	53.5	NA	37.2	NA	9.3	NA	[65]
Singh et al. (2022)	India	0.4	NA	0.8	NA	NA	NA	[36]
Mean	India	19.5	NA	13.6	-	4.6	NA	
Khan et al. (2014)	Bangladesh	2.3	6	NA	NA	AN	NA	[66]
Barber et al. (2015)	Malaysia	NA	33	NA	9.8		0.9	[25]
Briand et al. (2016)	Southern Laos	1	5.9	0	5.4	0	0.5	[67]
Williams et al. (2016)	Burkina Faso	NA	54.2	NA	0	NA	NA	[68]
Williams et al. (2016)	Gambia	NA	10.8	NA	0	NA	0	[68]
Williams et al. (2016)	Ghana	NA	56.1	NA	0	NA	0	[68]
Williams et al. (2016)	Mali	NA	31.3	NA	0.3	NA	0.3	[68]

Table 1 (continued)

Authors	Countries	% (Prevalence of gestational malaria)						References
		P.falciparum		*P.vivax*		Mixed		
		TBS	PCR	TBS	PCR	TBS	PCR	
Doritchamou et al. (2018)	Benin	NA	39.2	NA	0	NA	0	[27]
Umemmuo et al.(2020)	Nigeria	12.9	NA	0	NA	0	NA	[39]
Unger et al. (2019)	Papua New Guinea	4.7	5.1	0.6	2.2	0.5	0	[69]
Omer et al.(2017)	Sudan	37.8	NA	0	NA	0		[41]
Nega et al. (2015)	South Ethiopia	7.0	NA	8.8	NA	2.3	NA	[42]
Gontie et al. (2020)	West Ethiopia	2.3	NA	0.6	NA	0	NA	[70]
Feleke et al. (2020)	North, Ethiopia	3.4	NA	2.3	NA	0	NA	[71]
Solomon et al. (2020)	Southern Ethiopia,	5.2	NA	10.0	NA	0	NA	[72]
Subussa et al. (2021)	Oromia, Ethiopia	1.6	NA	1.9	NA	0	NA	[46]
Limenih et al. (2021)	Northwest Ethiopia	3.7	NA	2.8	NA	0	NA	[73]
Almaw et al. (2022)	Ethiopia	12.2	NA	4.8	NA	3.8	NA	[48]
Gemechu et al. (2023	West Ethiopia	10.9	NA	13.1	NA	0	NA	[74]
Mean	Ethiopia	5.7	NA	5.6	NA	0.8	NA	

TBS Thick blood smear, *PCR* Polymerase Chain Reaction, *NA* not applicable

P.falciparum. Uganda displayed a prevalence rate of 6.1%, while Sudan exhibited a wide range of prevalence, with figures between 18.6% and 56.8% determined through PCR analyses of cord blood samples. Outside of Africa, congenital malaria is less frequently reported but has been observed in South America, s particularly in Colombia. Notably, both *P.falciparum* and *P.vivax* have been identified, with their prevalence demonstrating significant variation depending on the diagnostic methodologies employed (Table 3).

Effects of malaria during pregnancy

The striking pathology of malaria in pregnancy, including placental, congenital and neonatal malaria, and its major complications, is summarized in additional file 4: Table S4 and Fig. 4.

The figure clearly illustrates several significant outcomes of malaria in pregnancy, highlighting the interconnected impacts on both maternal and fetal/neonatal health. Maternal effects include conditions such as hypoglycemia and anemia, which compromise the mother's health and increase susceptibility to secondary infections [6, 25, 40, 42, 43]. Severe cases may progress to life-threatening complications such as severe malaria both the mother and the fetus [40, 43, 84]. For the fetus or neonate, malaria poses risks such as low birth weight, preterm delivery, and growth restriction [10, 85], all of which are critical predictors of neonatal survival and long-term health including the maternal health [6, 32, 40, 43, 86–88]. More severe outcomes, including stillbirth, congenital malaria, and neonatal mortality, underscore the grave consequences of inadequate malaria management during pregnancy [6, 32, 40, 43, 86–88]. The complex relationship between maternal and neonatal effects reflects a pathophysiological cascade, where malaria-induced maternal complications negatively affect fetal development and survival. Maternal anemia and infections can impair the supply of oxygen and nutrients to the fetus [89], contributing to outcomes like intrauterine growth restriction and preterm delivery [90, 91].

Pregnancy-associated malaria remains a major public health challenge in endemic areas and poses risks to both mother and fetus. Current research has shown that infection with *P.falciparum* during pregnancy can lead to severe and significant organ dysfunction. This is attributed to the unique behavior of the parasite's schizonts, which form knobs on the surface of infected red blood cells (RBCs). These knobs express an adhesive protein called *P.falciparum* erythrocyte membrane protein 1 (PfEMP1), enabling the infected cells to adhere to receptors on the capillary and venous endothelium, a process known as sequestration. This sequestration and the formation of "rosettes" (the adherence of infected erythrocytes to uninfected cells) impair the spleen's ability to effectively clear the infected erythrocytes, ultimately leading to organ dysfunction [92, 93]. In contrast to the long-term immunity conferred by measles, frequent infections with *P.falciparum* have been reported to produce relatively short immunologic memory [94].

