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Dysregulation of placental vascular development- a mechanism for adverse pregnancy outcomes in placental malaria

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An estimated 85 million pregnancies are at risk of malaria each year [1]. Pregnant women are particularly vulnerable to *Plasmodium spp*. infection, which can lead to adverse consequences for both mother and baby, including maternal anaemia, preterm birth, foetal growth restriction, low birth weight, stillbirth and infant death [2].

P. falciparum infection causes the greatest morbidity in pregnancy. The underlying pathology of adverse birth outcomes is thought to derive from the accumulation of *Plasmodium*-infected erythrocytes in the intervillous spaces of the placenta, which interferes with maternal-foetal exchange, stimulating inflammatory immune responses and dysregulation of angiogenic pathways [3]. A recent study by Tran, et al has brought us one step closer towards understanding the mechanisms of how malaria infection impacts placental vascular development [4]. Previously, the authors found that foetal growth restriction in the setting of placental malaria was associated with C5a complement activation, through the dysregulation of angiopoietin 1 (Ang-1) and angiopoietin 2 (Ang-2), two modulators of vascular development [5]. Dysregulated balance between Ang-1 and Ang-2 have been associated with adverse pregnancy outcomes, including foetal growth restriction and preeclampsia [6,7].

In the current study, they apply findings from clinical samples collected from a cohort of pregnancies affected by placental malaria to a mouse model of malaria in pregnancy. In human samples, they found that placental malaria was associated with lower levels of Ang-1 levels, and elevated Ang-2/Ang-1 ratios. Turning to a *P. berghei* ANKA mouse model of malaria in pregnancy to further explore *in vitro* mechanisms, they found similar trends in these vasculo-modulators, which was also associated with foetal growth restriction and foetal loss. In Ang-1 heterozygous mice with lower endogenous levels of circulating Ang-1, they demonstrated that maternal malaria was associated with lower placental mRNA expression of Ang-1, Ang-2, and the Ang-1 receptor Tie2. Adverse pregnancy outcomes after *P. berghei* infection were also more pronounced in mothers with reduced Ang-1 levels. Micro-CT imaging of the placental vasculature in these mice showed impaired remodelling of the foetal vessels in response to *Plasmodium* infection, leading to increased placental resistance, a known contributor to poor foetal growth.

This work strengthens the mechanistic links between placental malaria, inflammation, placental vascular dysfunction, and adverse pregnancy outcomes. Of note, there are limitations to direct translation of findings between mouse and human, such as fundamental differences in placental architecture as well as the more extreme parasitaemia and clinical disease in the *P. berghei* ANKA model compared to commonly asymptomatic disease in human pregnancy. Analysis of clinical samples showed lower Ang-1 levels throughout gestation in pregnancies that were eventually found to have placental malaria. As the timing of maternal infection in this cohort not described, it is unknown whether decreased circulating Ang-1 predisposes to development of placental malaria or is a consequence of *P. falciparum* infection. Future work to confirm the molecular and anatomic findings identified in mouse placentas in human pregnancy is essential. Additionally, the pathophysiology of foetal growth restriction and adverse outcomes is likely multifactorial, and further research is needed to understand whether other correlates of adverse outcomes, such as inflammatory dysregulation of nutrient transport or cytokine response, also interact with the angiopoietin-Tie2 axis [8,9].

Importantly, these findings raise hope of identifying potential molecular targets to intervene and prevent adverse outcomes in the setting of malaria in pregnancy. While recombinant Ang-1 supplementation or targeted blockade of Ang-2 may be currently out of reach in low resource settings, other interventions that promote healthy vascularization, such as L-arginine supplementation, as suggested by the authors, may be more readily feasible [10]. Future efforts to reduce the global burden of malaria in pregnancy will require multipronged strategies that include primary malaria prevention, elimination, and in the setting of unavoidable infections, therapeutics to prevent pregnancy complications in high-risk individuals.

Contributions

NO and SLG wrote the manuscript. SLG supervised the work.

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Declaration of Competing Interest

The authors have no conflicts of interests.

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