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A MINI OVERVIEW OF MALARIA IN PREGNANCY

By
MAHFOUZ AHMADAL-AGROUDI[1], LAILA ABD EL-MAWLA MEGAHED[1], ELHAM MOHAMMAD ABDALLAH[1] and TOSSON ALY MORSY[2]
Military Medical Academy[1] and Department of Parasitology, Faculty of Medicine, Ain Shams University, Cairo 11566[2]

Abstract

Human malaria is caused by five species of Plasmodia: *P. falciparum, P. vivax, P. ovale, P. malariae* and *P. knowlesi*. Most infections are due to either *P. falciparum* or *P. vivax*, but mixed infections with more than one malarial species also occur. The majority of malaria-related deaths are due to *P. falciparum*. Generally, the pregnant women are a high risk group, as malaria can be a life threatening infection for both mother and fetus. Risk of stillbirth, spontaneous abortion, and other adverse pregnancy outcomes is increased in the setting of malaria, and pregnant travelers should be advised to defer travel until after delivery whenever feasible.

Key words: Egypt, Pregnant and non-pregnant women, Malaria, Risky, Management, Nursing

Introduction

Each year, 50 million women living in malaria-endemic areas become pregnant; one-half of these women live in Africa. It is estimated that 10,000 women and 200,000 infants die as a result of malaria infection during pregnancy; severe maternal anemia, prematurity, and low birth weight contribute to more than half of these deaths (Fried and Duffy, 2017). The continued public health burden of malaria is due to a combination of factors, including: 1- Increasing resistance of malarial parasites to chemotherapy, 2- Increasing resistance of the *Anopheles* mosquito vector to insecticides, 3- Ecologic and climate changes, and 4- Increasing travel to malaria-endemic areas by non-immune travelers (Cox-Singh *et al*, 2008).

Review, Discussion and Comment

Prevalence, Microbiology, and Epidemiology: For women who reside in malaria endemic areas, the prevalence of malaria is higher in primigravidas than in nonpregnant women or multigravidas. *P. falciparum* is the predominant species giving rise to heightened morbidity and mortality in pregnancy. *P. vivax* infection can give rise to some of the same complications as *P. falciparum*; however, the complications are less frequent and less severe.

Endemicity: The prevalence of malaria in pregnancy is related to intensity of transmission. Holo-endemic malaria refers to areas where there are very high rates of infection in the community (>60% of children less than 5 years of age are infected) and the exposure to the parasite is stable. Therefore, women have more frequent lifetime malaria episodes, thus greater immunity, so tend to have milder complications. In contrast, mesoendemic malaria refers to areas where transmission is lower (<20% of children less than 5 years of age are infected) and the exposure to the parasite is more unstable. With less exposure to the parasite, the development of natural immunity may be slower. Therefore pregnant women are more likely to develop severe complications such as pulmonary edema and hypoglycemia.

Malaria in pregnancy has generally been studied in holo-endemic areas, such as Sub-Saharan Africa. In these areas, the median prevalence of maternal malaria (defined as peripheral or placental infection identified by microscopy) is 28%. In mesoendemic areas, such as malaria endemic countries within the Americas, the prevalence of malaria is lower in both pregnant and nonpregnant women, although the rate appears to be rising. The median prevalence of malaria in pregnant women in low-transmission areas outside of Africa ranges from 1.8 to 17.4% (Desai *et al*, 2007).

In 2010, 41 cases of malaria in pregnant women were reported to the CDC; eight cases were severe (Mali *et al*, 2012).

Pregnant versus non-pregnant: The prevalence of peripheral parasitemia is higher in pregnant than in age-matched nonpregnant women living in the same geographic area both in holo-endemic and mesoendemic areas (Brabin, 1983). As an example, malaria surveillance in 430 pregnant and 250 non-pregnant women in Kinshasa found the prevalence of active malaria was 22 and 6%, respectively (McGregor, 1984). Similarly, in Gambia, the prevalence of parasitemia was 32% in pregnant women, but only 26% in non-pregnant women (Nosten*et al*, 1999).

Gravidity: In endemic areas, the prevalence of malaria (*P. falciparum* or *P. vivax*) generally decreases with increasing gravidity, but remains higher in pregnant women of any gravidity compared to nonpregnant women (Nosten *et al*, 1991). In Gambia, parasitemia was more common in primigravidas (64%) than in women having a second/third pregnancy (29%) or who have had four or more pregnancies (21%). Others have reported a two-fold increase in infection prevalence among primigravidas compared to other groups (Bouyou-Akotet *et al,* 2003). In contrast, low gravidity was not a risk factor for malarial infection in a study from Kinshasa (McGready *et al*, 2004).

One possible explanation for this discordance is that in areas of low or episodic malaria endemicity (and therefore low immunity), all pregnant women are similarly susceptible to malaria infection, whereas in areas of high endemicity (and therefore high immunity), women are most susceptible during their first pregnancy, because they have not yet acquired sufficient pregnancy-specific immunity.

Placental malaria: One of the unique features of malaria in pregnancy is the ability of *P. falciparum*- parasitized erythrocytes to sequester within the inter-villous space of the placenta. Notably, placental sequestration is not a feature of *P. vivax* infection (Rogerson *et al,* 2003).

The median prevalence of placental malaria in areas of stable transmission is 26%, but may be even higher when more sensitive methods for diagnosis of placental infection, such as histology or polymerase chain reaction (PCR), are utilized rather than microscopy alone (Ismail *et al,* 2000). .