Conversely, a study by Carvalho et al. (2010) reported that although the cytoadhesion of *P.vivax*-infected erythrocytes is about ten times lower than that of *P.falciparum*-infected erythrocytes, the strength of the interaction is comparable. Cytoadhesion of *P.vivax*-infected erythrocytes is mediated in part by VIR proteins encoded by *P.vivax* variant genes (vir), and this interaction is inhibited by endothelial cells [95]. Additionally, a study conducted in Brazil by Dombrowski et al. (2021) found that IgG against the *P.vivax* MSP_{119} protein was used as a marker for exposure during pregnancy [96].

Several studies have confirmed that infections with *P.knowlesi, P.malariae* and *P.ovale* in pregnant women can lead to adverse maternal and pregnancy outcomes. However, these infections appear to have milder consequences for those affected compared to the more severe effects of *P.falciparum* and *P.vivax* [25, 27]. Another study found that mixed *Plasmodium* infections were associated with a higher risk of preterm birth but did not result in lower birth weight compared to single-species infections [97]. Additionally, one study found that *P.malariae* infects the placental blood rather than the peripheral blood [27].

A study conducted in Thailand by Nosten et al. (1999) found that *P.vivax* malaria was more common in primigravidae compared to multigravidae and was associated with mild anemia and an increased risk of low birth weight [98]. Likewise, other studies reported that pregnant women, especially those in their first pregnancy (primigravidae), are at a higher risk of severe malaria and its complications [8–11]. However, the effects of *P.vivax* infection were less severe than those of *P.falciparum* infection. Additionally, Bôtto-Menezes et al. (2015) conducted a study in the Brazilian Amazon, which showed that clinical *P.vivax* malaria has serious health consequences for mothers and their babies, particularly in adolescents, primigravidae, and women with limited prenatal care [99]. This may be due to the fact that a febrile episode triggers activation of hypnozoites (dormant liver stages) and increased allelic diversity during relapse [100].

It has been shown that uncomplicated malaria occurs mainly in pregnant women and often leads to severe anemia [6, 25, 40, 42, 43]. Malaria during pregnancy leads to at least one complication, such as spontaneous abortion, fetal death, or premature birth, without further complications [6, 32, 40, 43, 86]. Another study also found an association between parasitemia and preterm delivery and stillbirth, suggesting that the increased risk of malaria is primarily due to fever and severe anemia rather than parasitemia itself [40, 43, 84].

Numerous studies have reported that malaria during pregnancy, caused by both *P.falciparum* and *P.vivax*, can lead to severe complications [10, 14, 88, 101]. These complications include severe anemia, cerebral malaria, multi-organ failure [102], spontaneous abortion, fetal growth restriction [10, 85], fetal death, premature birth, and maternal death [6, 32, 40, 43, 86–88]. Additionally, studies have shown that *P.vivax* infection during pregnancy can also cause severe pre-eclampsia and trigger acute respiratory distress syndrome (ARDS) [90, 91]. Furthermore, co-infection with COVID-19 and malaria can exacerbate the severity of morbidity and mortality [103]. These complications may result from malaria infection of the placenta, which can lead to pathophysiological changes during pregnancy, causing morphological changes in the placental villi and impaired gas exchange [89].

Placental pathology is one of the most important complications associated with malaria during pregnancy. Evidence suggests that the presence of malaria in the placenta can interact with and alter its angiogenic profiles, which are essential for healthy placental development and function. According to Ataíde et al. (2015), women who contracted malaria during pregnancy had lower levels of angiopoietin-1, a vital regulator of angiogenesis, leading to specific changes in the structure and function of the placenta, which could explain the pathological changes observed [104].

In a study conducted by Souza et al. (2013) in the Brazilian state of Acre, it was found that the placentas of women exposed to *P.vivax* had more lesions than those of unexposed women, despite limited evidence of hemozoin. The researchers found that *P.vivax* infection was associated with syncytial nodules, increased thickness of the placental barrier, and a higher presence of mononuclear cells [105]. Similarly, Chaikitgosiyakul et al. (2014) showed that active placental malaria acutely reduces the size, circumference, and vascularity of villi, thereby reducing the surface area per villus available for gas exchange. However, the increased number of villi per unit area offsets this change and persists after treatment.

The authors suggest that early detection and appropriate malaria treatment may reverse these histopathological and villous architectural changes [89].

In contrast, Machado Filho et al. (2014) point out that *P.vivax* infections in early gestation do not affect blood flow in the umbilical artery, but do affect fetal biometry in the second trimester and at birth [106]. Prasetyorini et al. (2021) reported in Maumere, Nusa Tenggara Timur, that *P.vivax* infection can cause acute, sub-acute, and chronic placental malaria in subclinically infected pregnant women, resulting in low birth weight in the infant [107]. On the other hand, Dombrowski et al. (2019) found that the histological findings in the placentas in *P.falciparum*-infected pregnant women included increased syncytial nuclear aggregates and inflammatory infiltrates in the placentas of newborns with reduced head circumference [108].

Pineros et al. (2013) studied the clinical manifestations of malaria in pregnant women living in malaria-endemic regions of Colombia and found that the disease presents a diverse clinical picture in this population. In particular, the authors reported that *P.vivax* infections in pregnant women frequently lead to organ-specific complications, with liver dysfunction being the most important complication observed [109]. Complementing these findings, Bhandari et al. (2021) conducted a study in India that showed liver disease is common in pregnant women and that the presence of malaria can exacerbate the severity of this disease [110].

