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Placental malaria: A threat to obstetric outcomes

Felicia Molokoane[1], Louisa Seopela[1], Adekunle Emmanuel Sajo[2]
[1]Maternal and Fetal Unit, Department Obstetrics & Gynaecology, Kalafong Provincial Tertiary Hospital and University of Pretoria, Pretoria, South Africa
[2]Gynaecologic Oncology Unit, Department of Obstetrics and Gynaecology. University of Pretoria, Pretoria, South Africa

Introduction

Placental malaria occurs when there is sequestration of Plasmodium falciparum infected red blood cells in the placenta. This is the primary mechanism by which malaria in pregnancy perpetuates its adverse perinatal outcomes such as miscarriage, stillbirth, preterm birth, intra-uterine growth restriction (IUGR), low birth weight and poor cognitive functions.[1,2]

Malaria in pregnancy is of great global health concern. In 2019, 229 million malaria cases were reported globally, and 11.6 million pregnancies were exposed to malaria infection in the moderate to high transmission countries.[2] The Central and West African sub-region accounted for about 80%, while the East and Southern African sub-region accounted for about 20% of malaria in pregnancy.[2]

South Africa has a low transmission of malaria. However, malaria cases in pregnancy are often seen, especially among the foreign nationals from malaria endemic countries, and the residents of the provinces along the South African border areas such as Limpopo, Mpumalanga and KwaZulu-Natal, which are the three malaria is endemic provinces in South Africa.[3,4]

The prevalence of placental malaria is inconsistent in the literature, because of variables used in the diagnosis such as gravidity, gestational age and investigative modalities. Some literature reported the prevalence of placental malaria using different definitions such as peripheral blood parasitaemia, placental histology and categorisation in terms of the trimester at the time of diagnosis. However, a prevalence of between 9% and 63% have been reported in endemic regions.[1,2,5-7] The incidence of malaria in pregnancy or placental malaria is unknown in South Africa, though an incidence of 0.87 per 1000 population at risk has been reported for the general population.[3]

Pathogenesis

After the pre-erythrocytic liver stage, Plasmodium falciparum infects the red blood cells (RBCs). P falciparum expresses a ligand called P. falciparum erythrocyte membrane protein 1 (PfEMP1) on the infected RBC membranes. In non-pregnant individuals infected with P. falciparum, the PfEMP1 in the infected (non-placental) RBCs binds to CD36 present in many tissues such as the vascular endothelium, macrophages and dendritic cells. In pregnancy, a variant of PfEMP1 receptor, called VAR2CSA with an active Duffy binding-like γ domain is expressed. The gene for VAR2CSA is over expressed by P falciparum in the placenta, and these parasites isolated from the placenta do not bind CD36 as opposed to those parasites isolated from non-pregnant women.5 This allows the infected RBCs to be sequestered and bind to the syncytiotrophoblast in the intervillous spaces. In addition, the VAR2CSA binds to the chondroitin sulphate A (CSA) in the placental intervillous spaces. The CSA has been consistently found to be the predominant receptor in the placenta. This sequestration causes obstruction of microcirculation which causes impaired tissue perfusion leading to local hypoxia.[7,8]

Placental malaria can impair trophoblastic remodelling of the uterine spiral arteries due to the compromise of the placental circulation, especially during the 16-20 weeks' gestation.[8] The presence of P. falciparum infected RBCs in the intervillous spaces causes the infiltration of inflammatory cells such as monocytes, macrophages, granulocytes, cytotoxic T cells and B-cells and the subsequent release of pro-inflammatory mediators.[6] There is release of cytokines and chemokines such as IL-2, TNF-α, IFN-γ, and reactive oxygen radicals to destroy the intracellular parasites. This leads to vascular lining damage and inflammatory changes in the placenta, such as thickening of the placental basement membrane, peri-villous fibrinoid deposits and syncytial knotting with an eventual compromise of the feto-maternal exchange system and poor pregnancy outcomes.[5,9]

Risk factors

Malaria in pregnancy helps women develop PfEMP1-specific antibodies that protect in subsequent pregnancies by blocking the interaction of PfEMP1 and CSA.[5] Primigravidae have a three-fold risk of placental malaria due to the lack of antibodies against VAR2CSA, unlike multigravidas, who are relatively immune to placental malaria. However, in low transmission regions, nearly all pregnancies are at risk of placental malaria, because of low immunity amongst the population of that region.[1,5] Women living with HIV are also prone to severe malaria and placental malaria because of impairment of antibody production to VAR2CSA, dysregulation of cytokine production and impaired IFH-g response.

