Congenital malaria: The least known consequence of malaria in pregnancy

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Summary Congenital malaria is the least known manifestation of malaria and a very neglected area of research. Most of the existing information is limited to case reports in children born to non-immune women. With the use of molecular techniques, congenital infection is being increasingly detected among infants born to semi-immune women in endemic countries. However, many gaps in knowledge remain. The mechanisms and timing of infection are unclear. Furthermore, there is a lack of information on the impact of congenital malaria infection on the subsequent risk of malaria and general morbidity in the infant. There is also a lack of consensus on the clinical guidelines for its management. More research is needed in order to establish adequate preventive and management recommendations to avoid this consequence of malaria in pregnancy.

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Introduction

Malaria causes between 200 and 500 million episodes and between 1 and 3 million deaths each year. While the greatest burden is in sub-Saharan Africa, malaria is increasingly being recognised as a problem in Asia and Oceania and the burden of disease is increasing.1 In endemic countries, this burden is concentrated largely among young children and pregnant women.2

Four species of the malarial parasite, Plasmodium falciparum, P. vivax, P. ovale and P. malariae, infect humans.3

Of these, P. falciparum is the major cause of morbidity and mortality, but P. vivax is also associated with significant disease. All species are transmitted by the bite of female anopheline mosquitoes.

Horizontal-vector transmission remains the most common way of contracting malaria. It can also be transmitted through transfusion of infected blood and vertically from the mother to the fetus. Congenital malaria will be the focus of this review. The classically accepted notion is that malaria transmission from mother to infant is limited to low transmission areas, where pregnant women have lower levels of acquired anti-malaria-specific immunity, while vertical transmission is rare in highly endemic areas.4 This is mainly based on the observation that few newborns develop clinical disease during the first few weeks of life.5-6 The rarity of congenital transmission is attributed to the
effectiveness of the placenta as a barrier to maternal infected red blood cells, to the passive transfer of maternal antibodies and to the protective effect of fetal haemoglobin (Hb F). However, recent reports suggest that congenital malaria is not as rare among newborns in Sub-Saharan Africa as previously thought and that the disease may go undiagnosed for a long period in a sick infant.

**Definition of congenital malaria**

There is no clear consensus on the definition of congenital malaria. Congenital malaria occurs when malaria parasites cross the placenta either during pregnancy or at the time of delivery. It is usually defined as the presence of asexual forms of malaria parasites in the peripheral blood within the first 7 days of life, or later if there is no possibility of postpartum infection by a mosquito bite (as would be the case in non-malaria endemic areas). This could occur with or without accompanying clinical manifestations. However, congenital malaria is frequently reported as the sole presence of parasites in cord blood. A standard and homogeneous definition would facilitate the establishment of clinical management protocols, as well as the comparability between different epidemiological and intervention studies of malaria in pregnancy.

**Prevalence of congenital malaria**

The prevalence of congenital malaria in non-immune mothers has been reported to be around 10%. Most reports of congenital malaria documented in the literature are case reports of infants born in non-endemic countries whose mothers have a travel history or origin in malaria endemic areas and who present clinical manifestations several days or weeks after delivery. *Plasmodium falciparum, vivax, ovale* and *malariae* have been detected in the peripheral blood smears of such babies.

However, in malaria endemic areas congenital malaria has classically been considered a rare consequence of malaria among pregnant semi-immune women. In these areas, reports of congenital malaria are sporadic and vary widely in prevalence between 0–23%. The reasons suggested for the variability in this prevalence range from: (1) differences in the definition of congenital malaria; (2) levels of maternal immunity; (3) the type of blood sample examined (peripheral blood of neonates or cord blood); (4) the expertise in blood-smear examinations; (5) the method of parasite detection (Giemsas staining or polymerase chain reaction (PCR)); or even (6) a reflection of true environmental differences.