Dharmaratne et al. (2022) have shown that antibodies against the *P.falciparum* antigens PfAMA1 and varicose antigen 2 Chondroitin sulfate A (PfVAR2CSA) can be useful for serologic surveillance of malaria infection in pregnant women, especially in regions with low malaria transmission [111]. Accordingly, Lopez-Perez et al. (2018) conducted a study in Colombia and found that men and children often have high levels of functional VAR2CSA-specific IgG. This study concluded that IgG responses to the *P.falciparum* antigen VAR2CSA are specific to pregnancy and are not triggered by exposure to *P.vivax* [112]. In contrast, Iyamu et al. (2023) demonstrated that the VAR2CSA protein is expressed on the surface of erythrocytes infected with *P.vivax* and facilitates their sequestration within the placenta. Antibodies targeting VAR2CSA have been primarily associated with infections during pregnancy, and antibodies directed against the *P.vivax* Duffy Binding Protein (PvDBP) were found to cross-react with VAR2CSA due to the presence of an epitope in the CRP1 domain, suggesting that CRP1 is a potential vaccine candidate that could target a specific CSA binding site within VAR2CSA [113]. A further study confirmed these results and showed that antibodies against PvDBP can induce antibodies that functionally recognize VAR2CSA. This revealed a new mechanism of cross-species immune recognition in *P.falciparum* malaria [114].

Charnaud et al. (2016) demonstrated that maternal–fetal transmission of anti-malaria IgG antibodies against *Plasmodium* species occurs in low-transmission environments. In contrast to *P.falciparum* IgG, the acquisition of *P.vivax* IgG is not associated with recent exposure, suggesting differences in the mechanisms of antibody acquisition. Transfer of IgG peaks in the final weeks of pregnancy, which has implications for the timing of future malaria vaccination strategies in pregnant women [115]. Dombrowski et al. (2020) found that, in the Brazilian Amazon, plasma IgG against the MSP_{119} protein of *P.vivax* serves as a marker for infection during the first trimester of pregnancy [116].

The available articles indicate that pregnant women infected with *P.falciparum* and *P.vivax* have higher plasma concentrations of pro-inflammatory cytokines than their uninfected counterparts [117, 118]. Furthermore, anti-inflammatory cytokines are positively associated with malaria infection [14]. In addition, the histopathological features and CD+cell profiles of infected placentas showed statistically significant differences compared to non-placental malaria cases [119–121], as summarized in Fig. 5.

The Figure illustrates the changes in pro- and anti-inflammatory mediators, histopathologic findings and expression of immune markers associated with *P.falciparum* and *P.vivax* malaria infection during pregnancy. Elevated plasma levels of cytokines such as IL-6, IL-10, IL -12 and TNF have been observed during *P.vivax* infection [122, 120]. Histopathologic changes include the presence of *P.vivax* and/or *P.falciparum* placental malaria, which show marked tissue changes [121]. Gene expression analysis shows increased levels of messenger RNA for genes related to the immune response (e.g. Fas, HIF1α) and for regulatory genes (e.g. FOXP3). In addition, activation of immune cells with upregulation of markers such as CD4+, CD8+and CD68+can be observed [121, 123, 124].This upregulation of both pro-inflammatory markers (e.g. IL-1β, TNF) and anti-inflammatory markers (e.g. IL-10, TGFβ) suggests a complex balance between immune activation and regulation during malaria infections in pregnancy.

Requena et al. (2016) found that VIR antigens induce the natural acquisition of antibody and T-cell memory responses that may be critical for immunity against *P.vivax* during pregnancy in different geographic regions [125]. Another study demonstrated that *P.vivax* infection by VIR antigens induces an IgG response [95, 126]. Although it was previously believed that *P.vivax*

Table 2 Prevalence of placental malaria across different countries and diagnostic methods (TBS or PCR)

Authors	Countries	% (Prevalence of placental malaria)						References
		P.falciparum		*P.vivax*		Mixed		
		TBS	PCR	TBS	PCR	TBS	PCR	
Carmona-Fonseca et al. (2013)	Colombia	1.5	NA	11	NA	NA	NA	[75]
Agudelo et al. (2013)	Northwest Colombia	1.6	10.7	1.6	5.8	0	0	[63]
Va´squez1 er al.(2018)	Colombia	0.7	2.8	0	0	0		[64]
Agudelo-Garc´ıa et al.(2017)	Colombia	NA	16.1	NA	10.2	NA	2.2	[34]
Cardona-Arias,Carmona-Fonseca (2022)	Colombia	0	10.1	0	4.8	0	1.3	[51]
Cardona-Arias and Carmona-Fonseca (2024)	Colombia	0.6	8.7	1.2	7.8	0	1.2	[6]
Bardají et al. (2017)	Colombia	0.5	1	0	2	0	0	[58]
Mean	Colombia	0.82	8.2	2.3	5.1	0	0.8	
Brutus et al. (2013)	Bolivia	0	NA	2.8	NA	0	NA	[57]
Bardají et al. (2017)	Guatemala	0	0	0	13.7	0	0	[58]
Bardají et al. (2017)	Brazil	0	0	0.14	0	0	0	[58]
Bardají et al. (2017)	India	0	NA	0	0	0	NA	[58]
Singh et al.(2022)	India	0	NA	0	NA	0	NA	[36]
Mean	India	0	NA	0	NA	0	NA	
Bardají et al. (2017)	Papua New Guinea	3.5	0.9	1.5	2.8	0	0	[58]
Mayor et al. (2012)	Papua New Guinean	12.5	NA	10	NA	0	NA	[59]
Lufele et al. (2017)	Papua New Guinea	NA	3.7	0	NA	NA	0	[52]
Mean	Papua New Guinea	8	2.3	3.8	2.8	0	0	
Doritchamou et al. (2017)	Benin	0	32.0	0	0	0	0	[27]
Ouédraogo et al.(2019)	Southern Benin	11.3	NA	0	NA	0	NA	[53]
Mean	Benin	5.65	32	0	0	0	0	
Bihoun et al.(2022)	Burkina Faso	NA	[a]86.8	NA	0	NA	0	[54]
Mwin et al.(2021)	Ghana	7	NA	0	NA	0	NA	[55]
Akinnawo et al. (2022)	Ghana	0	9.4	0	0	0	0	[56]
Asante et al.(2023)	Ghana	6.7	NA	0	NA	0	NA	[76]
LUUSE et al.(2024)	Ghana	NA	19.4	NA	0	NA	0	[77]
Mean	Ghana	4.6	14.4	0	0	0	0	
Umemmuo et al.(2020)	Nigeria	9.4	NA	0	NA	0	NA	[39]
Kalinjuma et al. (2020)	Tanzania	0	20.5	0	0	0	0	[78]
Tran et al. (2020)	Uganda	[a]44.3	NA	0	NA	0	NA	[79]
Solomon et al. (2020)	Ethiopia	1.7	NA	2.2	NA	0	NA	[72]
Limenih et al. (2021)	Northwest Ethiopia	3.7	NA	2.8	NA	0	NA	[73]
Mean	Ethiopia	2.7	NA	2.5	NA	0	NA	
Omer et al.(2017)	Sudan	[a]58.9	NA	0	NA	0	NA	[41]

