Review Article
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Malaria and pregnancy: a Venezuelan approach. Review article

Abstract

Aim: to review and describe exhaustively the implications of malaria in pregnancy, including its maternal, fetal, and neonatal clinical manifestations and effects; immunopathology and pathophysiology; advancements in its diagnostics, histopathology, and treatment options; and epidemiology, particularly in Venezuela, a country where its data is almost non-existent.

Methods: the information used to write this manuscript was obtained during a three-month period, between June and September 2022, from specialized literature, written in English and Spanish, related to malaria associated with pregnancy, mainly published during the last five years, using journals found in the most relevant medical digital archives, including PubMed, SciELO, Elsevier, Google Scholar, Latindex, and Cochrane Plus. Among the keywords used for obtaining this updated information were malaria; malaria in pregnancy; gestational malaria; placental malaria; congenital malaria.

Results: all the clinical forms related to malaria in pregnancy, including gestational, placental, and congenital malaria, can cause maternal-fetal alterations, that, in case of progressing, could lead to the death of this binomial. Their pathophysiology and immunopathology can explain the gestational and fetal symptomatology, as well as their complications, depending on the parasite form that affected them. There are new updates regarding the diagnostics, prevention, and treatment of this medical entity.

Conclusion: it is imperative to exalt the relevance of studying this disease in pregnant patients, especially in the Venezuelan topography, a focus of infection with a plethora of cases of said entity, whose lack of updated epidemiological data, regarding its prevalence and incidence, is profoundly preoccupying. Pregnant patients are not only one of the most vulnerable risk groups of this parasitosis, but also have the capacity of duplicating the risk of infecting the fetus.

Keywords: malaria, malaria, falciparum, malaria, vivax; placenta, pregnancy

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Introduction

Venezuela: a tropical country affected by a plethora of systemic infections, and currently immersed in one of the worst health crises in its history, negatively impacting on its population. Its topography and territorial characteristics have been the catalyzers of the appearance of many tropical diseases that are, both, emerging de novo and re-emerging, increasing their morbidity and mortality rates, which can act as simulators and overcome other concomitant entities, creating the need to amalgamate medical doctors of different specialties to solve the patient's status. However, pregnancy, as a mother-fetus binomial, doubles the rate of infection, feedback and progress in its deliberate cycle. This can compartmentalize malaria as one of the most serious tropical diseases that exist around the globe, particularly in Venezuela.[1,2]

With a powerful prevalence in more than 91 countries, paludism or malaria is a tropical anthropozoonosis that constitutes a serious public health problem worldwide. Transmitted via the bite of female mosquitoes of the genera *Anopheles*, this tropical disease is caused in humans by six out of the 120 species of obligate intracellular protozoa of the genus *Plasmodium*, these being *Plasmodium falciparum (P. falciparum), vivax (P. vivax), malariae (P. malariae), knowlesi (P. knowlesi), ovale curtisi (P. ovale curtisi)* and *ovale wallikeri (P. ovale wallikeri)*, with the first two leading the prevalence and incidence data.[3–7] On the other hand, there are three clinical presentations that define malaria associated with pregnancy, these being gestational malaria, - malarial infection in the pregnant patient, with presence or absence of fever -; placental malaria, - histological, molecular and/or microscopic evidence of malarial infection in the placenta, occurring in 13-64% of pregnant women with this zoonosis -; and congenital malaria, - fetal-neonatal disease originated by transplacental transmission or intrapartum asexual forms of *Plasmodium*.[8–10]

In this sense, malarial infections, as the main cause of morbidity and mortality in many developing nations worldwide, drastically affect pregnant women, constituting one of the most vulnerable risk groups of this medical entity, increasing the risk of complications in the mother-fetus binomial, particularly in highly endemic geographical areas.[11] An annual estimate of 4.3 million Latin American women is at risk of suffering from malaria in pregnancy,[12] causing the potential death of 75,000-200,000 children. Maternal deaths from these infections range from 0.5% to 23% in hospital studies, and from 3% to 18% in community-based studies.[13]

The increasingly tangible gravity of this situation is unstoppable, especially in Venezuela, where the publication of official data vanished years ago, relying only in the autonomous and unofficial publication of studies and clinical cases. For this reason, considering that it is a growing entity and that pregnant women are one of the most vulnerable populations to suffer the effects and complications of this tropical disease, the authors of this review article feel the urgent need to fully and exhaustively describe, in the most updated way possible, the entire spectrum of malaria associated with pregnancy, trying to answer the following research question: "what should we know about malaria associated with pregnancy, within the framework of Obstetrics and Gynecology?". An incipient and extensive search was held, regarding its global and Venezuelan epidemiology, clinical

characteristics, pathophysiology and immunopathology, maternal-fetal effects, diagnostic methods, prevention, and treatment.

Methods

The information used to write this manuscript was obtained during a three-month period, between June and September 2022, from specialized literature, written in English and Spanish, related to malaria associated with pregnancy, mainly published during the last five years, using journals found in the most relevant medical digital archives, including PubMed, SciELO, Elsevier, Google Scholar, Latindex, and Cochrane Plus. Among the keywords used for obtaining this updated information were malaria; malaria in pregnancy; gestational malaria; placental malaria; congenital malaria.

The inclusion criteria were articles published between 2015-2022; articles malaria associated with pregnancy; specialized books in Obstetrics and Gynecology, and Infectiology; published studies regarding malaria associated with pregnancy in Venezuela; and published manuscripts regarding updates within malaria associated with pregnancy. Among the exclusion criteria were articles published more than 20 years ago; manuscripts that were not related to malaria associated with pregnancy; and articles published in non-reliable sources and with questionable outcomes.