Recently, prevalences up to 33% have been reported in endemic areas, suggesting that the frequency of congenital malaria may be underestimated and that transplacental transmission of *P. falciparum* is not an uncommon event even in semi-immune women who usually have high levels of anti-malaria acquired immunity. This recently reported increase in the frequency of congenital malaria in endemic areas has been attributed to the interplay between several factors. These include increased resistance of *P. falciparum* to antimalarial drugs resulting in increased maternal parasitaemia, an increased virulence resulting from altered antigenic determinants and past under-reporting due to the difficulty of differentiating between truly congenital malaria and malaria that is acquired in the first few days of life (since most newborns do not have symptoms of malaria in the immediate neonatal period). It has also been suggested that a reduced transfer of protective antibodies from the mother to the newborn due to malaria chemoprophylaxis during pregnancy might also explain an increase in the frequency of congenital malaria. However, the difficulty in detecting low parasite densities, especially in newborns, may explain, at least in part, the low reported prevalence of congenital malaria among semi-immune women in endemic areas. Thus, with the recent use of more sensitive molecular assays such as the PCR, the frequency of detection of malaria infection has increased up to 10–32% for the peripheral blood of the newborn or for cord-blood samples, suggesting that congenital malaria occurs with greater frequency than was previously appreciated. However, caution is needed to interpret results based on PCR detection. Parasite macromolecules and not live parasites crossing the placental membrane may give a positive PCR result in cord blood. Recently, the presence of free circulating nucleic acids, which originated from a number of infectious agents in human plasma and serum and which do not necessarily represent active infection, have been shown using the very sensitive real-time quantitative PCR assay.

In most studies, cord blood samples had been collected to assess congenital malaria. When the newborn’s blood has been examined (at the time of birth or a few hours later), malaria parasites have been detected only rarely. In studies in which both cord and the infant’s peripheral blood have been collected, the frequency and severity of parasitaemia has always been lower in the baby’s peripheral blood than in cord blood.

**Mechanisms of congenital malaria**

The mechanisms and timing of vertical transmission are poorly understood. Postulated mechanisms for congenital transmission include maternal transfusion into the fetal circulation either during pregnancy or at the time of delivery, direct penetration through the chorionic villi, or through premature separation of the placenta. Various studies support each of these hypotheses. Since malaria in the infant is rare, it is widely believed that the placenta acts as an effective barrier preventing the transfer of malaria parasites from the maternal into the fetal circulation, suggesting that transmission at parturition or during labour may be the most likely mechanism. However, the transplacental transfer of maternal erythrocytes and leukocytes in normal pregnancies with uninfected placentas has also been reported, although the frequency and number of cells exchanged are usually low.

Factors that contribute to the development of congenital malaria are likely to be complex and multifactorial. The pre-existing level of malaria immunity in the pregnant woman is one of the most important factors. In low transmission areas, immunity is generally scanty and, thus, pregnant women when infected are almost always...
symptomatic and can develop severe disease. In contrast, in areas of high transmission such as sub-Saharan Africa, infection is frequent, although not commonly symptomatic and severe maternal disease is rare. However, even in these areas severe malarial anaemia may be an important cause of maternal mortality. Occurrence of a clinical attack of malaria during pregnancy may predispose to congenital malaria in the newborn. Acute fever in the pregnant woman may result in increased friability of the placenta. Clinical attacks are more common in infected women with low-levels of malaria immunity and, therefore, congenital malaria is expected to be more frequent in low transmission areas. However, vertical transmission has been also observed in infants of women who were asymptomatic throughout pregnancy. The risk of malaria infection and disease is also increased in the non-immune pregnant woman traveller to endemic areas.