TBS Thick blood smear, *PCR* Polymerase chain reaction, *NA* not applicable

[a] The prevalence of placental malaria was determined on the basis of the documented maternal infection

infection was not observed in Duffy-negative populations because the red blood cell surface antigen is required for parasite invasion [127], a study by Dhorda et al. (2011) in Uganda reported three *P.vivax*-positive cases in Duffy-negative African pregnant women [128]. Similarly, a study conducted by Boel et al. (2012) on the western border of Thailand analyzed the association between blood group and malaria in pregnancy and found that one-third of women (447 of 1,468) had at least one malaria infection during pregnancy. However, the ABO blood group phenotype was not associated with *Plasmodium* species of infection, frequency of malaria attacks, symptoms of malaria, hematocrit or parasitemia during pregnancy [129].

Table 3 Prevalence of congenital malaria by country and diagnostic method (TBS or PCR)

Authors	Countries	% (Prevalence of Congenital malaria)						References
		P.falciparum		*P.vivax*		Mixed		
		TBS	PCR	TBS	PCR	TBS	PCR	
Piñeros-Jiménez et al. (2011)	Colombia	0.9	0	3.4	0	0	0	[80]
Agudelo et al. (2013)	Colombia	0	0	0	0	0	0	[63]
Agudelo-Garc´ıa et al.(2017)	Colombia	0	1.4	0	2.1	0	0	[34]
Cardona-Arias,Carmona-Fonseca (2022)	Colombia	0	12.4	0	1.8	0	0.2	[51]
Cardona-Arias and Carmona-Fonseca (2024)	Colombia	0	3.8	0	1.7	0	0.2	[6]
Mean	Colombia	0.2	3.5	0	1.1	-	0.08	
Singh et al.(2022)	India	0	NA	0	NA	0	NA	[36]
Unger et al. (2019)	Papua New Guinea	1.1	2.3	0.5	0	0	0	[40]
Natama1 et al.(2017)	Burkina Faso	NA	4	NA	NA	0	NA	[81]
Tahirou et al.(2020)	Niger	26.5	NA	0	NA	0	NA	[82]
Hangi et al.(2019)	Uganda	6.1	NA	0	NA	0	NA	[83]
Omer et al.(2020)	Sudan	*56.8	NA	0	NA	0	NA	[41]

TBS Thick blood smear, *PCR* Polymerase chain reaction, *NA* not applicable

* Congenital malaria detected in newborns from placental infected mothers

Antimalarial treatment for malaria during pregnancy

Malaria in pregnancy can be particularly severe, and artesunate has become the treatment of choice for all trimesters [130, 131]. Although the reasons for this are not fully understood, *P.vivax* malaria is increasingly recognized as a cause of severe malaria [132]. The treatment of severe *P.vivax* malaria is similar to that of severe *P.falciparum* malaria [92, 133]. A single episode of *P.falciparum* or *P.vivax* malaria during the first trimester of pregnancy can lead to miscarriage [134]. The use of artesunate in early pregnancy has not led to any additional toxic effects [135, 136].

A study conducted by Saito et al. (2021) in the border region between Thailand and Myanmar found that dihydroartemisinin-piperaquine was well tolerated, safe, and showed satisfactory efficacy in pregnant women infected