Discussion

Epidemiology

According to World Malaria Report 2021, there were approximately 241 million malaria cases in the year 2020, in 85 endemic countries, experiencing a sublime increment of 12 million more cases than in 2019. Regarding mortality rate, there was also a sublime rise from its tolls in 2019, incrementing from 409 thousand to 627 thousand in 2020.[14] The African continent, particularly sub-Saharan Africa, accounted the highest prevalence of malaria in 2019 and 2020, with 94% of all global cases and deaths, followed by Southeast Asia, the Eastern Mediterranean and Western Pacific region, and the American continent.[14–17] Undoubtedly, there are groups at greater risk of acquiring this pathology than others, with special emphasis on neonates, infants under 5 years, pregnant women, and immunosuppressed patients.[16] The fight for its eradication remains a reality, visualized within the plan adopted by the National Assembly of the United Nations in 2015, titled "Global Technical Strategy for Malaria 2016-2030". Its primary objectives are to reduce its incidence and mortality rate by 90% by 2030, as well as to completely eradicate this disease from at least 35 countries by that year, and to prevent its resurgence from nations where it has already been eradicated.[18]

Annually, around 50 million pregnancies take place in malaria-endemic regions, and it is estimated that 10 thousand pregnant women and 20 thousand children perish as a result of their gestational-related infection.[19,20] In 2020, out of the of the 33.8 million pregnancies reported in 33 moderate and high transmission African nations, 34% (n=12 million) were exposed to malarial infection during these pregnancies, mainly in West Africa, with a 39.8% prevalence, followed by Central Africa (39.4%) and East and South Africa (22%). This high prevalence of gestational malaria resulted in 819 thousand newborns with low birthweight, a result of the low use of prenatal care services, with preventive antimalarial treatment during pregnancy. In fact, it is estimated that if more than 74% of these pregnant women had carried out these prophylactic measures in the aforementioned 33 African countries, at least 45 thousand newborns with low birthweight would have been prevented.[14]

In Venezuela, malaria transmission is geographically and topographically located in three endemic foci, these being the eastern, - formed by the states of Sucre, Anzoátegui, Monagas and western Delta Amacuro -; the western, - formed by the state of Portuguesa, Mérida, Barinas, western Apure, Táchira, Trujillo and Zulia -; and, finally, the southern, - which includes the states of Amazonas, Bolivar, Apure and eastern Delta Amacuro. Out of these foci, the most affected states are Bolivar, Amazonas and Sucre, and the most predominant species is *P. vivax* (70%), followed by *P. falciparum* (25-30%).[11,21] It should be noted that, in Venezuela, there is a shortage of published epidemiological studies on the prevalence of malaria associated with pregnancy, including in Bolívar and Amazonas; however, it has been possible to determine that most of this casuistry has been the result of *P. vivax* infections, unlike the rest of the world, where *P. falciparum* has had predominance over the rest of the *Plasmodium* species.[20] By the end of 2016, 3,000 cases of malaria were registered in Venezuela, with an increase of 76.4% over 2015.[22] By 2017, these rates had increased by 76%, reaching 316,40 cases,[1] without having an accurate estimate of how many of these corresponded to pregnant women, but, at least, 2000.[23] In 2018, there was a 55% increase in the incidence of cases of gestational malaria in Bolívar, Amazonas and Sucre.[11]

The publication of studies and cases of malaria associated with pregnancy in Venezuela dates from 1895, when Razetti and Rísquez reported, in the Society of Doctors and Surgeons (*Sociedad de Médicos y Cirujanos*), one of six cases of malaria in pregnancy.[24,25] Between 1943 and 1945, there were only nine reported cases of congenital malaria out of more than 22 thousand pregnant women admitted to the "Concepción Palacios" Maternity Hospital (*Maternidad "Concepción Palacios"*) in Caracas, Venezuela, which ultimately resulted in a miscarriage, five preterm births, two cases with severe anemia, and absolutely all of these patients presented febrile episodes during the puerperium.[2,26] By 1949, eleven cases of congenital malaria had been reported as an intrinsic complication of malaria in pregnant women.[21,27,28] Between 1953 and 1955, there was only one reported case of gestational malaria at the "Concepción Palacios" Maternity Hospital.[2,26] Almost forty years later, following this line of research, Dr. Carlos Carvajal presented his thesis at the University Hospital of Los Andes (*Hospital Universitario de Los Andes*), reporting seven cases of congenital malaria. In 2000, he, along with Guerrero *et al*., reported thirteen cases of congenital malaria in a retrospective study carried out between 1992 and 1999, in the state of Bolívar, and eight more cases, between 2000 and 2011, highlighting that most of these infections were caused by gestational malaria acquired during the third trimester of pregnancy.[27,28]

Between January 2000 and December 2002, Rodríguez-Morales *et al*. reported three cases of multiparous pregnant women, with an average age of 29 years, and an average gestational age of 21 weeks, with no obstetric history of miscarriages nor preterm births, who were admitted to the Santos Anibal Dominicci Hospital (*Hospital Santos Anibal Dominicci*), in the state of Sucre, due to infections by *P. falciparum*. All this small sample presented anemia, severe in one of them; two pregnant women also developed thrombocytopenia, severe in one of the cases, with normal renal function, and abundant endometrial bleeding; the third patient had no fetal nor neonatal complications.[29]

