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Short Communication

Malaria An Enemy to Fear During Pregnancy

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Abstract

Susceptibility to malaria increases with pregnancy, and one hundred and twenty-five million pregnant women in the world are at risk of contracting the disease, which causes morbidity and mortality in them, fetuses and infants. The objective of this paper is to comment on the general and specific characteristics of the epidemiological and pathophysiological field that define infection and disease in the mother and child binomial based on the documentary review that is currently available on the subject, in this sense it is shown the parasitic agents involved, placental sequestration is described, symptoms and complications of the pregnant woman, consequences of congenital malaria infection in the fetus and infant, the epidemiological behavior of the pathology and the need for new and more in-depth investigations is highlighted, since There is much that is not known about it.

Keywords: malaria; pregnancy; pathophysiology; placenta; newborn

Introduction

We tell you that malaria is a severe public health problem for the population in general and for pregnant women in particular. In this sense, it is estimated that 125 million pregnant women live in regions with active transmission of this protozoan capable of causing adverse effects on the delivery, mainly *Plasmodium falciparum* and *Plasmodium vivax* (also related to G6PD deficiency, a crucial enzyme in red blood cell oxidation-reduction; in *P. vivax*, management is complicated because primaquine, the main drug against hepatic hypnozoites and responsible for relapses, is contraindicated by the risk of maternal and fetal hemolysis). Pregnant women with the highest risk of infection are located in sub-Saharan Africa, Southeast Asia, the Western Pacific and South America (3% of the total population of women are at risk of infection) where coinfection with both parasites is present. Early ages, malnutrition (L-arginine deficiency determines low birth weight of the child), being primigravidae/secundigravidae and immunosuppression (for example HIV) continue to be the main risk factors for infection in pregnant women [1-8]. In areas of low malaria transmission, all pregnant women are at risk of acquiring the infection (because they have little or no immunity with a two to three times greater risk of serious illness in relation to non-pregnant women), and in areas of high transmission they are primigravidae/secondagravidae are the most affected compared to multigravidae (with higher levels of adhesion-blocking antibodies and increased phagocytosis and with rapid elimination of placental parasites without progression to chronic placental malaria infection), however, not everything seems be bad for pregnant women, since they are capable of developing antibodies against the VAR2CSA protein of the parasite (in areas of high transmission), whose role in the pathophysiology we will discuss later, resulting in this way partially protected against infection in subsequent pregnancies [5, 9, 10]. The increased sensitivity to malaria during pregnancy was for decades attributed to immunological changes specific to pregnancy, without explaining the reduction in the infection rate and the load of placental parasites in successive pregnancies, hence an alternative molecular model emerges which explains the ability of the infected erythrocyte to adhere to the vascular endothelium and allow sequestration in deep vessels, mediated by binding to a receptor different from the CD36 of non-pregnant women [11]. The adverse effects that *P. falciparum* produces almost exclusively on pregnancy are attributed to placental sequestration due to preferential accumulation of parasites in the intervillous space, since there are no studies of *P. vivax* that clearly demonstrate this phenomenon, but in pregnant women with little acquired immunity is capable of causing damage (because the inflammatory immune infiltrate varies between women and is inversely related to acquired immunity). Placental sequestration begins with the export of the VAR2CSA protein by the parasite to the erythrocyte membrane to