Placental malaria may be another predisposing factor for congenital malaria. Malaria infection of the placenta may be accompanied by intervillous infiltrates of monocytic cells and other antigen-presenting cells. This intervillous mononuclear inflammation (IVMI) is especially severe in the first pregnancy and it is associated with maternal anaemia and low birth weight. IVMI induces an alteration in the cytokine balance and may cause pathological changes in trophoblasts that can damage the syncytiotrophoblastic membrane. This may compromise the integrity of the placenta, affect fetal growth and impede the repair of tears in the syncytiotrophoblastic membrane, increasing the risk of transplacental transmission of infected erythrocytes to the fetus during pregnancy. One study found that the presence of cord-blood parasitaemia correlated with the severity of placental IVMI, especially among primigravid and secundigravid women, in whom placental malaria occurs more frequently. It has also been observed that primigravid and secundigravid women with placental malaria are at increased risk for congenital infection. However, malaria infection of the placenta alone does not adequately explain the occurrence of congenital malaria. Firstly, studies looking at the correlation between placental, maternal, cord and neonatal parasitaemia are scarce and contradictory. In some reports a significant positive association was found, but not in others. More importantly, congenital malaria may occur in the absence of a maternal history of malaria. In Zaire, 17% of the cases of congenital malaria occurred in women with negative parasitaemias at delivery and in the absence of placental malaria infection.

Maternal anaemia is another factor that may increase the risk of congenital malaria. Anaemia may increase the likelihood of bidirectional materno-fetal exchange by stressing the placenta, often causing an increase in placental weight by increasing cellular proliferation, remodelling of placental architecture and angiogenesis. Maternal human immuno-deficiency virus (HIV) infection might interfere with the transplacental transfer of protective antibodies through the reduction of immunological responses to malaria and, thus, potentially increase the risk of congenital malaria. However, there is no evidence to date of higher prevalence of congenital malaria or cord blood infections in infants born to HIV-positive, malaria-exposed women.

Consequences of congenital malaria

There is very little information on the consequences of congenital malaria on the subsequent susceptibility to malaria or on morbidity in general in the infant. This information is needed to guide treatment recommendations. Presence of malaria parasites in cord blood or in the asymptomatic newborn may be related to an increased risk of anaemia in infancy, as has been suggested in one African study. Vertical transmission of malaria is likely to have important implications for fetal and newborn development. Direct infection of the fetus may be associated with pre-term delivery and fetal growth restriction, or could increase the likelihood of stillbirth. Fetal or newborn exposure to blood-stage malaria antigens may also have profound long-term effects during infancy and childhood by priming the immune responses of the fetus, by inducing immune tolerance, or both. Depending on the effect on the fetal immune system (probably related to the timing of exposure to the parasite antigens in utero), this may be reflected in a reduced (priming) or increased (immune tolerance) susceptibility to malaria in the infant and child. Several observations have suggested that in utero exposure to malaria parasites or their soluble products occurs with considerable frequency. Parasite-specific IgM and IgE have been detected in 11–25% of cord-blood samples obtained from individuals in areas of malaria endemicity. Because IgM does not cross the placenta during gestation, the presence of P. falciparum-specific IgM indicates activation of B cells by malaria parasites in utero. In addition, up to 60% of newborns of malaria-infected women have demonstrated lymphocyte reactivity to blood-stage malaria antigens in their cord-blood mononuclear cells.

Clinical manifestations

In reports from countries without endemic malaria, congenitally acquired malaria has been recognised as a rare cause of fever, frequently accompanied by irritability, hepatosplenomegaly, anorexia, progressive haemolytic anaemia and thrombocytopenia. Other signs and symptoms include hepatomegaly, jaundice, regurgitation, loose stools and poor feeding. Occasionally, drowsiness, restlessness and cyanosis can also be seen. In contrast, in sub-Saharan Africa, where the highest P. falciparum transmission rates in the world are found, symptomatic neonatal infection is rare, suggesting that even if parasites were to be found in cord or neonatal blood, these would be infrequently associated with disease. Although the infected newborn can be ill shortly after birth (C.M., pers. comm.), it is usually asymptomatic at birth but clinical manifestations frequently appear within 10–30 days of birth. However, the disease can also be delayed for weeks or months. This delay in presentation of congenital malaria is thought to be due to some degree of resistance in newborns to multiplication of malaria parasites because of fetal haemoglobin, failure of the parasites to grow in cord blood, persistence of maternal IgG in the newborn’s blood and fast elimination of parasites from the fetal circulation. It is possible that because of this delay in the clinical presentation, many cases of
congenital malaria in endemic regions are misclassified as postnataally acquired from the bite of infected mosquitoes. The diagnosis and reporting of clearly documented cases are, thus, limited to areas of the world where malaria is not endemic.