Between 2005 and 2006, Gómez et al.[30] conducted a descriptive and cross-sectional study, with a sample of 449 pregnant women in the San Isidro Parish of Sifontes Municipality, in the state of Bolívar, resulting in an incidence of 27.4% of gestational malaria, out of which, 87% were due to *P. vivax* infection, mainly during the second trimester (41.5%); 0.8% of cases were due to placental

malaria. Out of the total sample, 71.5% (n=321) was symptomatic, and 26.2% (n=118) presented anemia. Concerning newborns, 3.3% had low birthweight and five pregnant women suffered miscarriages.[30] In 2016, Morao et al.[20] published a case of a malarial infection in pregnancy by *P. falciparum*, and two mixed cases originated by *P. vivax* and *P. falciparum* infections, respectively, who attended the "Concepción Palacios" Maternity Hospital. It is understood that the prevalence was small because this hospital center was, and still is, far from the endemic centers, but it was equally valid as to their study terms. Finally, between February and October 2019, Romero et al.[11] conducted a retrospective study with 52 pregnant women, aged 15 to 39, at the Hospital University Complex "Ruiz y Páez" (*Complejo Universitario Hospital "Ruiz y Páez"*), in the state of Bolivar, out of which, 71% (n=37) was infected with *P. vivax*, diagnosed during the third trimester of pregnancy. Although it is true that the majority of this sample did not present a serious symptomatology, 30% (n=13) suffered from severe anemia, and 44% (n=23) presented at least one maternal-fetal complication. On the other hand, 8% (n=4) suffered a miscarriage, and three intrauterine fetal demises took place in said sample; 12% (n=6), despite having suffered from preterm birth, did not suffer from any other complication. Also, a large percentage of this sample was adolescent, which is no coincidence, considering that Venezuela occupied the first position of Latin American fertility rate in this age gap, by 2018, with 85 births per 1,000 youngsters between 15 and 19 years of age. The symptomatology of these patients did not differ from literature reports, being severe headaches, febrile syndrome, and severe anemia, the most predominant. The most recurrent maternal-fetal complications were preterm birth, miscarriage, intrauterine fetal demise, intrauterine growth restriction, and oligohydramnios.[11]

Pathophysiology and immunopathology

The pathophysiology of malaria in pregnancy has not been fully understood to date. However, it is known that the immunological changes suffered during pregnancy predispose the patient to suffer from infectious diseases with greater severity. And this susceptibility tends to exacerbate exponentially facing infections by *P. falciparum*, increasing its severity, particularly in primigravida, tripling this risk above non-pregnant patients, and persisting during the immediate puerperium.[10] It is important to emphasize that the vascular development of the placenta influences the maternal-fetal gestational evolution and is carried out by three clearly demarcated processes. The first one is vasculogenesis, which, as its name suggests, consists of the neoformation of blood vessels from precursor cells, a process that takes place up to the gestational age of six weeks. Subsequently, ramifying angiogenesis occurs, where new vessels are also generated from those preexisting up to 25 weeks of gestation. Finally, nonbranching angiogenesis is carried out, where placental terminal villi are generated, and, thus, the diffusion of oxygen and nutrients takes place.[31] These processes depend on a bidirectional balance between pro and anti-angiogenic factors, regulated mainly by vascular endothelial growth factor (VEGF), angiopoyetin 1 and 2, placental growth factor (PIGF) and soluble fms-like tyrosine kinase 1 (sFlt-1).[32] The establishment of the placental vascular bed is completed around the twelfth gestational week, which means that by the first trimester of pregnancy, the pregnant woman may become infected with *P. falciparum*.[31]

The infectious mechanisms of the parasite, as well as the adverse effects and maternal-fetal complications associated with the infection, are mediated by a variant of the erythrocyte membrane protein family 1 (PfEMP1), called VAR2CSA, - an antigen with a molecular weight of 350 kDa, expressed on the surface of infected erythrocytes -, which binds to its membrane receptor, i.e., chondroitin sulfate A, - a syndecane 1 (CD138)-bound glycosaminoglycan in the syncytotrophoblasts of the intervillious spaces of placental tissue. VAR2CSA has multiple regions of Duffy Binding-like (DBL) domains and interdomain-like domains, out of which, DBL 2, 3, 5 and 6 are those that bind to chondroitin sulfate A. This binding induces migration from the peripheral circulation of parasitized erythrocytes into the host tissue, a process called erythrocyte sequestration,[9,10,33–42] and the release of bioactive molecules by the parasite, including glycosylphosphatidylinositol, stimulates maternal mononuclear cells.[43] All this occurs in three clearly demarcated phases: the active-acute phase, being the one where there is a minimal presence of placental parasites in fibrin pigment deposits; in the active-chronic phase, the presence of such parasites increases; and in the last phase, where pigments do not present parasites.[9]

