Review Article

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Diagnosis & management of imported malaria in pregnant women in non-endemic countries

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Malaria in pregnancy is an important cause of maternal and foetal morbidity and is a potentially life-threatening infection. With ever-growing global exchanges, imported malaria in pregnancy is becoming an issue of concern in non-endemic countries where women, because of low immunity, have higher risk of severe diseases and death. Malaria in pregnancy is a dangerous condition which can be associated with important consequences for both mother and child such as stillbirth, low birth weight, maternal anaemia. In non-endemic-countries it is more frequent in its severe form which can lead to maternal death if not treated adequately. Specific anti-malarial interventions such as the use of repellents and insecticide treated bed nets in addition to chemoprophylaxis should be used by pregnant women if they are travelling to endemic areas. In cases of confirmed infection, specific treatment regimens vary according to gestational age and the presence of complications. Malaria should be considered a global health problem, increasingly involving western countries. Clinicians all over the world need to be prepared for this emerging disease both in terms of prevention and therapy.

Key words Malaria - placental malaria - *Plasmodium falciparum* - pregnancy - prevention - severe malaria - travel

Though the incidence of malaria is reducing worldwide, cases reported in Europe connected to travel have remained unchanged in the last years[1]. Every year, there are more than 80 million travellers visiting malaria-endemic areas and many of them are women of child-bearing age[2]. This poses a serious question considering that pregnant women are more at risk of contracting malaria if comparing them to non-pregnant women[3-5]. Malaria in pregnancy is a relevant determinant for both maternal and foetal morbidity and mortality and is especially dangerous in those geographical areas with low rates of transmission. In these areas, women are not immune and can have a rapid progression to severe form of the disease with a higher incidence of respiratory distress and cerebral malaria[2,6]. When malaria is diagnosed early and promptly treated before its progression to severe disease, prognosis is good with full recovery[1].

Considering migration routes and world globalization, it will become more frequent to face diseases like malaria in non-endemic countries, therefore, clinicians worldwide will need to be ready to recognize such diseases and know how to treat them.

Epidemiology

The European Centre for Disease Prevention and Control reports 8349 malaria cases in Europe in 2018 and these data have not changed since 2008[7-10]. Near the totality of cases (99.9%) were associated with travels; instead, only a minority of cases were linked to 'baggage' malaria and blood transfusion. Autochthonous transmission was reported in many countries, in particular, Spain, Germany, the Netherlands, France, Italy and Greece[1]. *Plasmodium falciparum* (*P. falciparum*) is the main cause of cases signaled in Europe, especially found in people coming back from journeys in sub-Saharan Africa. On the contrary, even though malaria is not a disease frequently presented by newly arrived migrants moving to Europe for the first time, the data indicate recurrent forms of malaria in this group due to *P. vivax* or *P. ovale*[1]. Hence, malaria remains an issue also for those countries categorized as malaria-free because of cases arising from endemic regions. Moreover, these imported cases often determine many complications in non-endemic countries with, in particular, retarded diagnosis, costly treatment and can be associated to secondary local transmission. The involvement of non-endemic countries has also worsened the phenomenon of drug resistance and detected eradication goals[11].

Risk factors

The population most sensitive to the harmful consequences of malaria is represented by pregnant women and children. The effects may be various, depending on the geographical area and the *Plasmodium* species involved[12]. Pregnant women have a higher susceptibility to this infection compared to non-pregnant women and this could be related to the immunological and hormonal changes occurring in pregnancy[6]. Parity and maternal age are two important determinants that can influence the risk of contracting malaria in pregnancy[3]. In area of high-endemicity, primigravidae are the most affected, whereas in area of low transmission all gravidities have the same risk[6]. In the first case, primigravidae develop antibodies to the VAR2CSA protein expressed by malaria parasites, and this protects them for the following pregnancies; this does not happen in the second case where women do not acquire immunity and consequently are exposed more easily to serious forms of the disease[13].

Other important determinants influencing the gravity of the disease are represented both by the *Plasmodium* species and the health and nutritional conditions of people involved. Adolescents and adults living in high-transmission areas frequently develop less severe forms. On the contrary, younger children, women at their first pregnancy and travellers to areas of high endemicity are more prone to develop severe forms, which in most cases are due to *P. falciparum*[14]. Another important connection is the one involving maternal HIV infection and placental malaria. The retrovirus infection hinders the production of antibodies by the maternal immune system directed against specific antigens expressed by malaria-infected red blood cells. On the other hand, malaria infection can worsen HIV viral load and the risk of its transmission to the foetus. Further, the success of antimalarial drugs is lower in HIV-positive patients. However, anti-HIV treatment can hamper *P. falciparum* growth *in vitro* so determining lower gravity of malaria infection[15,16].

Clinical manifestations of malaria in pregnancy are strongly influenced by geographical area. Pregnant women in areas with a high incidence of the disease usually have no or a few symptoms because of acquired partial immunity. Women in areas of lower incidence or women who had a recent journey to a country of high endemicity develop severe forms of this disease[17]. These women need to start therapy as early as possible to avoid the risk of serious and potentially lethal manifestations[6].

