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Malaria during pregnancy: a balancing act

Successful pregnancy requires mothers to maintain immune competence against a wide array of microbes without rejecting the foreign conceptus. In general, local immunoregulatory mechanisms at the fetomaternal interface allow pregnancy to proceed, while systemic immune responses prevent undue susceptibility to most infections.

Malaria is an important exception. Pregnant women have increased susceptibility to *P. falciparum* and *P. vivax* but not to *P. malariae* and *P. ovale* malaria parasites (species-specific susceptibility), and susceptibility to *P. falciparum* and *P. vivax* decreases with successive pregnancies (parity-specific susceptibility). Pregnancy-related "immunosuppression" has been invoked to explain susceptibility, and cellular immune responses are measurably altered during pregnancy, but these alterations do not explain either the species-specific or parity-specific nature of pregnancy malaria susceptibility. *P. falciparum* parasites infecting pregnant women have a phenotype (defined by adhesive and serologic features) that is distinct from isolates collected from nonpregnant populations. Women in endemic areas develop antibodies against these isolates during their first pregnancy, but not before. *P. falciparum* is distinguished by its ability to bind endothelial receptors and sequester in deep vascular beds, including the intervillous spaces of the placenta where the parasite concentrates to high density. Over successive pregnancies, women develop anti-adhesion antibodies that block parasite binding to chondroitin sulfate A on the placental syncytiotrophoblast, and the development of these antibodies correlates with the development of protective immunity, thus providing an explanation for parity-specific susceptibility.

Successful pregnancy has been characterized by an immunologic bias away from Type 1 and toward Type 2 cytokines. In the placenta, the mass of sequestered malaria parasites elicits an inflammatory infiltrate, principally of monocytes/macrophages and devoid of natural killer cells, that is limited to the intervillous space without involving surrounding tissue. In conjunction, malaria alters the balance of pro- and anti-inflammatory cytokines in the pregnant woman. Placental levels of IL-2, IFN-g, and TNF-a are elevated among women exposed to malaria, and placental IFN-g and TNF-a in exposed women are associated with poor pregnancy outcomes, including low birthweight. Malaria-induced placental inflammation, and specifically pro-inflammatory cytokines, appear to subvert healthy pregnancy, including a putative role in fetal growth retardation, echoing earlier findings that related Type 1 anti-trophoblast responses with recurrent unexplained abortion.