Although it is true that so far it has not been possible to fully conclude what is the pathophysiological mechanism of *P. vivax* in malarial infections in pregnancy, it is believed that both parasitic forms share the same cytoadhering mechanisms, but the latter has less interaction force within the intervillous space and with the placental blood vessels, which could explain it, even though the erythrocytes infected by *P. vivax* are in said space, There is usually no evidence of an increase in the number of inflammatory intervillous cells, except hemozoin as a breakdown product in macrophages.[35] However, what is known is that both produce deregulation of the previously mentioned pro and anti-angiogenic factors and trigger inflammatory reactions and responses that alter the normal vascularization of the placenta and consequently the uteroplacental blood flow and the transport of oxygen and transplacental nutrients, by decreasing their diffusion surface, causing intrauterine restriction growth, preterm birth, low birthweight and intrauterine fetal demise.[9,10,31,32,35] There is also an increase in blood flow resistance in the placental arteries. Also, infection that occurs in the early stages of pregnancy, during the first trimester, causes intrauterine restriction growth in the late stages, producing a decrease in the weight of the placenta and, therefore, of its vascular development, in any of the three processes of vasculogenesis, ramifying or nonbranching angiogenesis, causing inhibition in uterine trophoblastic migration, decrease in the volume of blood transported throughout intervillous spaces, which is clinically manifested in the second and third trimester of gestation. Nonetheless, if infection occurs in the late stages of pregnancy, placental vascularization tends to be increased by compensatory processes that tend to protect the mother and the fetus from reduced oxygen and nutrient transport, although this could trigger the generation of an enlarged placenta.[31,34,42]

In addition, malarial infection in pregnancy directly affects the biogenesis pathway of L-arginine and nitric oxide, which could also explain what has been described so far. L-arginine is the immediate precursor of nitric oxide synthase in the genesis of nitric oxide, whose bioavailability levels are necessary to regulate the previously mentioned pro-angiogenic factors that allow adequate placental vascularization, by trophoblastic expression of VEGF and PIGF, and, in that way, decreasing anti-angiogenic factors. Once this takes place, nitric oxide acts as a vasodilator and modifies maternal-fetal hemodynamics to allow optimal fetal growth. When there are deficiencies of L-arginine and nitric oxide, - as evidenced in malaria-induced hemolysis, with its respective release of free cellular hemoglobin -, a disruption of placental angiogenesis and vascular remodeling occurs, increasing the placental vascular resistance, vasoconstriction, microvascular dysfunction, placental insufficiency, preeclampsia, fetal growth restriction and preterm birth.[32]

Also, in these infections there is a greater stimulation of maternal immunity by activation of antigenic pattern recognition receptors (PRRs), including Toll-like receptors (TLRs), induced by the parasite's pathogen-associated molecular patterns (PAMP), thus triggering an inflammatory response,[32] characterized by a powerful cascade of proinflammatory cytokines that interfere with uteroplacental hemodynamics and causing inflammation of the intervillous space.[35,44] It is essential to take into account that the immune responses generated by *Plasmodium spp*. depend on the antigenic variability of the parasitic strain; its genotype and phenotype; the type of antigen recognized by the receptors of antigen-presenting cells; and the type of receptor that recognizes that antigen, such as the Toll, Garbage, Fcγ or complement types.[45]

During a normal pregnancy, tumor growth factor (TGF)-β, interleukin (IL)-1 and IL-6 activate Th17 cells, leading to the production of IL-17 as a potent inflammatory inducer, a process indispensable for implantation. Then, there is a shift towards Th2 type responses, with the subsequent release of IL-4, IL-9 and IL-10, a process controlled by regulatory T lymphocytes, allowing the growth of deciduous and trophoblastic cells in the placenta. In contrast, in malarial infections associated with pregnancy, the immune responses of antigen-presenting cells are altered and, at the same time, an increase in regulatory cells is promoted, which generates an immunological imbalance that results in immunodeficiencies of T helper lymphocytes. In placentas infected by *Plasmodium spp*., an overactivation of proinflammatory cytokines occurs, including tumor necrosis factor (TNF), IL-1β, IL-6, IL-8 and IL-12, increasing the expression of histocompatibility complex type II (MHC-II). TNF-α and IL-6 stimulate lymphocyte production of Th2 cytokines, including IL-10. IL-6 also induces the production of IL-17 by Th17 lymphocytes, whose inflammatory responses can cause a deleterious gestational state. IL-12 stimulates the production of interferon (IFN)-γ, which increases the risk of uterine contractions, produces increased levels of nitric oxide and free radicals, and also activates NK lymphocytes, known as pro-abortion cells. TNF-α stimulates erythrocyte cytoadhesion and, in conjunction with prostaglandins, may induce preterm labor. Both inflammatory infiltration and macrophage accumulation in the placenta reduce the maternal-fetal intervillous compartment, inducing low birthweight. IL-10 is considered a cytokine that protects the immunopathological processes of malarial infection, as it is an anti-inflammatory molecule that inhibits the production of TNF-α, IL-1 and IL-6. Therefore, low concentrations of IL-10, associated with high concentrations of IL-17, are associated with low fetal weight. It has also been shown that low levels of IL-5 are associated with an increased risk of preterm births and small babies for gestational age.[43,45,46] This cytokine storm causes disorders in the transport of amino acids and glucose, as well as in the expression and distribution of the molecules transporting nutrients and growth hormones.[34, 42]

Malarial infection in pregnancy also activates the complement system, at a systemic level and in the mother-fetus interface, with excessive increase of C1q, C3d, C4, C9, C3aR and C5aR, inducing a proinflammatory state in said interface by synergistic induction of the inflammatory cascade associated with the complement. This also results in deregulation of pro-angiogenic factors, including VEGF, sFlT-1 and angiopoyetins 1 and 2, as well as impairment in fetal neurodevelopment, preventing optimization of the fetus' intrinsic neuronal complex. Likewise, nitric oxide depletion, pro-inflammatory cascade and oxidative stress increase the extracellular levels of hemoglobin and heme group, generating the production and release of free radicals, activation of the complement system, proinflammatory and procoagulant effects, platelet and leukocyte adhesion, cell death and endothelial dysfunction, microvascular damage, - especially at the placental level -multiorgan dysfunction, particularly renal injury, and severe disease.[32,47] In that sense, this triggers a a reversible acute placental insufficiency, characterized by chorionic villus degeneration, fibrin deposition and malaria pigment, inflammation of the placental basement membrane and macrophage accumulation in the intervillous spaces.[35]

