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Malaria in pregnancy: late consequences of early infections

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While progress has been made controlling malaria world-wide, efforts have stalled in many countries [1]. Pregnant women, especially first-time mothers, called primigravidae, remain a particularly vulnerable population. During pregnancy, infection with *Plasmodium falciparum* can result in miscarriage, stillbirth, premature delivery and fetal growth restriction [2, 3], and malaria in pregnancy has been estimated to lead to 100,000 fetal and infant deaths each year [2].

P. falciparum has the unique ability to sequester in the placenta, where infected red blood cells bind to the syncytiotrophoblast, the layer of cells lining the maternal blood spaces of the placenta. This process is mediated by a parasite protein called VAR2CSA exported to the RBC surface adhering to chondroitin sulfate A, a glycosaminoglycan sugar expressed on the syncytiotrophoblast [4]. Antibody to VAR2CSA develops with repeat exposure over successive pregnancies, and inhibits this binding [5].

The placental parasitisation is accompanied by a maternal inflammatory response, and leucocytes, particularly monocytes, can be found in large numbers in the delivered placentas of some women, especially primigravidae [6]. At delivery, inflammatory responses to malaria are associated with low birth weight and maternal anaemia (reviewed in [7]).

The pernicious effects of malaria in pregnancy begin long before delivery, but identifying the critical time windows for intervention is challenging. We know little about malaria's effects in the first half of pregnancy, especially the first trimester. This is in part because in many high burden countries, few women attend antenatal clinic in early pregnancy. A mix of social, cultural and logistic issues are likely drivers. Examples include distance and need for partner consent, fear of sorcery affecting the pregnancy, and facility level factors including user fees [8]. Access to pregnancy testing and obstetric ultrasound, which can provide incentives for early presentation, is also rare.

Malaria in pregnancy can be prevented with long-lasting insecticide impregnated mosquito nets (LLINs), and intermittent preventive treatment (IPTp). IPTp is the regular administration of curative doses of antimalarials at monthly intervals starting at about 16 weeks' gestation. Unfortunately, uptake of these measures remains depressingly low. In 2017 only 27% of women received WHO's recommended three doses of IPTp, and 61% slept under an LLIN [1].

In recent years, several longitudinal studies have suggested that malaria in the first half of pregnancy can cause fetal growth restriction [9, 10] and may also result in earlier delivery [11], which together contribute to lower birth weight babies. This suggests that malaria infection occurring early in pregnancy before IPTp is presently recommended may have important effects on pregnancy outcome. A recent publication provided new insights into how pregnancy affects susceptibility to malaria. Using a cohort of Beninese women recruited before conception, the authors showed that in many women, the rates of carriage of microscopically-detectable infection were increased as early as the fifth week of gestation compared to before conception [12], highlighting the potential for malaria to play a role in placental development very early in pregnancy

How could malaria in early pregnancy affect fetal and placental development? A study from the Democratic Republic of Congo gave insights into a possible mechanism: malaria in the first half of pregnancy was associated with abnormal patterns of blood flow on Doppler ultrasound later in pregnancy [10]. The placenta's plumbing is largely established in the first half of pregnancy, when placental trophoblast cells invade in and around the maternal spiral

arteries of the uterus to convert them into low resistance, high capacity blood vessels, able to supply enough blood and nutrients to the rapidly-growing fetus. In an in vitro study *P. falciparum* infected plasma affected trophoblast migration, suggesting malaria may affect development of the placental circulation by impairing the process by which trophoblasts cause vascular remodelling [13].

As well as invading the uterus to develop an adequate maternal blood supply, the fetal cells of the placenta also form the villous tree, a complex vascular network under the syncytiotrophoblast's protective covering. The angiogenesis of this villous tree is controlled by a complex network of angiogenic factors, and its development is susceptible to disturbance by placental oxidative stress [14]. In malaria infection, placental sequestration and associated inflammatory response may result in oxidative stress and impaired vascular development. For example, in a murine model of malaria in pregnancy, C5a (an inflammatory component of the complement cascade) was shown to mediate some of the negative impacts of malaria on placental vascular development [15]. Thus, the placental inflammatory response to malaria can inhibit normal placental vascular development

Another possible mechanism underlying malaria's effects on placental angiogenesis was recently described. Pregnancy malaria in humans was associated with both lower levels of l-arginine, a key component of nitric oxide (NO) biogenesis, and an increase in asymmetric dimethylarginine, an inhibitor of NO biogenesis, while in a mouse malaria model, l-arginine supplementation restored placental angiogenesis [16]. L-arginine supplementation is a potential intervention that could mitigate malaria's negative effects on placental angiogenesis and on fetal growth; given we have few possible interventions to restore poor fetal growth or prevent pre-term delivery, it is worthy of further study.

Even though we know that malaria, early in pregnancy, is deleterious, we do not know how early this increase risk manifests. To answer this question, researchers have recently begun enrolling cohorts of young women who are hoping to conceive so that they can be followed from the first trimester. In the current issue of the journal, Sofie Moeller and her colleagues have examined how the timing of malaria infection during pregnancy affects placental development [17]. Enrolling women either before conception or in the first trimester of pregnancy, they followed their pregnancies closely with repeated malaria testing and provision of IPTp and LLINs to decrease malaria episodes in later pregnancy. From 538 women followed up, they closely examined the placentas of 138. Women were grouped according to the timing of their infection, including <15 weeks' gestation, 15-22, 23-27 and ≥28 weeks' gestation, and controls with no documented infection by PCR or microscopy; women with repeat infections were excluded.

The placentas were examined using stereology, to characterize the placental villi for type, length, surface area and volume, and the vessels within the villi for length, surface area and diffusion distance from the mother's blood. Notably, malaria in early pregnancy (before 15 weeks' gestation), but not at the later time points, was associated with significant reduction in the volume of the villi, and in the length and surface areas of transport and diffusion blood vessels within the villi. There was also an increase in diffusion distance, and a possibly compensatory increase in diffusion surface area. Similar but less pronounced effects were seen with malaria at 15-22 weeks, while malaria late in pregnancy was actually associated with a rebound *increase* in several of these parameters. The authors also observed significant relationships between diffusion vessel surface and birth weight or gestational age, and between transport vessel length or surface and gestational age. Taken together,

these data suggest that malaria infection in the first trimester of pregnancy, in particular, can have lasting effects on placental development, which seem to affect pregnancy outcomes.

There are a few caveats to consider: this was a relatively small study, with 68 malaria-infected women. Moreover, most women were multigravidae (second or later pregnancy), and at lower risk of malaria (although declining malaria transmission in the study site might have decreased their acquisition of protective immunity). Also, malaria-infected women in the first trimester were treated with quinine instead of artemisinin combination therapy, so some of the differences found could have been confounded by this. Finally, one might expect impaired placental villous and vascular development to result in decreased fetal growth rather than premature delivery, as reported by Moeller et al.

Nevertheless, this study clearly indicates a need to look more closely at the consequences of malaria in the first trimester of pregnancy, and, possibly, to evaluate interventions to protect pregnant women during this period. The finding that malaria prevalence increases as early as week 5 of gestation suggests that pre-conceptional intervention could, at least theoretically, be of benefit to clear infection before conception Another strategy to investigate is to use highly sensitive screening for malaria in first pregnancy, combined with safe effective treatment of infected women. Such early interventions may have the potential to prevent many unnecessary poor birth outcomes in malaria-endemic countries.

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