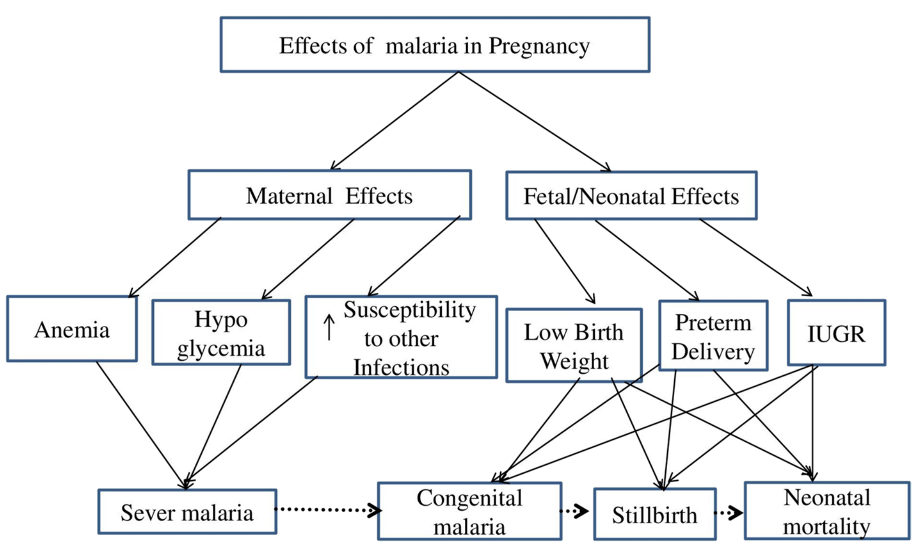

Fig. 4 The impact of malaria in pregnancy on maternal and fetal health

with *P.falciparum* in an area with widespread artemisinin resistance. Chloroquine also proved to be a safe treatment for pregnant women infected with *P. vivax* [137].

Conversely, Waheed et al. (2015) documented the case of a pregnant woman with *P.vivax* infection in Pakistan who showed chloroquine resistance despite appropriate treatment [138]. Similarly, Rijken et al. (2011) reported that a pregnant woman on the western border of Thailand developed chloroquine-resistant vivax malaria despite adequate chloroquine treatment [139]. In addition, a 3% prevalence of hearing loss was observed in newborns of mothers who had contracted *P.viva*x malaria and had taken chloroquine during pregnancy [140]. A case study by Sankar et al. (2020) in India found that quinine could not prevent transplacental transmission of *P.vivax* infection [141]. In Colombia, 95.8% of pregnant women responded to chloroquine monotherapy to cure their acute attack of uncomplicated *P. vivax* malaria [142].

Other studies have reported that mefloquine is safe and effective for malaria prophylaxis in the second half of pregnancy [143]. A study by Barnadas et al. (2007) found that sulfadoxine-pyrimethamine (SP) is effective as monotherapy, for intermittent preventive treatment of pregnant women or children [144] (Additional file 5:Table S5).

Intermittent preventive treatment and nutritional interventions for malaria in pregnancy

Intermittent preventive treatment in pregnancy (IPTp) has been shown to have significant benefits for maternal and neonatal health in malaria-endemic regions. Studies have demonstrated that IPTp-SP can reduce the prevalence of maternal *P.falciparum* infection, low birth weight and preterm birth, particularly in women in their first and second pregnancies [21, 145–147], and that it can reduce placental malaria parasitemia and maternal anemia [146, 148, 149]. Another study showed that antimalarial drug combinations containing mefloquine (MQ) are currently recommended for malaria treatment in pregnancy and that MQ alone is recommended for prophylaxis in pregnant women traveling to endemic countries [150]. In contrast, another study showed that IPT-SP is ineffective in preventing malaria infection [151].

The efficacy of IPTp-SP has been in both HIV-negative and HIV-positive pregnant women. In HIV-negative women, IPTp-SP with three or more doses has been shown to significantly improve birth weight and reduce the risk of low birth weight by 56% compared to fewer than three doses [147]. In HIV-positive women, monthly SP regimens have been shown to be superior to the standard two-dose regimen, with lower rates of placental and peripheral malaria parasitemia, particularly in primigravidae and secundigravidae [146, 152, 153].

However, there are some contradictions and challenges associated with IPTp-SP. The efficacy of this measure can be compromised by parasite resistance to SP [147]. Additionally, SP cannot be administered concomitantly with co-trimoxazole, a drug often recommended for infection prophylaxis in HIV-positive pregnant women [152]. Furthermore, submicroscopic infections, which frequently occur during pregnancy, cannot be effectively prevented by SP-IPT [154].

In conclusion, while IPTp-SP has shown significant benefits in reducing the adverse effects of malaria in pregnancy, further research is needed to address challenges related to drug resistance and to identify alternative medications for HIV-positive women. Integrating comprehensive counseling about IPTp-SP into antenatal care and addressing health system challenges are critical to improving uptake and effectiveness [155]. Future strategies may need to target women before their first antenatal care visit and effectively treat and prevent all malaria infections, including submicroscopic ones [154].

Similarly, malnutrition, particularly protein-energy malnutrition and micronutrient deficiencies, impairs immune function, and makes pregnant women more susceptible to malaria infection [156]. Conversely, malaria exacerbates nutritional deficiencies, creating a vicious cycle that severely compromises maternal and child health. The report emphasizes the importance of breastfeeding, the timing of complementary feeding, and the quality of complementary foods in protecting infants from malaria [156].

Taking nutritional supplements during pregnancy can have a positive effect on the health of the mother, the course of the pregnancy, and the health of the child [157]. For example, red palm oil (RPO), a good source of vitamin A, has been associated with some protection against malaria in children over 36 months of age, and vitamin A reduced febrile malaria episodes and parasite counts, particularly in children aged 12 to 36 months [158]. Another study showed that vitamin A and zinc supplementation prevented placental malaria in pregnant women [159]. In contrast, another study reported that vitamin A supplementation did not change the incidence of malaria during the study [160]. In general, although some studies suggest a potential benefit of vitamin supplementation in reducing malaria complications during pregnancy, the overall evidence remains inconclusive.