Obstetric outcomes and complications

There are several adverse outcomes associated with malaria that affect both the mother and the newborn. The infiltration of P falciparum infected RBCs in the intervillous spaces of the placenta is responsible for the complications.

Table 1: Effects of malaria in pregnancy

Maternal	Fetal
Anaemia	Stillbirth
Pulmonary oedema	Preterm birth
Hypoglycaemia	Low birth weight
Cerebral malaria	IUGR
Puerperal sepsis	Congenital malaria
Pre-eclampsia	
Death	

Diagnosis

Placental malaria is difficult to diagnose during pregnancy. Microscopy of peripheral blood films fails to identify a proportion of these infections because parasitized RBCs sequester in the placenta. In addition, rapid diagnostic tests (RDTs) used to diagnose non-

Correspondence
Felicia Molokoane
email: felicia.molokoane@up.ac.za

pregnant individuals are less efficient for diagnosing placental malaria. A newer version of RDT called a susceptible rapid diagnostic test (HS-RDT) has high sensitivity compared with light microscopy and conventional RDTs. PCR is another diagnostic modality, but it is time-consuming. Nonetheless, the gold standard for placental malaria diagnosis is via placental histology. The histopathologic changes in placental malaria include the presence of hemozoin pigment, peri-villous fibrin deposits and decrease in villous surface areas.[1]

A pathological classification categorizes placental malaria into three categories using the Rogerson criteria:

1. An active infection characterized by the presence of parasitized RBCs in the intervillous space, malaria pigment in RBCs and monocytes in the intervillous space but no pigment in the fibrin
2. Active-chronic infection typified by the accumulation of pigment in fibrin/fibrin-containing cells
3. Past-chronic infection is characterized by malaria pigment confined to fibrin or cells within the fibrin in the absence of parasites.[1,6,8]

Vaccines

The concept of natural production of antibody formation against VAR2CSA in women previously exposed to malaria in pregnancy has been used to produce vaccines against this glycoprotein to protect women, especially primigravidae in endemic regions as well as all women in low transmission malaria zones.

Currently, two vaccines namely PRIMVAC and PAMVAC have been developed, and two vaccine trials (ClinicalTrials.gov, NCT02647489 and NCT02658253) are in early-stage clinical trials.[1,10,11] It is, however, not clear how VAR2CSA-based vaccines would be adapted to counteract VAR2CSA sequence diversity and provide wide immunity against placental malaria.

Prevention

Malaria in pregnancy and, by extension, placental malaria, can be controlled using the WHO three prong strategies of vector control, use of chemoprophylaxis and early diagnosis and effective early treatment of malaria cases in pregnant women.[2,12]

The Anopheles mosquitoes that are vectors for P falciparum can be controlled by using indoor residual sprays (IRS) and consistent use of insecticide treated nets (ITNs). This strategy, including good environmental sanitation, will reduce mosquitoes and the subsequent transmission of parasites among humans. The second strategy is implementing the use of intermittent preventive treatment with Sulphadoxine-Pyrimethamine (IPTp-SP) in endemic regions, regardless of resistance to SP. IPTp-SP (1500mg/75mg) is recommended to be taken from the 13th week and not beyond the 36th week of gestation, and the doses are administered at least four weeks apart. The initial recommendation was three doses in pregnancy, but this caveat/clause had been removed from the recent recommendations.[2,12,13] In 2019, an estimated 426,000 low birthweights were averted by IPTp-SP in 33 moderate to high transmission countries in the WHO African region.[2] The third strategy is prompt treatment of malaria cases in pregnancy with effective Artemisinin-based combination therapy (ACT). There are no specific South African guidelines for the prevention of malaria in pregnancy, except for case management policy. However, there is a national guideline for the control of malaria in the general population residing in the malaria areas of South Africa, basically through vector control, use of insecticide treated nets and use of chemoprophylaxis.[4,14,15]

Despite these preventative strategies, the prevalence of placental malaria and low birth weight remain a considerable threat to pregnancies in malaria regions in South Africa.

Conclusion

Malaria in pregnancy is a significant public health problem in endemic countries and leads to poor birth outcomes. The diagnosis of placental malaria is challenging, as the peripheral microscopy may miss a significant proportion of infected women due to the sequestration of the parasite in the placenta. Therefore, malaria should be suspected in pregnant women with a history of recent travel to any of the malaria endemic areas or provinces during pregnancy.

South Africa should develop a national guideline for the prevention of malaria in pregnancy, especially for people living in malaria endemic provinces pending the elimination of malaria in the Republic of South Africa.

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