REVIEW ARTICLE

Malaria in Pregnancy: an overview

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INTRODUCTION

Malaria is a parasitic disease affecting red blood cells that is transmitted by female mosquitoes of the Anopheles genus. *A. gambiae* and *A. funestus* are the main vectors of the disease in Africa (1). Following infection by sporozoites found in the mosquito's salivary glands, the host's liver cells are initially used by the parasite to grow and multiply. Parasites released into the circulation subsequently infect red blood cells, proliferate in them and eventually cause them to burst. Of the four parasitic protozoa causing malaria, *Plasmodium falciparum*, *P. vivax, P. malariae*, and *P. ovale, P. falciparum* is the most common and the most dangerous, causing between 700,000 and 2.7 million deaths annually, most of which are in children and pregnant mothers (1). The millions of pregnant women residing in regions where malaria is endemic are particularly vulnerable to the effects of *P. falciparum* infection. The severity of malarial infections is also considerably increased in pregnant women and their unborn children as a specific form of the disease afflicts them: placental malaria. This review aims at introducing the reader to the implications of malaria infection during pregnancy.

THE PLACENTA AND IMMUNE EVASION

Pregnancy causes a number of physiological changes that affect the way the *Plasmodium* parasite invades its host. Down regulation of normal maternal immune response is necessary to prevent rejection of the conceptus. Cell-mediated immunity (Th1) is particularly suppressed during pregnancy, and the mother is increasingly reliant on humoral immunity (Th2) for protection. It was believed that this suppression accounts for pregnant women's increased risk of malaria infection. However, it has been shown

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that despite this depression, the maternal immune system continues to respond to the parasite and that antibodies preventing *P. falciparum*'s attachment to the placenta can be produced and correlate with better outcomes for the fetus (2). Moreover, significant variations in risk and severity of infection between women in their first pregnancy (primigravides) and women having had multiple pregnancies (multigravides) have been reported, with risk and severity decreasing in proportion to the number of pregnancies (3,4). These observations are not explained by mothers' suppressed immune system, but suggest that immune build-up is achieved after several pregnancies and infections.

In placental malaria, it has been suggested that the parasite can temporarily evade the immune system by hiding within the vascular placenta found only in pregnant women (5). Indeed, while peripheral circulation can be free of parasites, high placental parasitation is sometimes observed in infected mothers (6). Although both *P. vivax* and *P. falciparum* can be found in the placenta, *P. falciparum* is sequestered there more frequently and at higher density (7). Red blood cells infected by *P. falciparum* are sequestered in the placenta by binding to membrane proteins expressed specifically on its endothelium (8,9). *P. falciparum* is known to express variant proteins on the surface of infected erythrocytes (IEs). These proteins can interact with various endothelial proteins, resulting in the adherence of IEs to endothelium and their sequestration in organs. Chondroitin sulphate A (CSA)(8) and hyaluronic acid (HA)(9) are proteins expressed by placental endothelium to which proteins expressed by IEs can bind. The sub-population of IEs capable of biding will be preferentially sequestered in the placenta and thereby temporarily evade an immune response. Because the sub-population of parasites causing IEs binding to CSA should not usually infect non-pregnant hosts (8), primigravides have never been immunologicaly

primed against this particular sub-population.

Eventually, the mother develops an effective humoral response to placental malaria by producing antibodies inhibiting IEs binding to placental proteins such as CSA (10). In a study recently conducted in western Kenya, both infected and non-infected women showed increased production of these antibodies, which was associated with increased birth weight and gestational age of newborns (11). Indeed, the study showed that secundigravides producing anti-adhesion antibodies delivered babies were on average, 398 g heavier and 2 weeks more mature than babies delivered to secundigravides without anti-adhesion activity.

Why the placenta offers a favorable milieu for immune evasion is still debated. Some contend the placenta is immunologically malaria-naïve (12) while others suggest that immunosuppressive factors synthesized locally - estrogens, for example - act with more vigor locally, thereby allowing the parasite to thrive (13). According to the former explanation, longer exposure periods are necessary for the maternal immune system to recognize placenta-sheltered parasites and respond appropriately. According to the latter, reduction of cortisol and estrogen levels with higher parity reduces vulnerability. This question is likely to remain unresolved until the exact mechanisms providing immune privilege to the fetus by its immediate environment are elucidated.

Unfortunately, placental malaria is alarmingly common in endemic regions of sub-Saharan Africa, as was shown by a study conducted in Tanzania showing evidence of malaria infection in 75.5% of placenta samples (5). In Kenya, active or past malaria was detected in 64% primigravides (14). Placental malaria prevalence can, however, vary greatly from region to region. A French team working in Madagascar found prevalence to vary from 2.1% in the eastern unstable-transmission region to 26.2% in the western part of the island (15). Nevertheless, infection, in any region, carries important risks.

