Pathogenesis of malaria in pregnancy

Even though we have good tools to prevent and treat malaria, it remains a tragically common disease in poor countries, especially in Africa. Pregnant women are particularly susceptible to malaria, causing anaemia and poor birth outcomes. There is marked sequestration of *Plasmodium falciparum*-infected erythrocytes (IEs) in the placenta, but the pathogenesis of malaria in pregnancy is still incompletely understood. Both intermittent preventive therapy and insecticide-impregnated bed nets are effective protective measures, but new measures are also needed.

Epidemiology

Malaria causes maternal anaemia and contributes to an estimated 10,000 maternal deaths each year. Moreover, malaria infections result in 75,000-200,000 low birth weight babies each year, due to combinations of preterm delivery and fetal growth restriction. The most dangerous form of malaria for pregnant women is *P. falciparum*; *P. vivax* infections also cause poor birth outcomes.

Pregnant women are at greater risk of malaria infection and of symptomatic malaria disease than non-pregnant adults for several reasons. First, they are more attractive to mosquitoes. Second, once infected, parasite burdens are higher in pregnant women than in non-pregnant adults. This may be because pregnancy weakens the host immune response to parasites and because large numbers of parasites sequester in the placenta.

In areas of high transmission, such as much of sub-Saharan Africa, malaria is most frequent in first pregnancies, and this gravidity dependent susceptibility is a key feature of disease epidemiology. Prevalence of infection peaks early in pregnancy (between 13-16 weeks), declining towards term. HIV infection increases susceptibility to malaria, resulting in more prevalent and higher-density infection, and a relative loss of gravidity-dependent immunity. In low transmission areas, women of all gravidities are affected.

Placental pathology

*P. falciparum* causes three specific changes in the placenta. IEs containing mature trophozoite and schizont parasite stages accumulate in the intervillous spaces (the lake-like structures through which maternal blood circulates), sometimes to very high densities. Placental malaria may be accompanied by intervillous infiltrates of monocytes and macrophages, some containing malaria pigment (hemozoin). Finally, hemozoin may also be seen in fibrin deposits, and these pigmented fibrin deposits can persist after resolution of episodes of infection. Each of these changes (parasites, monocytes, or pigmented fibrin) has been associated with poor birth outcomes.

Sequestration of IE plays an important role in all *P. falciparum*-associated pathology. In the brain and other viscera, ICAM-1 and CD36 are the primary ligands for IE. In the placenta, in contrast, IE adhere to chondroitin sulphate A (CSA) and hyaluronic acid, which are expressed by syncytiotrophoblast that line the placental intervillous spaces.

Placental IE express variant surface antigens (VSAs), which mediate cytoadherence. The major VSAs are the P IEMP1 (*P. falciparum* erythrocyte membrane protein 1) receptors, coded for by plasmodial var genes. One var gene, var2csa, appears to be responsible for CSA binding. Deletion of var2csa largely or completely abolishes CSA adhesion, and placental isolates usually transcribe high levels of var2csa and levels of antibody to VAR2CSA recombinant proteins correlate with protection in some subgroups. Thus, VAR2CSA may be a promising vaccine candidate.
Malaria may evade the host immune response in the placenta by altering the response. Placental malaria causes increased synthesis of inflammatory cytokines like TNF, interleukin-2 and interferon γ. Increased placental TNF has been associated with low birth weight and anaemia. Some of the mechanisms by which malaria may result in premature delivery or fetal growth restriction are illustrated in Figure 1.

**Undernutrition and malaria**

Maternal nutrition before and during pregnancy is another important determinant of birth weight. In a recent study in Kinshasa, the effects of malaria were most evident in undernourished mothers. Maternal macronutrient supplementation has been shown to improve birth weight, and it may be that combined nutritional and malaria interventions would give optimal fetal protection from growth restriction.

**Timing of infection and fetal growth restriction**

Few studies have attempted to examine the relationship between malaria infection during pregnancy and pregnancy outcome. Figure 2 illustrates the relationship between fetal growth, gestation, and timing of currently-used interventions.

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Figure 1. Potential pathogenic mechanisms by which placental malaria affects placental function and results in intrauterine growth retardation or preterm delivery. Reproduced with permission.

IRBC – infected red blood cell; CSA – chondroitin sulfate A; IUGR – intrauterine growth retardation; PTD – preterm delivery.
interventions\textsuperscript{22, 25}. Presently, it is unknown whether infection early in pregnancy may compromise ultimate fetal growth potential, although one study suggests this may be the case\textsuperscript{26}.

**Malaria and the neonate**

Newborns in areas of high malaria transmission are relatively protected from malaria in early life, although the mechanisms are not fully understood\textsuperscript{27, 28}. Cord blood infection is commonly detected, especially when sensitive molecular diagnosis is used\textsuperscript{29, 30}, but symptomatic neonatal infection is rare in endemic areas\textsuperscript{31}.

Contributing factors may include innate mechanisms (including fetal haemoglobin and $p$-amino benzoic acid-deficient breast milk), cultural ones (swaddling of newborns, decreasing their exposure), transplacental transfer of protective antibody\textsuperscript{32, 35}, and priming of neonatal responses by transplacental transfer of parasites or their products\textsuperscript{34, 35}. In case reports from the US, newborns of non-immune women have developed severe febrile illness due to *P. falciparum* or *P. vivax* malaria\textsuperscript{36}. The apparent rareness of similar cases in babies of semi-immune women suggests a central protective role for transplacental antibody transfer. HIV infection interferes with this process\textsuperscript{37, 38}, possibly increasing susceptibility of children of HIV-infected mothers to malaria.

**Prevention of malaria in pregnant women**

Effective and affordable ways to protect pregnant women from malaria are discussed in the article by Heather Jeffery in this issue. Unfortunately, only 2-50\% of pregnant women in malaria-endemic area currently sleep under bednets and relatively few women receive the recommended intermittent preventive treatment (IPT)\textsuperscript{39}. Additionally, due to the emergence of resistance, new IPT regimens are needed. Such drugs will need to be evaluated closely for safety in pregnancy, as well as for efficacy and, because

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**Figure 2. Relationship between timing of IPT, fetal growth rates, and potential vulnerability of mother and fetus to deleterious effects of malaria.**

The fetal growth rate varies over the course of pregnancy, peaking at about 36 weeks (blue curve). In the context of moderate SP resistance, IPTp (vertical green arrows) may or may not clear infection, and offer a shortened period of prophylaxis against reinfection (attached horizontal black arrows)\textsuperscript{25}. Reinfection during the period of vulnerability may affect fetal growth (double headed arrow). The effects of malaria early in pregnancy (dotted arrow) on fetal growth are less well understood. Reproduced with permission\textsuperscript{22}.

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Conclusions
Our understanding of the pathogenesis of malaria in pregnancy has improved significantly in recent years, but important gaps remain. Many challenges remain in developing and implementing interventions to protect pregnant women from malaria. A recently inaugurated Malaria in Pregnancy Consortium, funded by the Gates Foundation and EDCTP, will accelerate progress in protecting pregnant women and their infants from malaria.

Acknowledgements
SJR is supported by the NHMRC of Australia and by the Malaria in Pregnancy Consortium. SRM is supported by the NIH. We thank Sarah Landis for the prototype of Figure 1.

References