Pregnant women develop anti-VAR2CSA antibodies after a single exposure to placental parasites, so studies targeting antibodies directed at nonpolymorphic immunogenic epitopes could provide information about the pregnant woman's exposure history. Seropositivity for VAR2CSA, with its respective IgG cascade, is an indication of infection acquired during the gestational period.[33] Primigravida of high transmission areas are more likely to suffer from infection, but they develop a higher specific immunity that gives them greater protection in their subsequent pregnancies, unlike those that live in areas with less transmission, since they do not have such immunogenic protection, so if they acquire the disease, the clinical presentation will tend to be more severe. Multiparous living in low-transmission areas do not have the anti-VAR2CSA antibodies that result from previous infections during pregnancy.[10]

Clinical manifestations and maternal-fetal complications

Clinically, malaria in pregnancy can be severe or not severe, depending on maternal immunity and the endemicity of the geographical area that the pregnant women inhabit.[9,10] The incubation period may vary from seven days to months after the mosquito bite, depending on immunity and the use of prophylactic drugs, but usually tends to range from 7 to 30 days.[10] The initial symptomatology is usually nonspecific, - highlighting fever, chills, headache, malaise and generalized weakness, nausea, vomiting, diarrhea, and abdominal pain -and patients can also be asymptomatic. In contrast, severe presentation in pregnant women, as defined by the World Health Organization (WHO), is characterized by one or more of these criteria: neurological deterioration, severe normocytic anemia, acute renal failure, respiratory distress syndrome, hypotension, hypoglycemia, disseminated intravascular coagulation, acidosis, jaundice, spontaneous bleeding, hemoglobinuria, acute pulmonary edema, recurrent generalized seizures, cerebral malaria, and parasitemia greater than 5%. Pregnant women, having a state of immunosuppression, are more likely to suffer from parasitic sequestration by the placenta, which increases the risk of severe malaria and, therefore, increases the risk of suffering from maternal-fetal complications. In fact, pregnant women with this infection and some comorbidity, particularly HIV infection, have a higher risk of developing severe malaria with more maternal-fetal complications than HIV-negative patients.[9,10]

P. falciparum causes the adverse effects of pregnancy for both the mother and the fetus and, less often, *P. vivax*. *P. knowlesi* infection is rare during pregnancy, and may be associated with preterm labor, low birthweight, and maternal anemia. Very little is known about the effects of *P. ovale* and *P. malariae* on pregnant women. *P. vivax* infection can not only trigger multiple malaria episodes by reinfection or relapse, but is also more prevalent in Latin American countries, where acquired immunity dependent on pregnancy is not fully known and is inconsistently reported.[8,47–49] The prevalence of malaria increases in the first two trimesters of pregnancy and the risk may not immediately return to its pre-conceptional levels post-labor.[34] At this point, low density parasitemia is a common consequence, particularly from acquired pre-conceptional infections. However, these infections

tend to multiply and become high-density parasitemias, especially in primigravida, following the formation of the VAR2CSA-condoritin sulfate A complex in syncytotrophoblasts.[33]

In areas with high transmission, the prevalence is higher in young pregnant women, in primigravida or in two-times multiparous patients, and in women with comorbidities, particularly HIV.[34] In regions with lower endemicity and more instability in the transmission of the disease, pregnant women tend to be more symptomatic and present more maternal-fetal complications, including severe maternal anemia, liver dysfunction, preterm deliveries, low birthweight fetuses and congenital malaria,[11] and this risk increases significantly when traveling to an area with even greater endemicity and transmissibility.[29] As a matter of fact, in a sample of 542 pregnant women with imported *P. falciparum* infection, reported by Käser et al.,[50] between 1991 and 2014, 9% (n=46) suffered from severe malaria, suffering from complications such as cerebral malaria, severe anemia, acute lung edema, disseminated intravascular coagulation, postpartum hemorrhage, hypotension, and acute respiratory distress syndrome.[50,51] However, pregnancy has the potential to exacerbate the infectious course of malaria, exponentially increasing its lethality; in fact, childbirth can exacerbate its chronic infection, compromising the cardiovascular system during puerperium.[2,14,52]

In general terms, malarial infections produce 3 to 15% of anemia cases, which results from the depletion of parasitic erythrocytes with the release of merozoites, immunological destruction of parasitized erythrocytes, loss of red blood cell deformability, and/or bone marrow dysfunction that generates an ineffective erythropoiesis process. 25% of these constitute cases of severe anemia in pregnant women living in endemic regions, product of placental erythrocyte sequestration, hemolysis, ineffective erythropoiesis, inhibition of reticulocyte release, premature destruction of erythrocytes during their maturation phase in bone marrow, and/or hypersplenism.[2,14,35,52–56] Severe anemia is defined as hemoglobin values of less than 7 g/dl and this can cause a high maternal and fetal morbidity and mortality, and complications, such as low birthweight fetuses, preterm birth, and death from postpartum hemorrhage. In P. vivax infection, maternal anemia tends to be milder.[9,11]