facilitate adhesion to chondroitin sulfate A (CSA, a unique receptor that supports the adhesion of the parasitized erythrocyte to the placenta) in syndecan-1 anchored in the placental tissue [12], this event is associated with the recruitment and retention of monoclonal cells in the placenta, which we believe determines the adverse effect of malaria on the outcome of childbirth [5, 11, 13]. It is necessary to mention that there are several alterations that *P. falciparum* produces on the placenta, among them the following stand out: infiltration with mononuclear cells with higher levels of the cytokines TNF-a and IFN-g, and the chemokine CXCL9, which is regulated by IFN-g (generate deficiencies in the transplacental transport of glucose and amino acids and alteration of the growth hormone axis, although studies support, but do not prove, that inflammatory mediators contribute to the sequelae of placental malaria), deposits of malarial pigments, thickening of the basement membrane of the trophoblast, syncytial knots, complement deposition and alteration of placental angiogenesis (with impairment of nutrient transport). We believe that it is the set of all mechanisms, and not one in particular, that leads to changes in the architecture of the villi and in the nutrient exchange surface, as well as alteration of utero-placental blood flow (there is evidence of changes in umbilical artery blood flow during the first half of pregnancy) with severe impairment of fetal growth during pregnancy [5, 10, 11, 14-19]. Pregnant women after infection with malaria parasites may be asymptomatic, develop severe anemia, or die as a result of complications such as renal failure, pulmonary edema, and cerebral malaria, especially in those with a poor acquired immune response. The general maternal mortality rate due to malaria ranges between 0.5-23%, whether in areas of high or low transmission; however, the data are limited and inconsistent, therefore, more and in-depth research on the subject is required [5, 20, 21]. The anemia of pregnant women infected with *Plasmodium* spp, from mild to severe, is due to hemolysis, increased splenic clearance of erythrocytes and reduced production of these red cells due to the action of the parasite. In this sense, contributions from malaria have been reported to severe anemia of up to 26% and up to deaths per 100 000 live births due to malaria-induced anemia in endemic areas, however, other reports attribute little or no role to malaria as a factor involved in the development of anemia during pregnancy [5, 21-23]. In relation to the product of conception, malaria increases the risk of low birth weight (it doubles as a consequence of intrauterine growth retardation [70% of which in endemic areas is due to malaria due to deficiency in the supply of oxygen and nutrients to the fetus] and prematurity [36% in malaria-endemic areas due to the host's immune response against the parasite]), for example, in endemic areas 20% of newborns have low weight. Likewise, placental infection with malaria is associated with higher infant mortality rates (in some regions, increases of 3 to 20 times in the probability of infant mortality are reported) and the association between placental infection and parity establishes that primigravidae have two to seven times higher probability of low birth weight newborns relative to multigravidae [5, 24-26]. Regarding the time of infection and its role on the weight of the newborn, data from the first trimester are limited; from the second and third trimesters it is known that the probability of a low birth weight newborn is greater in the second [24-26]. Congenital malaria has a prevalence of up to 33% (marked by the presence of asexual *P. falciparum* parasites in peripheral blood or umbilical cord blood in newborns during the first 7 days of life), but without certainty that they cause clinical disease, When symptoms occur, they appear between 10-30 days of life, including fever, hepatosplenomegaly, hemolytic anemia, thrombocytopenia and feeding intolerance (they may occur later), which can progress rapidly and be fatal [5, 20, 27]. In childhood, placental malaria causes a series of adverse effects that need to be mentioned and investigated in greater depth, such as: increased risk of early malaria infection in children between 4 and 6 months of age (due to interference with the passage of maternal antibodies to the fetus and the development of Treg cells that induce immune tolerance of the fetus to malaria antigens), increased susceptibility to infections other than malaria (measles and tetanus), decreased size and weight in the first year of life, increased mortality of infants, and anemia [5, 28-31]. Furthermore, malaria generates between 12-20% of fetal deaths in low or intermediate endemic regions for this pathology (which can be considered a tolerant phenotype, the fetal mortality rate is lower in areas of high endemicity), prevalence that decreases if mother receives treatment and with the use of insecticide-treated nets, the probability of fetal death doubles with the detection of *P. falciparum* in peripheral blood or placenta samples. It is prudent to point out that most of the information on malaria comes from imported cases and descriptions of clinical cases, therefore, more research should be carried out in order to improve the pathophysiological and epidemiological understanding of congenital malaria [5, 32-33]. To close this document that aims to describe and comment on the general and specific aspects that define malaria in pregnancy, it can be stated that it continues to be an important public health problem; that the parasitic agents involved are *P. falciparum* and *P. vivax*, mainly the former; that the risk factors continue to be those indicated by the first investigations; that placental sequestration mediated by the VAR2CSA protein of the parasite is the main mechanism in the pathophysiological field; that changes in the architecture of the chorionic villi are a consequence of the sum of a series of events induced by the parasite and the host; and that the pregnant woman develops symptoms and complications that can end her life. In addition, the fetus may be affected with intrauterine growth retardation and prematurity in relation to the time of infection; that congenital malaria is common with symptoms that can lead to death in the infant; that the infant is more susceptible to early malaria infection and other infections as a consequence of blocking the passage of maternal antibodies to the fetus; that more studies on congenital malaria are required, since the information we have comes from imported cases and the description of clinical cases, as well as the relationship between placental malaria and cytosine profiles of the umbilical cord, and also on how malaria placenta can continue to influence the health of the newborn. Finally, it is recommended that pregnant women have special consideration during massive campaigns for malaria control because teratogenicity and embryotoxicity complicate the application of medications (primaquine is associated with greater hemolysis of erythrocytes in patients with G6PD deficiency), vaccines or measures against the transmitter; the routine examination and timely treatment of pregnant women in low-endemic areas in order to prevent the risk of serious illness and death; consider chemoprophylaxis (pyrimethamine/dapsone) for its demonstrated ability to generate low rates of parasitemia and higher hematocrit [reduces moderate and severe anemia by 40%] and its important role in reducing children with and with low birth weight the decrease in perinatal mortality.

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