PLACENTAL MALARIA AND POOR PREGNANCY OUTCOMES

Pregnancy malaria is a direct cause of numerous poor outcomes for both mother and fetus. Maternal effects include anemia, cerebral malaria, pulmonary edema and kidney failure (3,4,14). Poor outcomes for the fetus include abortion, stillbirth, premature delivery, low-birth weight (LBW), and intrauterine growth retardation (4,5,14,16,17).

The *Plasmodium* parasite's life cycle requires it to multiply within IEs, and ultimately cause them to burst. *P. falciparum* is known to be able to infect up to 5% of a host's red blood cells. The direct destruction of such an important number of IEs is an important cause of malarial anemia. However, it is not the only one. A recent study showed *P. falciparum* produced modifications in both IEs and uninfected erythrocyte (UEs) membranes (18). These changes, which mimic red blood cell's normal aging process, are attributed to oxidative-stressed induced by *P. falciparum* infection. UEs exposed to IEs become old prematurely and are cleared by the host's reticulo-endothelial system, thus contributing to malarial anemia. 75,000 to 200,000 infant deaths are estimated to be related to pregnancy malaria in Sub-Saharan Africa (19).

Anemia (hemoglobin [Hg] < 11g/dL) is associated with active pregnancy malaria. This association is similar in primigravides and multigravides (14). The adjusted odds ratio (OR) for severe anemia ([Hg] < 7g/dL) in gravidities 1 to 4 during active infection is 2.21 (CI: 1.36 - 3.61) (14). Similar results were found in a study in Gabon, where infection was associated with anemia in all gravidities with moderately ([Hg] < 7 - 9 g/dL) or severely anemic mothers having higher parasite densities than women with low anemia (20). Severe maternal anemia in turn has major and harmful effects on the fetus' development, and has been linked, independently from its etiology, to LBW, prolonged labor, increased induction rates and operative deliveries (21).

As stated earlier, during healthy pregnancies, Th1 immune actors are subdued, and Th2 actors more relied upon. Th1 cytokines are embryotoxic and in rodent models, they are known to induce spontaneous abortions or still-births (22). It has been shown that placental malaria leads to an increase of Th1 cytokines in the placenta (23,24,25). This cytokine-imbalance has been linked to intra-uterine growth retardation and premature birth (12). A study comparing placental cytokines from women living in nonmalarious and malaria-holoendemic regions found Th1 cytokines to be absent in the former group, and abundant in the latter (23). IFN-γ and IL-2 were only present in women exposed to malaria. These pro-inflammatory factors and other immune responses to malaria infection are thought to be associated with syncytiotrophoblast necrosis, irregular thickening and scarring of trophoblastic membrane, and breakdown of placental integrity observed in parasitized placentas(16,26). This in turn impairs maternal-fetal nutrient and metabolite exchanges, and impedes normal growth. Placental malaria also induces production of chemokines recruiting and activating monocytes(25). Monocyte infiltration and accumulation as macrophages in intervillous space is another risk factor for low birth weight. Indeed, although macrophages play an important role in controlling the parasitic infection, a number of inflammatory mediators they produce can also damage tissues.

Thus, while the safe haven afforded to the parasite by

the placenta probably increases the severity of the mother's disease, the Th1 immune response taking place in the placenta accounts for poor pregnancy outcomes. Newborns having active placental malaria were found to have a significantly lower weight than those having had past placental malaria or no infection (27). LBW has been repeatedly and consistently associated with placental malaria (4,5,14,17). In regions of stable-transmission malaria (high exposure, adult women more likely to have acquired immunity), primigravides were more likely to have LBW babies than multigravides (5,14,17). On the other hand, multigravides were not found to be protected in regions of unstable-transmission (low exposure adult women less likely to have acquired immunity), presumably because the level of exposure required for multigravides to gain immune competence is only reached in stable-transmission regions (17). Long-term effects of placental malaria have been reported: anemia and malaria infection are more common at 2 and 6 months of age respectively, if the child was born to a mother with placental malaria(28). Maternal infection within one week of delivery was linked to increased risk of infant death (OR: 4, CI: 1.2 - 13.7) (29).

P. falciparum, malariae and *ovale* parasites can be found in umbilical-cord blood of infected mothers, which could be transmitted directly to the fetus. Although there are conflicting results on the possibility of congenital malaria (30), there are cases (31,32) and a survey in sub-Saharan Africa (33) that report newborns being congenitally infected. Unfortunately, more research is needed in order to guide health policy and to develop treatments for congenital transmission.