The combination of iron and folic acid supplements with SP-IPTp has been associated with a significant reduction in neonatal mortality in malaria-endemic countries in sub-Saharan Africa [161]. While the administration of iron alone had a negative impact on malaria prevalence in pregnant women in some studies, the combination of iron/folic acid supplements with SP-IPTp appears to have a protective effect against neonatal death [161], as summarized in (Additional file 6:Table S6). This suggests that a balanced approach to supplementation and malaria prevention may be necessary to achieve optimal results.

Discussion

Malaria remains a major global health problem, with *P.falciparum* and *P.vivax* being the main causes of pregnancy-associated malaria. Malaria control efforts have significantly reduced the risk to pregnant women in most endemic areas, with the exception of sub-Saharan Africa, where population growth has exceeded the progress made in malaria control. Therefore, implementing strategies to mitigate the risk of malaria during pregnancy remains critically important [162–164].

P.vivax, a malaria parasite, is known worldwide for its wide geographic distribution and complex biological characteristics, which pose a challenge for its control and eradication. This parasite can form dormant stages, known as hypnozoites, in the hepatocytes (liver cells). Studies have shown that pregnant women often have polyclonal infections, which can result from either relapses or reinfections. In addition, the genetic diversity of *P.vivax* is remarkable, with the existence of different haplotypes (groups of genetic variations) and the ability to develop at lower temperatures, in contrast to the lower genetic diversity observed in *P.falciparum.* Interestingly, *P.falciparum* has been linked to specific genotypes associated with asymptomatic infections at the time of delivery. A phylogenetic analysis examining the evolutionary relationships between the organisms shows that the *P.vivax* population is globally distributed among pregnant women [163–166].

The review also emphasizes the impact of infections with *P.malariae, P.ovale* and *P.knowlesi,* which are detected early in pregnancy and are presented in maternal peripheral and placental blood at delivery. Although *P.falciparum* and *P.vivax* infections during pregnancy have been extensively studied, non-falciparum infections in women infected with these parasites also have a significant impact on pregnancy outcomes [27, 68].

Our review has shown that primigravidae women are more susceptible to malaria infection than women with a higher parity. Similarly, studies have indicated that primigravidae have an increased risk of severe malaria and associated complications [8–11]. A study conducted by Singh et al. (1999) in India also found that malaria is more common in primigravidae than in multiparous women, and that malaria during pregnancy increased the risk of placental and congenital malaria [167]. This suggests that the physiological changes in the first pregnancy, which affect immune function and increase susceptibility to *Plasmodium* infection, make primigravidae particularly vulnerable to this disease and its complications [13].

Pregnancy-associated malaria is a major public health concern due to its harmful effects on maternal and fetal health. Severe maternal malaria is linked to`several serious complications, including ARDS, neurologic disorders caused by cerebral malaria, liver and renal dysfunction, anemia, thrombocytopenia, and fatal placental malaria [168–170]. Additionally, other studies have reported that severe maternal malaria can result in cerebral malaria, associated neurologic sequelae, malarial anemia, respiratory distress, hypoglycemia, and other pregnancy-related complications [131, 169, 171–173]. The pathophysiology of severe malaria infection involves a multifaceted process [174]. It is characterized by the metabolic products of malaria parasites, including the digestion of hemoglobin and damage to components of the erythrocyte membrane. Infection also involves the action of pro-inflammatory and anti-inflammatory cytokines and the adherence of malaria parasites to the vascular endothelium, leading to sequestration and rosette formation [173].

The prevalence of congenital malaria and its harmful effects on the health of newborns and infants is a major issue in sub-Saharan Africa, Latin America and Asia. A ten-year review conducted by Cardona-Arias and Carmona-Fonseca (2022) in Colombia underscores this observation [175]. The available evidence suggests that malaria during pregnancy may have a detrimental effect on fetal health. Intrauterine growth restriction, low birth weight and reduced fetal viability, including stunted growth and cognitive development in children, have been observed in association with chronic disease in adulthood [176, 177]. In addition, reduced birth weight and head circumference have been associated with *P.vivax* infections and gestational, placental, and congenital malaria [178]. Malaria-associated stillbirths and low birth weight have been observed in women with low protective immunity, possibly because acute infection causes a shortened pregnancy [179, 180]. This may be due to adherence of infected red blood cells to the placental vasculature, leading to inflammation, impaired blood flow and significant maternal anemia, which reduce the oxygen-carrying capacity of the blood. The inflammatory response triggered by malaria can also damage placental tissue, leading to poor placental function and disrupting the exchange of oxygen and nutrients between mother and fetus. This can lead to fetal hypoxia, growth restriction and developmental problems [176].

Malaria in pregnancy has a complicated pathophysiology characterized by a complex interaction between the malaria parasite, the maternal immune system and the placenta [10, 16, 181]. Sequestration of infected red

