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Placental malaria and pre-eclampsia through the looking glass backwards?

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Abstract

Placental malaria and pre-eclampsia occur frequently in women in developing countries and are leading causes of fetal growth restriction. Reduced placental perfusion, loss of placental integrity and endothelial cell dysfunction are characteristics of both conditions, and several common factors can be implicated in their causation as well as leading to a cascade of responses with pathophysiological effects. Discrimination between risk factors which result in a loss of endothelial integrity from pathogenic factors which occur as a consequence of this is essential for understanding the potential influence of malaria on pre-eclampsia. This article summarises the evidence linking the two conditions in relation to their epidemiological, immunological, haematological and biochemical characteristics as well as the pathological similarities and differences related to placental structure and function. The potential similar role for nitric oxide synthase involvement in both placental malaria and pre-eclampsia is considered. Several research implications are highlighted which follow from this analysis. We consider that there is no clear dividing line between pathogenic mechanisms related to both conditions, a better understanding of which should be of benefit to millions of women in developing countries.

Keywords: Placenta; Malaria; Pre-eclampsia

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1. Introduction

Both pre-eclampsia and *Plasmodium falciparum* malaria commonly occur in human pregnancy, and both are associated essentially with 'a sick placenta'. At least 50 million pregnancies are exposed every year to malaria infection, which may result from single or mixed infections with any of the species of Plasmodium that cause human malaria. The occurrence of malaria infection is increased up to 10-fold in primigravidae living under holoendemic conditions (Brabin, 1983). *P. falciparum* infection is the most studied species and the most important parasite associated with low birthweight in first pregnancies in Africa. Pre-eclampsia affects approximately three times this number of pregnancies globally and approximately 10% of all human births (Robilland et al., 2003). Both disorders have a markedly increased prevalence in first pregnancies, but there are no clear predictive indicators of disease for either condition.

Although pre-eclampsia and maternal malaria would be expected frequently to occur concurrently in malarious areas, their interaction on the health of the mother and her baby has been little studied (World Health Organisation, 1987). Accurate estimates of the incidence of pre-eclampsia in developing countries are few. Rates of 0.7–4.7% have been reported from Asia, with severe pre-eclampsia complicating 5–10% of cases (Robson, 2002). In a large study of 16,590 births in a holoendemic malarious area of northern Nigeria, pre-eclampsia incidence was 10.6% in primigravidae and 3.9% in multigravidae (Harrison et al., 1985a).

In this article, we review the commonality of factors affecting the placenta that are associated with both conditions as well as consider mechanisms of pathogenesis which relate to both and could contribute to their interaction and severity.

2. Epidemiology of malaria and pre-eclampsia

Placental parasitaemia occurs twice as frequently in first compared to later pregnancies in women living under stable conditions for malaria transmission (Brabin, 1983). This susceptibility relates to selection of *P. falciparum* parasites that adhere to chondroitin sulphate A (CSA) and/or hyaluronic acid receptors expressed on syncytiotrophoblast as part of glycosaminoglycan molecules (Fried and Duffy, 1996), resulting in an accumulation of infected erythrocytes in the intervillous spaces that promote inflammation. Parasite-expressed protein(s) mediating adhesion to CSA have conserved epitopes targeted by anti-adhesion antibodies. Specific antibodies which develop against these parasite variants inhibit parasite adhesion in the placenta and are associated with protection from malaria in subsequent pregnancies (Fried et al., 1998a; Staalsoe et al., 2004). This partly explains the increased susceptibility of primigravidae to falciparum malaria. Pre-eclampsia occurs also more frequently in primigravidae in both malarious and non-malarious areas. For example, in a malarious area of Nigeria, the relative risk for pre-eclampsia in primigravidae compared to multigravidae was 1.55 (95% CI, 1.41–1.69) and for eclampsia 11.06 (95% CI, 8.45–14.48) (Harrison et al., 1985a). In Mauritius, which is non-malarious, the corresponding excess risks were 1.32 (95% CI, 1.08–1.61) for pre-eclampsia and 2.12 (95% CI, 0.63–7.28) for eclampsia (Poonyth et al., 2003); these are lower than for the malarious area, and this difference is significant for eclampsia.