While it is true that gestational malaria can affect the transplacental transfer of antibodies to the fetus, - decreasing its immune responses to various pathogens, and increasing the risk of congenital malaria, malaria and anemia in the child, febrile diseases, and infantile systolic hypertension,[34,57–61] placental malaria truly constitutes the main route by which this infection associated with pregnancy can cause perinatal adverse effects, regardless of whether the mother is symptomatic or not, doubling the risk of intrauterine fetal demise.[9,56,62] Regarding congenital malaria, there are factors that can relatively protect the fetus from acquiring this pathology, including previously acquired maternal immunity, fetal hemoglobin ratio and *P. vivax* infection.[63]

In this sense, fetal complications include miscarriage, fetus with low birthweight (less than 2500grams) resulting from intrauterine growth restriction, and preterm delivery (less than 37 weeks gestation).[10,64–69] Peripheral maternal parasitemia is also associated with adverse effects on infants, including anemia, neonatal and infant mortality, and congenital malaria. Symptoms of the latter tend to appear after 10 to 30 days post-labor and include fever, hepatosplenomegaly, hemolytic anemia, thrombocytopenia, and food intolerance.[10] In fact, an estimated 100,000 children die each year from malarial infections as a result of preterm births, low birthweight and neonatal anemia.[64] *P. vivax* infections during the first trimester tend to be associated with low birthweight and height, as well as decreased fetal head circumference development. Low birthweight increases neonatal morbidity and mortality, inhibits its proper growth, and may trigger, in the future, delayed psychomotor development in the newborn, being a risk factor in the increase in perinatal, neonatal, and infant mortality[2,14,52] and can cause chronic diseases in adulthood.[47]

On the other hand, studies have shown that the risk of developing placental malaria is increased in pregnant women with greater parasitic load and clinical episodes of malaria, meaning two or more episodes of symptomatic infection or more than 50% of positive samples for loop-mediated isothermal amplification, a DNA amplification technique, increasing the incidence of preterm birth, decreased fetal growth rate and small neonates for gestational age, the latter being defined as neonatal weight which is ten percentiles below what they should be for their gestational age, doubling the risk of developing malarial infection.[9,62,64,70] This was evidenced in the study carried out by Tran et al.[64] in 228 pregnant women, where primigravida had a higher incidence of placental malaria.

Two of the most recurrent maternal-fetal complications are miscarriage or intrauterine fetal demise during the first trimester, especially in primigravida, and preterm delivery.[2,14,52] There is a quantitative relationship between *P. falciparum* infection, to a greater extent, and *P. vivax*, with increased risk of intrauterine fetal demise. In fact, about 20% of all these deaths in sub-Saharan Africa are attributed to malaria in pregnancy due to *P. falciparum*, particularly in areas of low to intermediate endemicity. Moore et al.,[71] in their systematic review and meta-analysis, determined that these probabilities significantly increase in *P. falciparum* infections detected in placental and peripheral blood samples during childbirth, and tend to decrease, but not disappear, even after a properly well treated infection during pregnancy, which does not occur with *P. vivax* infection.[71] On the other hand, the mechanism by which malarial infection induces preterm birth is not yet known for certain, but is thought to be the result of placental insufficiency occurring in placental malaria, which also induces intrauterine growth restriction and causes a decrease in the fetus/placental weight ratio.[72] Kapisi et al.,[73] and Lufele et al.[74] showed a greater relationship between preterm births in pregnant women and placental malaria, particularly in those candidates for early induction of labor. Studies have shown that infection by *P. falciparum* generates a lower placental volume, unlike *P. vivax*, where there is no alteration in placental volume. Placental inflammation, caused by the latter, causes thickening of said tissue, which could explain the appearance of other complications throughout pregnancy, including vaginal bleeding, uterine contractions, loss of amniotic fluid, Intrauterine fetal demise, and miscarriage. Such thickening could arise from a compensatory mechanism generated by maternal anemia, although this requires more comprehensive studies.[35]

Doppler velocimetry studies carried out in endemic malaria regions have demonstrated changes in maternal-fetal blood flow during pregnancy, leading to intrauterine growth restriction and fetuses with low birthweight, especially in *P. falciparum* infections. However, when infection occurs early, the most appropriate marker for estimating such restriction is fetal head circumference. In addition, these studies have shown a greater transient hemodynamic distress in the placental circulation, with an increase in its resistance, due to the degradation of vascular beds caused by chorionic villus degeneration, leading to further branching and capillarization as an adaptive process.[35]

Another frequent complication from *P. vivax* infection is the loss of fetal well-being, manifested as fetal tachycardia, as a result of a cardiac output and blood pressure increase, including an augment

in the redistribution of the cardiac output to other target organs. Fetuses also tend to have decreased biparietal diameter and head circumference.[35] Dombrowski et al.[47] established the relationship between *P. falciparum* infection and the increased incidence of decreased neonatal head circumference and microcephaly (P<0.05). This may be due to the inflammatory cascade that occurs during this infectious process, generating histopathological alterations associated with imbalance in the production of pro and anti-angiogenic factors at the placental level. This ischemic and hypoxic state, in addition to the oxidative stress processes, alters the transport of nutrients and gas exchange within the fetus, resulting in said cranial malformations.[47]