Diagnosis

If untreated, congenital malaria caused by *P. falciparum* is potentially rapidly lethal, especially in babies born to non-immune women. A correct aetiological diagnosis is decisive in treating the disease. However, because of its rarity, congenital malaria may go undiagnosed for a prolonged period in a seriously ill infant, especially in non-endemic malaria countries. As the number of immigrants from malaria-endemic areas into non-endemic countries continues to increase, congenital malaria should always be suspected in the differential diagnosis of unexplained fever in infants born to women from these areas.

In malaria endemic areas, examination for malaria parasites in the newborn is limited to infants with acute symptoms and no routine screening is done, mainly for logistical and economic constraints. In these areas, since clinical manifestations of neonatal malaria may be indistinguishable from those of neonatal sepsis, examination for malaria parasites should be included as part of the routine investigation of newborns with fever or clinical suspicion of sepsis. In addition, it has been suggested that babies born to mothers with a history of febrile illness within the last 2 weeks of pregnancy should have a blood smear taken for malaria parasite examination. Again, this is rarely done in practice due to limited resources in malaria endemic countries.

Prevention of congenital malaria

Prevention of malaria in non-immune pregnant women travelling to endemic areas is difficult. For this reason, pregnant women should defer non-essential travel. They should use vector control measures (insect repellents and insecticide treated nets (ITNs)) and receive malaria chemoprophylaxis. The selection of drugs for malaria treatment and prevention in pregnancy has recently been reviewed in detail.

The World Health Organisation (WHO) recommends that pregnant women living in stable (high) malaria endemic areas, should be protected against the infection by using ITNs and receiving intermittent preventative treatment (IPT) with sulphadoxine-pyrimethamine (IPTp). These two measures have been shown to be effective in reducing the prevalence of peripheral and placental infection, as well as of anaemia and low birth weight babies. It could be expected that they will also be associated with a reduction in congenital infection, however, this needs to be confirmed in future studies.

Treatment of congenital malaria

There is very little information regarding the clinical management of congenital malaria. In order to establish treatment recommendations it would be useful to distinguish between babies born to non-immune women, in which case congenital *falciparum* malaria, whether symptomatic or not, should be treated with quinine (10 mg/kg orally every 8 h, or same dosage in intravenous infusion until oral administration is possible).

In endemic areas, if the infection is symptomatic, antimalarial treatment should be administered either parenterally or orally as above, depending on the severity. However, in these areas newborns have some degree of resistance to malaria parasites due to immunological factors acquired both passively and actively (see section above) and they may be able to control and clear the infection without receiving specific treatment. Thus, there is no clear consensus on how to manage asymptomatic, usually low-density parasitaemias that are more commonly found than actual disease. Studies on the effects of congenital malaria in infants from endemic areas would help to make decisions on the appropriate clinical management.

The alternatives to antimalarial drugs for the treatment of malaria in the newborn are also extremely limited. Infants less than 6 months of age have been systematically excluded from drug trials for safety concerns. Furthermore, the widely accepted notion that infants are protected from malaria in the first 6 months of life has also influenced this situation. There is experience with quinine, chloroquine and, more recently, artemisinin derivatives (F. Nosten, pers. comm.) given to newborns with good tolerability. Sulphadoxine-pyrimethamine is not recommended by the manufacturer in the first 6 weeks of life and, in the case of mefloquine and amodiaquine, there is no specific mention by the manufacturer with regard to their recommendation in neonates.