The course of the disease generally involves an incubation period varying from 10 to 21 days. The disease should be suspected in case of one or more of these events: (*i*) recent travel to an area of high endemicity for this disease; (*ii*) high body temperature and flu symptoms; (*iii*) low platelets count; and (*iv*) miscarriage and sepsis[17].

Complications of malaria in pregnancy

Malaria infection in pregnancy is associated with serious negative consequences on both mother and foetus. The principal foetal effects are foetal growth restriction, abortions, stillbirth and neonatal death[18]. In pregnancy, the augmented risk of contracting infection and having negative consequences due to the disease

is related to the accumulation of infected red blood cells in the placenta. In *P. falciparum* infection, this accumulation is favoured by the binding between the protein VAR2CSA, an antigen expressed by infected red blood cells and the placental chondroitin sulphate A. Placental sequestration of infected erythrocytes leads to an inflammatory response which has been associated with negative consequences, especially foetal growth restriction, maternal anaemia and pregnancy loss[19-22].

Stillbirth

A meta-analysis by Moore *et al*[23] showed that the stillbirth rate associated with *P. falciparum* malaria in pregnancy was doubled in areas with a low incidence of the disease, confirming the connection between the severity of the disease and the geographical area. Early diagnosis and treatment of malaria is important in pregnant women even in the absence of symptoms to lower the possibility of stillbirth[24].

Low birth weight

Low birth weight (LBW) together with maternal anaemia, is the most frequently reported severe effect described[25]. Eisele *et al*[26] described malaria as the determinant of 14 per cent of all LBW babies all around the world and of the 11 per cent of child mortality due to LBW in Sub-Saharan Africa. As described before, *P. falciparum* infection determines the accumulation of infected erythrocytes in the intervillous space with consequent inflammatory cascade activation with an influence on vascular flow, erythropoiesis, nutrient transport and, at the end, an important effect on placental functionality and foetal growth[27]. The infection, especially if contracted at an early age of pregnancy, has an important effect on the development of placental vascularization and, consequently, on foetal growth[28].

In endemic countries, maternal malnutrition must be considered as another possible cause of LBW. Malaria and maternal malnutrition have been studied as primary causes of LBW by Cates *et al*[29] showing that women presenting with both conditions have a higher incidence of LBW, with malnutrition being the strongest determinant.

Anaemia

Plasmodium infection is responsible for both haemolysis and reduced erythropoiesis, determining anaemia[13]. Normally in pregnancy oral iron supplements are considered necessary for the prevention of maternal iron deficiency anaemia, but for women with malaria it is not clear whether iron supplementation is beneficial or not. Many epidemiological studies have observed a lower incidence of malaria in women with anaemia[30-33]. Different hypotheses have been proposed to explain this fact. Malaria parasite survival is dependent on the presence of iron, and its absence makes the parasite unable to thrive. In particular, iron deficiency suppresses erythropoiesis leading to lower possibilities of success for the parasite to attack the host. Iron deficiency also influences negatively the host immune status. Iron shortage reduces nitric oxide production by the host macrophages, which is normally used to fight against malaria parasites[34]. However, as the studies conducted so far have not gained clear results, they advise to follow WHO's existing recommendations that is to advise iron supplementation also for those women living in endemic areas who adopted adequate prevention techniques and therapies[31,35].

Post-natal effects

A systematic review suggested that malaria in pregnancy could have long-term effects on the immune system of the newborn dysregulating the development of immunity against different pathogens, including *P. falciparum*[36].

Symptoms of severe malaria in pregnancy

Malaria in pregnancy requires multi-speciality involvement, including physicians, obstetricians and paediatricians[37]. Among all symptoms typical of severe malaria, the most frequent conditions for pregnant women are hypoglycemia and pulmonary oedema[37]. Low blood glucose can be associated with quinine treatment, which causes marked hyperinsulinaemia. The maternal clinical manifestations vary from no symptoms to cold sweats, impaired state of consciousness, epilepsy and are often accompanied by foetal distress. Acute pulmonary oedema is also frequent. It occurs mainly within one week of the birth with chest signs and an augmented breath frequency. Other conditions are severe anaemia, which is added to the anaemia typical of pregnancy. Foetal distress, LBW and foetal death are usual. Post-partum haemorrhage and puerperal sepsis are common. Frequently symptomatic falciparum malaria can favour the onset of uterine contractions and therefore trigger a premature labour with a poor prognosis[33,38].

Diagnosis

The gold standard for malaria diagnosis in clinical practice remains the microscopic examination of serial blood films. Afterwards, new techniques have been introduced, in particular rapid diagnostic tests which are sensitive to all types of *Plasmodium*. However, these do not reach the sensitivity and specificity of the classical method and, in particular, these cannot determine parasite count which is a key factor in determining prognosis and therapy[39]. In conclusion, the new methods must be considered as a support to the conventional ones and not as their substitutes.

Blood microscopical examination

The use of standard techniques in pregnancy is hampered by the fact that because malaria parasites are trapped in the placenta, they may not be found in the circulatory stream and, consequently, not being detectable by the microscopy. Therefore, diagnosis of parasite infection in pregnancy would require checking the placenta as well and this can only be done after delivery. Because of this impediment, the only alternative is to use peripheral blood films[40].