Most of malarial infections associated with pregnancy in endemic nations are submicroscopic,[45,75,76] resulting in higher rates of maternal anemia. In contrast, submicroscopic *P. vivax* infections do not tend to lead to severe maternal-fetal complications. Mixed submicroscopic infections increase the risk of preterm birth.[77] According to Kalinjuma *et al*., malnutrition lowers the risk of submicroscopic placental malaria, weakening the host's humoral immunity; the opposite occurs with obesity. The first could be explained because pregnant women with macronutrient deficiency tend to lack essential micronutrients, mainly iron, which in turn decreases the risk of developing malarial infection during pregnancy, exacerbating the anemic symptomatology. Anemia and the lack of use of antipaludic prophylaxis are also risk factors for malaria in pregnancy in endemic areas.[13]

Diagnosis

The most classic and widely used method for diagnosing paludic infections is microscopy,[78] especially for *P. falciparum*, since the low parasitemia that accompanies *P. vivax* infections makes its diagnosis more difficult. Once the peripheral blood sample is taken, usually from the softest part of the fingers, it is stained with Giemsa stain, and examined under immersion oil, evidencing the presence of parasitized erythrocytes. Most of the equipment can detect 20parasites/µl, although, depending on technological advances, there are some that can detect between 100 and 500parasites/µl, exponentially increasing their costs.[79] In pregnant women, it is recommended to perform three thick drops, at least one during each fever peak. Newborns of women with malarial infection should also have a thick drop performed on them at the time of delivery, taking two samples: one from the maternal surface of the placenta and another from the umbilical cord. From that moment, newborns should have a weekly thick drop performed on them during a 28-days-period.[20] It should be noted that there is a 5 to 50% parasitic detection in these samples of pregnant women, since it has lower sensitivity than other diagnostic methods; in addition, placental erythrocyte sequestration usually produces negative results. However, thick drops of blood from placental intervillous spaces have greater diagnostic sensitivity.[79]

Of course, thick drop is not the only existing diagnostic option. It is imperative to mention rapid diagnostic tests, whose use has been growing exponentially and globally, since 1990,[80] mainly for symptomatic cases accompanied by high parasitemia,[78] greater than 200parasites/µl.[34] Most of these immunochromatographic tests, which are nonquantitative, are nitrocellulose strips containing anti - histidine-rich protein 2 (HRP-2), lactate dehydrogenase (pLDH) and aldolase,[79–81] which are specific or non-specific antigens for *P. falciparum*. Once the antigen-antibody immunocomplex is produced, it is captured in a stationary phase that produces a visible and colored line, indicating that malarial infection exists there. The former allows the diagnosis of malaria associated with pregnancy, especially when the parasites are found in placental tissue, with a sensitivity of 50-90% and a specificity of 76-99%;[79,82] however, once the infection is treated, HRP-2 levels tend to decrease, so it is not recommended to use this test at that time, to avoid false positives, unlike pLDH tests, which can be used after treatment. In fact, the latter have shown greater specificity for *P. vivax*.[79] Rapid diagnostic tests have been very useful as screening in prenatal consultations; but, at the time of delivery, they may not detect placental malaria that could be diagnosed histopathologically.[34] Its usefulness in asymptomatic pregnant women is practically null, so other diagnostic tests should be used in these specific cases.[83]

On the other hand, the histological biopsy study of the maternal surface of placental tissue[79] has high sensitivity to detect an active or past paludic infection,[79,84,85] allowing them to be classified as acute, if parasites do not cause any change, or chronic, if there are immune cells and malarial pigment.[79] Past infections tend to have accumulation of hemozoin in fibrin deposits; while, in the active ones, there is evidence of inflammation of intervillous spaces, due to the presence of leukocyte infiltrates.[78,86] In chronic infections, fibrinoid necrosis, thickening of the placental basement membrane, syncytial nodes, and mononuclear infiltrates in the intervillous spaces are usually evidenced, which is considered a poor clinical prognosis for the pregnant woman.[79] But, when the histological study of the placenta cannot be carried out, it is recommended to perform the diagnostic method of polymerase chain reaction (PCR), which, in addition to being highly sensitive, it is quantitative and allows detecting low density parasitemia. However, among its limitations it can be mentioned that its realization takes a lot of time, as well as highly specialized laboratories.[34,78,79]

There are other highly potential methods for diagnosing malaria in pregnancy, such as flow cytometry, mass spectrometry, and loop-mediated isothermal amplification. However, it is imperative to combine all the aforementioned methods with the use of ultrasound in each of the prenatal consultations to monitor fetal growth and determine its possible risks, especially in primigravida and asymptomatic pregnant patients or with low parasitic loads, particularly at weeks 8-14 and 18-24. In this way, pregnant women with high risks of maternal-fetal complications, including preterm birth, intrauterine growth restriction, preeclampsia and/or HELLP syndrome, can be categorized, regarding the severeness of their respective case.[79]

Prevention and treatment

Considering that the mother-fetus binomial has a high susceptibility to complications of malarial infection, pregnant women must be treated as early as possible.[20] However, the most appropriate preventive measures must also be taken, including the use of pyrethrin-impregnated mosquito nets and appropriate repellents authorized for their use in pregnant women, as well as the use of long-sleeved shirts and pants, and the avoidance of travels to endemic areas.[21,87] WHO also recommends the use of sulfadoxine-pyremetamine intermittently, but only in countries with high prevalence, which would not apply to Venezuela. If these are not available, the combined use of dihydroartemisinin-piperaquine could be a suitable substitute for them.[21,78,87–91] Studies have even shown the possible effectiveness of the prophylactic combination of azithromycin with intermittent sulfadoxine-pyremetamine.[92] The use of trimethopm-sulfamethoxazole is still being studied for its adverse effects on the mother and fetus.[93]