A particular case and one for which there is even less information, is that of *P. vivax* congenital infection. This presentation has not been associated with a relapsing presentation, presumably because sporozoites are unable to penetrate the fetal circulation from the maternal bloodstream, preventing the development of hepatic foci. Thus, primaquine is not needed for the newborn infant and treatment of congenital malaria consists of the eradication of parasite-infected red blood cells only. An effective regimen for susceptible *P. vivax* is oral chloroquine, 10 mg/kg as the base, followed by three doses of 5 mg/kg at 6, 24 and 48 h after the first dose.

Treatment and prophylaxis of malaria during pregnancy

Treatment and prevention of malaria during pregnancy is currently a challenge for malaria control due to the failing efficacy of the recommended drugs, mainly chloroquine (for treatment) and sulphadoxine-pyrimethamine (SP) (for prevention). However, there is, as yet, very little evidence on the safety and efficacy of the new artemisinin-based combinations (ACTs) for pregnancy. At present, in semi-immune women, the recommendation for treating uncomplicated malaria is based on 7-days oral quinine in the first trimester followed by the ACT recommended in the country in the subsequent trimesters, while quinine is recommended for severe malaria in all trimesters.
In the non-immune pregnant woman who develops clinical disease, the risk of severe disease is particularly high and parenteral quinine is generally recommended for the treatment of *P. falciparum*. Acquisition of malaria in areas of high quinine resistance may warrant treatment with parenteral artemisinins, although these are not generally available. With respect to malaria prevention, chloroquine-proguanil is recommended by the World Health Organisation for travel to areas with chloroquine-sensitive malaria. Mefloquine can be recommended for travellers to areas of chloroquine-resistant malaria. Doxycycline is contraindicated in pregnancy and there is no safety and efficacy data for atovaquone-proguanil (Malarone™) in pregnancy. The use of vector control measures such as ITNs and repellents should be recommended.

**Conclusions**

Congenital malaria is a much neglected area of research. This may be explained by the widely accepted assumption that malaria transmission from the mother to her newborn child is a very rare event and that, perhaps with the exception of non-immune women, it is infrequently associated with disease. However, the use of polymerase chain reaction (PCR) techniques for detecting parasites in cord and newborn blood indicates that congenital malaria is not as rare as previously thought in endemic areas. Of the many gaps in knowledge on congenital malaria, there is an urgent need to evaluate the short and long term consequences of the congenital infection in the infant. This will help to establish adequate recommendations for its prevention and clinical management. However, it is also essential that a standardised definition and methodology for its detection is established. This will allow and facilitate comparability between different studies and the evaluation of clinical protocols. The impact of malaria control in the pregnant woman through the recommended tools, i.e. insecticide treated nets (ITNs) and intermittent preventative treatment (IPT), on the risk of congenital malaria needs to be evaluated in future studies of malaria prevention in pregnancy. Finally, a deeper understanding of the mechanisms, timing and factors (level of specific immunity in the mother, anaemia and other co-morbidities such as HIV) contributing to vertical transmission is needed to help with planning and deciding upon the best preventative strategies. Meanwhile, congenital malaria should always be suspected in the differential diagnosis of unexplained fever in infants born to women from endemic areas and from those women with a history of recent travel to malaria endemic areas.

**Practical points**

- Congenital malaria should be suspected in the differential diagnosis of unexplained fever in infants born to women who come from malaria endemic areas.
- There are no clearly established protocols for the clinical management of congenital malaria.

However, the infant with congenital malaria born to a non-immune woman should be treated with quinine.
- Non-immune pregnant women should defer non-essential travel to endemic areas.
- Prevention of malaria in the pregnant women is based on chemoprophylaxis and the use of vector control measures.

**Research directions**

- The definition of congenital malaria.
- The mechanisms and timing of infection.
- The short and long term impact on the subsequent risk of malaria and general morbidity in the infant.
- The impact of prevention strategies for malaria in pregnancy on the risk of congenital infection.

**References**