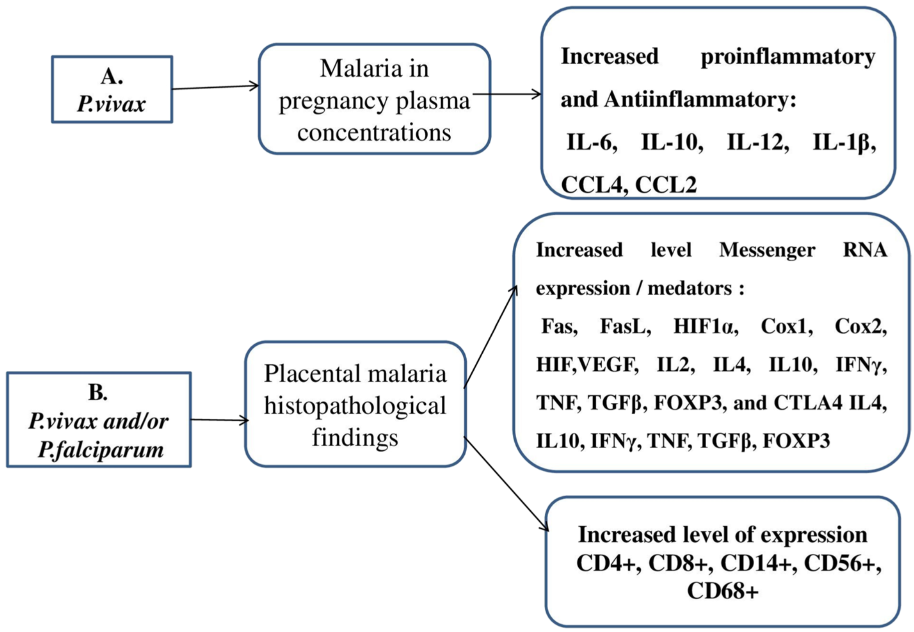

Fig. 5 Inflammatory responses and mRNA expression in maternal and placental malaria caused by *P. vivax* and *P.falciparum*

blood cells in the placenta, facilitated by specific parasite ligands such as VAR2CSA, triggers placental inflammation, reduced blood flow and impaired nutrient exchange [19, 182, 183]. Consequently, this cascade of events can lead to impaired fetal growth and development, ultimately contributing to an unfavorable pregnancy outcome [10, 16, 181].

Malaria during pregnancy can exacerbate the condition of patients with drug-resistant parasites, anemia, endemic poverty, and malnutrition [87, 184]. Even with prompt treatment, one or more asymptomatic infections with *P.falciparum* or *P.vivax* during the first half of pregnancymay result in a smaller-than-expected fetal head circumference in the middle trimester [185]. Strategies for the prevention of malaria in pregnancy should focus on early pregnancy [10, 186].

Malaria during pregnancy can manifest in different ways,, from asymptomatic parasitemia to severe disease. Typical symptoms include fever, chills, headache, and muscle pain [14, 187, 188]. Nevertheless, the altered immune response associated with pregnancy can lead to atypical symptoms or even an asymptomatic course, posing a challenge for accurate diagnosis and treatment [181, 189, 190].

Accurate diagnosis and effective treatment of malaria during pregnancy are essential for the well-being of both the mother and the developing fetus. Early detection of *Plasmodium* parasites can be performed through various methods, such as TBS, RDTs, and PCR [127, 137].

In this review we observed a significant difference in diagnostic viability between PCR and TBS. The different diagnostic results emphasize the need to select appropriate tools for surveillance and diagnosis. High prevalence rates in regions such as Niger and Sudan underscore. the need for improved maternal screening and preventive measures, while the absence of congenital malaria in India may be due to effective control measures or underreporting associated with diagnostic limitations [191–193].

Timely and appropriate antimalarial treatment, tailored to the gestational age and severity of the disease, is crucial for the effective treatment of malaria in pregnancy. Artemisinin-based combination therapies (ACTs) are the recommended treatment for uncomplicated malaria during the second and third trimesters of pregnancy, while quinine and clindamycin are often used during the first trimester. In addition to effective treatment, preventive measures are essential to reduce the incidence and impact of malaria during pregnancy. These measures include IPTp-SP, the use of ITNs and the use of IRS in conjunction with nutritional interventions [130, 160, 181, 194].

Malaria treatment options for pregnant women with uncomplicated, chloroquine-resistant *P.falciparum* or *P.vivax* infections are limited to mefloquine or quinine plus clindamycin. However, the availability of quinine is limited, and increasing resistance to mefloquine further restricts these options [195]. Artemether-lumefantrine (AL, Coartem) is effective and safe in the treatment of malaria during pregnancy [196]. The WHO has endorsed the use of ACTs, including AL, as a treatment option for uncomplicated malaria during the second and third trimesters of pregnancy and during the first trimester when other treatment options are not available. These updated recommendations are based on current evidence and are in line with the WHO malaria treatment guidelines [197]. In addition, intravenous artesunate is recommended for severe malaria and is the preferred treatment for reducing mortality, including in pregnant women, due to its higher efficacy and safety profile compared to quinine. Since primaquine and tafenoquine may only be used to a limited extent during pregnancy due to their possible hemolytic effects, recurrent malaria may occur after malaria treatment [198].

Recrudescence, the reappearance of *Plasmodium* parasites after treatment, may persist for a prolonged period during pregnancy, regardless of the antimalarial treatment used [199]. Studies have shown that the use of ACTs is associated with longer intervals of recrudescence compared to other treatment regimens. The occurrence of concurrent *P.vivax* infections treated with chloroquine has also been associated with a longer interval before recurrence. To accurately assess the efficacy of antimalarial drugs in pregnant women, it is recommended that the follow-up period be extended either until delivery or day 63, whichever is later [200–202].

Prevention of malaria in pregnancy requires chemoprophylaxis, vector control measures, and strengthening of health systems to enable early diagnosis and treatment [203–205]. IPTp has been shown to significantly reduce malaria prevalence and improve pregnancy-related outcomes [203, 204]. IPTp-SP is recommended for pregnant women in areas with moderate to high malaria transmission. Recent studies have shown that although IPTp-SP is effective, the development of drug resistance (particularly to SP) is a growing problem [206–208]. However, some countries are now exploring alternative drugs or combination therapies for IPT [209–211]. To support this, in areas of high seasonal malaria transmission, seasonal malaria chemoprevention with a combination of mefloquine, or amodiaquine and SP is being used as a strategy to reduce the incidence of malaria in pregnancy [206, 211–213].