The pharmacological treatment in uncomplicated malaria, by *P. falciparum*, depends on the trimester of gestation. In the first trimester, the most propitious antimalarial drugs are oral quinine (10mg/kg every 8 hours for 7 days) with clindamycin (5mg/kg/dose every 8 hours for 7 days); if the latter is not available, quinine monotherapy is also functional, as well as the combination of artersunate with

clindamycin, as second line. The evolution of the pregnant patient treated with quinine should always be closely monitored, especially its possible adverse effects, including tinnitus, hearing loss, dizziness, and postural hypotension. During the second and third trimester, the use of combined therapy with artemisinin is recommended, since this reduces the parasitic load on the first day of therapy and the second compound, although it has a more slightly delayed effect, eliminates residual parasites, preventing further exacerbation of the malarial infection. This therapy includes combinations of artemeter with lumefantrine, dihydroartemisinin with piperaquine, oral artesunate with mefloquine, oral artesunate with amodiaquin, and oral artesunate with sulfadoxin-pyremetamine. As a first option, artemeter with lumefantrine, or mefloquine (25mg/kg in two doses, divided into 15mg/kg and 10mg/kg) can be used with oral artesunate (4mg/kg for 3 days).[21,78,86,94]

In contrast, in the case of *P. vivax* and *P. malariae* infections, oral chloroquine (25mg/kg for 3 days) is still considered the optimal and safest treatment to eliminate blood asexual forms and gametocytes, - not hypnozoites -, even though there has been a more progressive resistance to this treatment. The use of artemisinin combination therapy has had benefits, except for the combination of artesunate-sulfadoxine-pyremetamine. Nevertheless, it is essential to remember that the teratogenic effect of primaquine makes it contraindicated in pregnancy, mainly because of the risks of inducing severe hemolysis in patients with glucose-6-phosphate dehydrogenase deficiencies. However, it can be indicated during puerperium with doses of 15 mg/day for 14 days, only if the patient was infected with *P. vivax*. While, in severe malaria, the treatment of choice is parenteral artesunate, in maximum doses.[21,78,84,95,96]

It has been determined that the use of two doses of intermittent preventive mefloquine, in pregnant women with malaria, without HIV infection, reduces the risk of peripheral maternal parasitemia at the time of delivery by 35%, as well as maternal anemia by 16%, compared to the use of intermittent sulfadoxine-pyremetamine, without important adverse effects of the former. Although, patients may present more nausea, vomiting, asthenia, and dizziness. While, in HIV-positive pregnant women, combined therapy of three doses of intermittent preventive mefloquine with prophylactic cotrimoxazole is recommended, reducing the risk of peripheral maternal parasitemia at the time of delivery by 48%, and of placental malaria by 72%.[97]

It is well known that, for years, studies related to anti-malarial prophylaxis have been carried out. The generation of natural antibodies, particularly those that act against the 190-230kDa antigenic protein on the surface of *P. vivax*, called MSP-119, has been associated with increased protection against malaria in nonpregnant women, whereas anti-VIR antibodies and Duffy binding proteins (DBP) have protected pregnant women from maternal-fetal complications, including low birthweight, as well as anti-DBL1 and DBL2 IgG, anti-condroitin sulfate A and anti-VAR2CSA, protecting pregnant women from placental infection, preterm birth and maternal anemia.[34,47,98] Nonetheless, scientific evolution, in its perennial for the greatest protective potential, achieved one of the most important, impactful and hopeful advances in malaria prophylaxis. On October 6th, 2021, WHO approved the RTS,S/AS01 anti-*P. falciparum* vaccine, being the first approved vaccine against this or any other parasitic infection, obtained from the pre-erythrocyte stage of the parasite and directed towards the sporozoitic stage or the infected hepatocyte. For now, it was only approved for use in children, but this represents progress and hope for more vulnerable population groups, such as pregnant women. It should be noted that it only works against *P. falciparum*, so it is necessary to wait for the other *Plasmodium* species, such as *P. vivax*, with high presence in Venezuela, to be protected by this immunogenic form.[99,100]

Lastly, it is essential to remember that cases of malaria associated with pregnancy must be managed in an interdisciplinary way. Not only should the uterine dynamics be regularly and strictly monitored, but also the levels of maternal-neonatal glycemia, preferably every 8 to 12 hours, and of neonatal hemoglobin, excluding cases of congenital malaria. If maternal hemoglobin levels are below 7g/dL, patient should receive a blood transfusion immediately. Also, the possible adverse effects of pharmacological antimalarial treatment previously described should be monitored, and if there are suspicions of secondary or associated bacterial infection, it is imperative to collect blood and urine cultures, initiating empirical therapy with specific antimicrobials.[21]

Conclusion

With this narrative review, the importance of knowing and studying the medical-demographic characteristics of malaria associated with pregnancy was confirmed, and it could be evidenced by how deleterious its complications in the mother-fetus binomial can be if the infection continues to progress. The authors exalt and reiterate the importance of having notions about this entity for various reasons: 1. The lack of updated official data, regarding the prevalence and incidence of malarial infections associated with pregnancy is deeply worrying, especially as there are so many outbreaks in the Venezuelan topography; therefore, we invite the competent authorities to fulfil their role in publishing updated epidemiological information on pregnant women suffering from malaria. 2. Pregnant women constitute one of the most vulnerable population groups exposed to this parasitosis, always doubling the risk of infecting the fetus. Knowledge is the fundamental key to prevent diseases and, thus, achieve the incipient goals eradicating this parasitic disease, not only in Venezuela, but worldwide.

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