WORKING AGAINST A VICIOUS CIRCLE

There seems to exist an alarming synergism between infectious diseases working against health-care workers' efforts to immunize vulnerable populations. Of the 5 million neonates estimated to die each year, 30-40% succumb to infectious diseases (34). Neonates are greatly dependant of maternal immunoglobulins transferred during gestation for protection against infectious agents. The mother passes to her child antibodies that her immune system produces in response to infection or supervised immunization (i.e.: vaccination). Immunization of pregnant women living in developing countries is thus crucial to diminish the number of neonates dying of infectious diseases.

It is now recognized that immunization programs in malaria-endemic regions will have to take into account the adverse effects of malaria infection. First, malaria impedes materno-fetal antibody transfer, thereby decreasing the effectiveness of the natural immunological development of the fetus. Placental

malaria infection was found to reduce materno-fetal antibody transfer for herpes simplex virus 1 by 69% (35). This reduction has been attributed to the premature birth caused by placental malaria, which is known to result in decreased materno-fetal antibody transfer (36), and also to the direct competitive-inhibition of immunoglobulin selective transport to fetus by elevation of malaria specific and non-specific immunoglobulins caused by infection (37). By the same token, placental malaria decreases materno-fetal transfer of antibodies developed by the mother following vaccine-immunization. This likely will affect the efficacy of immunization campaigns targeting neonates via pregnant women. It is also reasonable to expect that malarial infection inhibits immune response to vaccination directly in the mother. Indeed, studies have shown that adults and children on anti-malarial chemoprophylaxis developed enhanced antibody immunity compared to non-treated subjects, in response to tetanus toxoid and diphtheria, and tetanus toxoid and meningococcus vaccination, respectively (37). Finally, the newborn's immune system has been shown to be adversely affected by malaria infection during pregnancy (38). IFN-production by T-lymphocytes was decreased, possibly resulting in an impaired Th1 differentiation and weakened cell-mediated immune response to infection. This puts newborns, who are already vulnerable, at further risk of infection.

DISEASE-DISEASE INTERACTIONS: MALARIA AND HIV

Synergism between malaria and HIV infection is yet another dreaded possibility. HIV infects, disables and ultimately destroys CD4+ lymphocytes essential for the development of anti-malaria antibodies. It has thus been hypothesized HIV infection could increase the risk of concomitant malaria infection, parasitemia, morbidity and mortality.

Indeed, Steketee *et al.* report HIVSP multigravides had a significantly higher parasitemia prevalence than HIVSN multigravides (52.9% to 28.5% OR :1.85, CI : 1.46-2.35) and higher incidence of placental malaria in HIVSP multigravides than HIVSN multigravides (34.8% to 12.4% OR:1.85, CI : 1.46-2.35) (39). Recent studies corroborate this finding. Antibodies against variant surface antigens (VSA) on IEs (binding CSA) thought to protect against placental malaria were found to be lower in pregnant HIVSPs than in pregnant HIVSNs, and inversely proportional to viral load (40). Decreased materno-fetal transfer of antibodies to certain malaria antigens were observed in HIVSPs compared to HIVSNs (41).

The hypothesis that malaria infection in pregnancy can facilitate mother-to-child transmission (MTCT) of

HIV has also been explored, but remains controversial. A randomized control trial at Johns Hopkins University found the risk of MTCT associated with placental malaria was 2.89 (42) while the International Centre for Reproductive Health noted no correlation between placental malaria and *in utero* or peripartal transmission of HIV-1 (43).

The results presented above indicate HIV infection puts pregnant women at increased risk of developing malaria. HIV prevalence in pregnant women reaches as high as 25-45% in sub-Saharan Africa (39,41), a part of the continent comprising numerous high malaria endemic zones. On the other hand, malaria infection could increase HIV MTCT, further aggravating the AIDS epidemic. The measures to approach the complex interplay between the two diseases are not readily apparent. Total eradication of both is of course the ultimate goal. As such, any studied endeavor to reduce their transmission is desirable. However, the importance of the impact of reducing HIV prevalence in pregnant women on placental malaria remains unclear. Studies comparing malaria infection in HIVSP gravides on triple therapy and in HIVSP gravides not on therapy could yield crucial information and help direct future public health policy. Even if HIV significantly affected malaria prevalence, measures to reduce it should include vector-control and the development of a vaccine.