Regarding nutritional interventions for malaria in pregnancy, there is evidence that supplementation of vitamins and minerals (e.g. iron/folic acid) may be effective in reducing the impact of malaria and nutritional deficiencies on maternal and neonatal health. Similarly, a balanced diet can generally meet increased nutrient requirements during pregnancy, but supplementation may be required for certain nutrients such as vitamin D, folic acid and iron [214]. Overall, a combination of proper nutrition, vitamins or minerals supplementation and malaria prevention strategies can help improve maternal and infant health in malaria-endemic regions. However, further research is needed to establish a causal link between malaria in pregnancy and malaria in infancy [215] and its synergistic effect with malaria prevention strategies in pregnancy.

Similarly, the appropriate use of ITNs and application of IRS is essential components of malaria control, and their use remains a cornerstone in the prevention of malaria in pregnancy. The WHO now recommends widespread provision of ITNs to pregnant women, particularly in regions with malaria epidemics. In addition, the introduction of ITNs has contributed to a significant reduction in malaria transmission. Better health outcomes for pregnant women and their children depend on the continued development and refinement of malaria prevention strategies and their implementation in routine antenatal care [21, 130, 216, 217]. Other vector control measures like environmental management (eliminating mosquito breeding sites) also may be used in some regions.

Currently, RTS, S/AS01 (RTS, S) is the only malaria vaccine specifically recommended for use in pregnant women. There are no other vaccines available at this time for the prevention of malaria in pregnancy, apart from RTS, S, which is used in malaria-endemic regions, particularly during the second or third trimester of pregnancy [218, 219]. However, it's important to note that the overall approach to preventing malaria in pregnancy involves a combination of strategies, and vaccines are just one part of the broader malaria prevention and control measures.

Limitations of the study

The limitation of this systematic review is that only articles published exclusively in English peer-reviewed, and open access journals were included, potentially excluding relevant studies from non-peer-reviewed sources or grey literature. In addition, the exclusion of articles without full-text access or articles focusing on non-pregnant populations or non-malaria conditions may have resulted in valuable data from broader or more diverse studies not being included. Furthermore, the requirement for sufficient data on prevalence, interventions, or outcomes related to malaria in pregnancy may have led to the exclusion of studies with incomplete or limited information that could have provided useful insights. These inclusion and exclusion criteria may have led to selection bias, limiting the generalizability of the results.

Conclusion

This systematic review provides a comprehensive analysis of the current state of research on malaria in pregnancy, highlighting recent advances and identifying key areas for future investigation. Malaria in pregnancy remains a major public health challenge worldwide, with a particularly heavy burden in sub-Saharan Africa. *P.vivax* is the most prevalent species worldwide, while *P.falciparum* is mainly restricted to Africa. In addition to gestational malaria, placental malaria and congenital malaria are also significant problems, mainly caused by *P.falciparum* and *P.vivax* even though other species also contribute infection. These infections lead to serious consequences such as premature birth, low birth weight and increased morbidity and mortality for mother and fetus. Antibody responses to *P.falciparum* and *P.vivax* exhibit remarkable temporal variability, with high malaria antibody levels being maintained by dynamic immune responses triggered by intermittent exposure to the parasite. Pro and anti-inflammatory mediators are immune marker expressions associated with malaria infections during pregnancy. The persistent presence of PfVAR2CSA antibodies suggests that maternal immunity acquired during pregnancy may provide protection for subsequent pregnancies. A multifaceted approach that includes effective prevention, timely diagnosis and appropriate treatment is essential in the control of malaria in pregnancy. Regular follow-up, early diagnosis and prompt treatment are key pillars in preventing malaria-related morbidity in pregnancy. Artesunate is the drug of choice for all forms of malaria at any stage of pregnancy. Although resistance to chloroquine has been identified in *P.vivax*, chloroquine remains the drug of choice for *P.vivax* in some countries. ACTs, such as artemether-lumefantrine (AL, Coartem), are the preferred treatment for uncomplicated *P.falciparum* cases at all stages of pregnancy. In addition, the use of IPTp-SP, nutritional supplementation, ITNs and IRS are effective preventive measures for malaria during pregnancy. Ongoing research and continuous updating of clinical practice are essential to overcome the challenges of malaria in pregnancy and improve maternal and child health.

Abbreviations

ARDS	Acute Respiratory Distress Syndrome
CSA	Chondroitin sulfate A
IRS	Indoor Residual Spraying
INTs	Insecticide-treated bed Nets
IPTp	Intermittent Preventive Treatment in pregnancy
PCR	Polymerase chain Reaction
PICO	Population Intervention Comparison Outcome
RDT	Rapid Diagnostic Test
TBS	Thick blood smear
VAR2CSA	Varicose Antigen 2 Chondroitin Sulfate A
VIR	Variant Immune Response
WHO	World Health Organization

Supplementary Information

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Additional file 1.

Additional file 2.

Additional file 3.

Additional file 4.

Additional file 5.

Additional file 6.

Authors' contributions

A.M. Conceptualize, data extraction, interpretation, and writing the review. G.A. critically review the manuscript of this review. D.Y.critically reviewed the manuscript of this review. M.S.critically reviewed the manuscript of this review.

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All Data is provided within the manuscript or supplementary information files.

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