

ABSTRACT

Co-infection with malaria and Epstein Barr virus (EBV) have been implicated in the etiology of endemic Burkitt's lymphoma (eBL) but the precise mechanism by which these two agents lead to the pathogenesis of eBL has been partially elucidated. In addition, living in a malaria holoendemic area is a risk factor to earlier primary EBV infection that results in higher viral loads and poor control of the virus, a risk factor in the etiology of eBL. Children from Chulaimbo, a malaria holoendemic region are infected with EBV early in life when typically maternal antibodies should protect them against the infection. This study investigated the effect of maternal malaria infection during pregnancy on the transfer of EBV-specific IgG antibodies and fetal lymphocyte homeostasis in pregnant women from Chulaimbo. The specific aims were: to determine the effect of malaria infection during pregnancy and maternal hypergammaglobulinemia on the transfer of EBV-specific antibodies; to determine the effect of *in utero* malaria exposure on cord blood cytokines and chemokines; to determine the effect of *in utero* malaria exposure on cord blood Treg cells and characterize B and T-cells in cord blood following *in utero* malaria exposure. In a longitudinal analysis, 70 pregnant women were analyzed from Chulaimbo (malaria holoendemic area); flow cytometric analysis of Treg cells, B and T-cell phenotypes were performed on cord blood mononuclear cells (CBMCs). Maternal total IgG was measured using Enzyme-linked Immunosorbent Assay (ELISA) while EBV serological analysis and cord blood cytokine levels was done by Luminex assays. Differences in antibody, cytokine, Treg, B and T-cells between malaria-exposed and -unexposed were compared using Mann-Whitney U test. Multivariate regression analysis assessed the effect of malaria exposure on the transfer of EBV-specific antibodies while controlling for a set of confounders. A higher proportion (63%) of the infants were exposed to malaria *in utero*. Maternal malaria infection during pregnancy resulted in significant reduction in the transfer of anti-VCA and anti-EBNA1 antibodies to the neonates by 13% and 22%, respectively. The levels of cytokines and chemokines between malaria-exposed and -unexposed cord blood were comparable. Significantly higher frequency of Treg cells was observed in malaria-exposed compared to -unexposed cord blood ($p=0.0005$). There were higher transitional B-cells and activated classical memory B-cells but lower naïve B-cells in malaria exposed cord blood compared to unexposed cord blood ($p=0.0089$, $p=0.0257$ and $p=0.0053$, respectively). However, T-cell homeostasis in cord blood was not affected by maternal malaria infection during pregnancy. Results suggest that malaria exposed neonates are susceptible to early primary EBV infection due to low antibody levels, reduced transfer of maternal antibodies, inhibition of EBV-specific immune responses by the increased Treg cells and altered B-cell homeostasis. Findings from this study will help to explore potential avenues for delaying the early primary EBV infection in children experiencing holoendemic malaria who are at risk of eBL.