WHERE WE STAND: PREVENTION, VACCINES, POLITICAL ACTION

In the face of mounting evidence of the relative failure of traditional chloroquine malaria chemoprophylaxis in pregnant women (20, 42) and of logistics/financial reasons, the World Health Organization (WHO) has put forward new guidelines for combating and preventing malaria during pregnancy (45). These recommend that women living in high transmission areas in Africa receive intermittent preventive treatment (IPT) with an effective antimalarial agent such as sulfadoxine-pyrimethamine (SP) at scheduled antenatal visits. All pregnant women in targeted areas should undergo at least two sessions of IPT after first fetal movements. SP ITP is associated with a reduction in placental malaria in HIVSNs, but not in HIVSPs (46). SP should not be administered more than once a month, and not be given during the first trimester, since it is an anti-folate drug and so a potential risk for congenital defects. Preventive measures that can be used during the first trimester include chloroquine, quinine, quinide and insecticide-treated nets (46,48).

Unfortunately, implementation of the WHO guidelines is burdened by the notorious problems complicating health service delivery in the developing world: the logistical challenges of reaching remote regions, resource scarcity, lack of infrastructure, etc. However, the size of the population affected - more than 40% of all births worldwide occur in areas with endemic malaria (48)-malaria's well documented effects on both mother and fetus, and the apparent synergistic interplay between it and various infections make it critical to push for full implementation. ITP and some forms of chemoprophylaxis have been demonstrated to have a dramatic positive impact on the outcome of newborns, such as LBW (49).

Parallel efforts to control pregnancy malaria are focused on the development of effective vaccines. As was stated above, placental malaria arises when infected red blood cells segregate in the placenta by binding the CSA and HA receptors (8,9). Malaria resistance in multigravides has been linked to the presence of antibodies targeting binding-proteins found on the surface of IEs that permit placenta-segregation (10,11). These antibodies prevent adhesion and clustering of IEs in the placenta, protecting the mother and the child from severe morbidity associated with placental malaria. *P. falciparum* erythrocyte membrane protein 1 (PfEMP1), a subdomain of which binds CSA (50), is being investigated as a candidate for a placental malaria vaccine. Eliciting production of anti-adhesion antibodies by vaccination would provide immune-naïve women the protection resistant multigravides benefit from. A pregnancy malaria vaccine could save thousands of lives every year and boost the efficiency of immunization campaigns in malaria-endemic regions. Such a vaccine, however, would only be useful in preventing placental malaria. Although current research is focusing on PfEMP1, multiple parasite-encoded antigens known as variant surface antigens (VSA) are potential targets, as they cause IEs segregation in other organs. The isolation of a VSA expressed by most or all sub-population IEs and not by normal human cells would be the first step in the development of a truly "broad-spectrum" malaria vaccine.

The optimism of these scientific advances should not cloud the socio-economical importance to public health. Without resources, it is impossible for any government to provide its citizens with adequate care, especially when facing robust and vicious diseases like malaria and HIV. As was recognized by the World Trade Organization's (WTO) General Assembly in August 2003, the developed world's governments should allow and facilitate the transfer of some of these resources to needy nations at a minimal cost.

Canada just recently became the first country to implement the WTO's decision by passing Bill C-9 *An Act to amend the Patent Act and the Food and Drugs*

Act (which received Royal Assent on May 14th 2004). This bill allows Canadian pharmaceutical companies to seek compulsory licenses to produce patented medicines and export them to eligible countries. The bill includes a list of 56 covered medicines (Schedule 1) and gives the federal Cabinet the authority to add products to this list. Schedule 1 is based on the World Health Organisation's Model List of Essential Medicines. Although none of the products included on the list can be matched to antimalarials catalogued by Winstanley *et al*. in their review on the subject (51,52), some antibiotics that are included can be put to use in combination with antimalarials for better treatment (52). It is important to note that production of most antimalarials is today free of patent restrictions.

However, newly developed drugs-for example designed to fight placental malaria-will not automatically be available for compulsory licensing. Indeed, recommendations by the ministers of health and industry are initially required for the federal Cabinet to add a product to Schedule 1. Such an addition could face the opposition of interested pharmaceutical companies and ultimately be defeated. This was the fate of the motion introduced by the New Democratic Party to add to Schedule 1 medicines used to treat community-acquired pneumonia (53). Many share the fear that the pharmaceutical lobby will end up neutralizing the present form of Bill C-9. For this reason, NGOs and other civil society organizations are pressuring the government to abolish Schedule 1 and to modify a number of other controversial aspects of the bill.

CONCLUSION

Malaria infection during pregnancy has important adverse effects on both mother and fetus, and causes a great number of deaths around the world. Fortunately, many of these deaths could be avoided each year by prophylaxis programs and parallel preventive measures. Research and public health policy should be geared towards prevention of malaria infection during pregnancy.

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