Placental histological examination

Histological examination of placental tissue at delivery is a sensitive method for the detection of active or past malaria infection. Past infection is detected as the malaria pigment, haemozoin, most commonly deposits in fibrin[41]. Active infection can be accompanied by intervillositis: leukocytes (principally monocyte) infiltrates. This is particularly seen in primigravidae with reduced pregnancy-associated malarial immunity[41].

Rapid diagnostic tests (RDTs)

RDTs use monoclonal antibodies to recognize specific parasite antigens in the blood circulation. The ones with the highest sensitivity are those which recognize histidine-rich protein-2[6,40]. The introduction of polymerase chain reaction (PCR) has made it possible to recognize different subtypes of *Plasmodium* and to study low-count parasitaemia[19]. It is the method with the highest sensitivity to recognize the level of parasites, but it needs qualified personnel and adequate machinery that are not always available in disadvantaged areas[35].

Malaria prevention in pregnancy

Expectant women travelling towards areas of high risk should use specific anti-malarial interventions. These include strategies to reduce the risk of mosquito bites and specific drugs for chemoprophylaxis and therapy, especially in endemic areas.These strategies of prevention are necessary for all women travelling in areas of high endemicity and include reducing possible exposure to mosquitoes by living in protected environments avoiding to stay outdoors during the night, protecting body skin with clothes and using treated bednets with (pyrethroids like permethrin)[42]. Further use of chemoprophylaxis is necessary and strictly recommended. Chloroquine is the drug of choice for prophylaxis when travelling to regions where resistance to this medicine has not been described. When chloroquine is administered in the prophylactic dosage, there are no foetal risks described[43]. The only other drug approved for chemoprophylaxis is mefloquine (MQ), which can be used if resistance to chloroquine is present[43]. Doxycycline must not be used by expectant women because of negative effects on foetal teeth and bones caused by tetracycline, a medicine belonging to the same category[43]. Furthermore, primaquine is not recommended in pregnancy because it can induce haemolytic anaemia in a foetus with favism. All these precautions and therapies are recommended for women seeking pregnancy, and there is no need for them to wait for a precise time frame before starting pregnancy after chemoprophylaxis[43].

Therapies

First trimester

Medicines that can be used in this period are quinine, chloroquine, clindamycin and proguanil. This is the time of greatest concern for potential teratogenicity because organogenesis mainly occurs during this period. The recommended first-line treatment for non-complicated falciparum malaria is quinine + clindamycin (10 mg/kg bw twice a day) for seven days (or quinine alone if clindamycin is not available). If this treatment is not available or does not give results, an artemisin-based combination therapy (ACT) or oral artesunate (AS) + clindamycin is recommended[44]. Artemether lumefantrine may be used during the first trimester if other treatment options are not available, and if the potential benefit is judged to outweigh the potential risks[45].

Second and third trimesters

In the last two trimesters of pregnancy, the recommended treatment for uncomplicated falciparum malaria is represented by ACTs[44]. The

artemisin component acts by reducing parasites count on the first day of therapy. The other component [*i.e.*, lumefantrine (LM), piperaquine (PQ), amodiaquine (AQ) or mefloquine (MQ)] has a delayed effect, killing residual parasites thus preventing a new exacerbation of the disease as long as it exceeds the necessary concentration in the blood[46].

The recommended ACTs schemes by the WHO for uncomplicated falciparum malaria are five, in particular: artemether + LM (AM-LM), dihydroartemisinin + PQ, AS + MQ, AS + AQ, and AS + sulphadoxine-pyrimethamine[44]. Among these, AM-LM is the first choice combination to use for malaria without complications in the last two trimesters of pregnancy[47]. MQ can be used in the last two trimesters of pregnancy, but only if administered in association with an artemisin derivative; quinine can cause hypoglycemia and it should be prescribed (with clindamycin) only if there are no other possibilities. Primaquine and tetracyclines are not recommended in pregnancy[44].

The WHO guidelines[44] promote the use of intravenous AS instead of quinine. In fact, intravenous AS has demonstrated its remarkable efficacy in lowering the risk of lethal effects and is not associated with hypoglycemia, which is a dangerous side effect typically found in the case of therapy with quinine[37].

Conclusions

Malaria in pregnancy is a cause of concern globally. There are both maternal and foetal risks associated, especially in non-endemic areas, such as western countries, where there is little immunity against malaria. In these areas, there is a higher risk of developing severe forms that can lead to life-threatening conditions for the mother such as respiratory distress, cerebral malaria or even death, if not recognized and treated promptly. For the foetus also several adverse effects have been described such as stillbirth and LBW. Taking into account the wide migration flows and the high number of people travelling every year to endemic areas, malaria should be considered a global health problem, increasingly involving western countries. Clinicians worldwide need to be prepared for this emerging disease in non-endemic countries. A desirable situation would be that clinicians can give adequate advice to women travelling to endemic areas in terms of prevention, as well as being able to promptly recognize and treat all pregnant patients. This will reduce severe complications for both mother and child.

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