Placental infection may be detected even in the absence of peripheral parasitemia in mothers. In an area of stable malaria transmission in Tanzania, no parasites were observed in the maternal bloodstream of 46.3% of the women with histologic evidence of placental malaria (Salanti *et al,* 2003).

Immunity: Immune responses occur following infection with malaria. Pregnancy selects for parasite clones that have the ability to adhere to the placenta. Partial immunity to these clones develops with successive pregnancies. Individuals living in endemic areas may develop partial immunity to disease following repeated infections and have a lower prevalence of parasitemia compared to nonimmunes. These individuals are referred to as "semi-immune" or having "non-sterilizing immunity." Partial immunity does not prevent infection: following a bite by an infected mosquito, these individuals will still develop parasitemia, but the severity of symptoms is typically limited. Partial protection wanes quickly after leaving an endemic area.

Pathogenesis: Pregnancy-associated *P. falciparum* malaria is characterized by sequestration and multiplication of a distinct population of malarial parasites in the placenta. These parasites express a specific class of variant surface antigens (VSAs) that mediate adhesion of parasite-infected erythrocytes to chondroitin sulfate A (CSA) on the syncytiotrophoblast lining the intervillous space (Salanti *et al,* 2004). This process appears to involve upregulated transcription of var2csa (Crocker *et al,* 2004), which is expressed on the surface of CSA-adherent infected erythrocytes. Once these parasites adhere to the surface of trophoblastic villi, they induce accumulation of inflammatory leukocytes. Placentas with active malaria showed adhesion of infected erythrocytes to syncytio-

trophoblast, syncytial degradation, increased syncytial knotting and rarely localized villi destruction (McGregor *et al*, 1983). This process may be exacerbated by neovasculature development of at an immunologically privileged site (Shulman and Dorman, 2003)

In holo-endemic areas, the frequency of both placental infection and poor pregnancy outcome decrease with successive pregnancies; nonimmune pregnant women, especially nulliparas, are at higher risk for adverse maternal-perinatal outcomes compared to multiparous controls (Beeson *et al*, 2005).

The unique VSA types expressed on pregnancy-associated malaria (PAM) parasites can be serologically classified as sex specific (ie, men from malaria-endemic areas do not develop VSA antibodies) and gravidity dependent (ie, women acquire anti-VSA immunoglobulin G as a function of gravidity). Thus, the observed protection afforded multigravidas may result from maternal antibodies (e.g., anti-VSA) that prevent cytoadhesion of parasite to the placenta (Staalsoe *et al*, 2004). This theory is supported by the observation that primigravid women without histological evidence of PAM have uniformly low VSA-PAM-specific plasma IgG concentrations at delivery, which are not significantly different from those in unexposed pregnant women despite lifelong *P. falciparum* exposure. Primigravid women with acute or chronic PAM have low-to-medium VSA-PAM IgG, likely indicating slow development of a primary response to VSA-PAM, while a high proportion of multigravid ones have moderate-to-high VSA-PAM IgG values, suggested fast and boostable memory responses protecting multigravidas from PAM complications as low birth weight, maternal anemia (Vleugels *et al*, 1987).

Pregnancy-induced immune suppression may also account for the more severe disease experienced by primigravid nonimmune women. Primigravidas express higher cortisol levels compared with multiparous women, which leads to greater depression of cell-mediated immunity (Rasheed *et al*, 1993). Other indirect support for role of depressed cell-mediated immunity comes from the observation that specific malarial antibodies are not decreased during pregnancy, but when lymphocytes from pregnant women are challenged with malarial antigens, the lymphocyte proliferative responses are depressed compared to lymphocytes from non-pregnant women (Brabin *et al*, 1990).

Clinical Manifestations: Clinical picture varies according to underlying region endemicity. In areas of stable malaria transmission (holo-endemic regions) where partial immunity is common, most malarial infections in pregnant women are asymptomatic, but the mother remains at risk for anemia and the fetus is at risk for low birth weight. But, women residing in the mesoendemic areas, or those returning to the holo-endemic area after a prolonged absence, malaria is more likely febrile illness, severe symptomatic disease, preterm birth, and death of mother or fetus (Diagne *et al*, 2000). In areas of low or unstable malaria transmission where pregnant women have little immunity, symptomatic malarial disease is the rule and serious complications may occur.

Parasitemia peaks in the second trimester in both the primigravidas and multigravidas, and the increased risk for pregnancy-associated malaria persists for 60 days postpartum. There is a semiquantitative relationship between the degree of parasitemia and severity of disease. *P. falciparum* is associated with especially high levels of parasitemia since it invades red cells of all ages; occasionally, more than 50% of red cells are infected (Warrell *et al*, 1990).

Clinical manifestations of malaria are nonspecific and variable. Virtually all nonimmune individuals would experience fever, which may or may not be periodic. Other frequent symptoms include: chills, sweats, headache, myalgias, fatigue, nausea, abdo minal pain, vomiting, diarrhea, jaundice, and cough. (Clinical manifestations of malaria vary with geography, epidemiology, immunity, and age. In areas where malaria is highly

endemic, groups at highest risk include young children (6- 36 months), who can develop severe illness, and pregnant women, who are at risk for delivering low birth weight newborns. In areas where malaria is transmitted throughout the year, older children and adults develop partial immunity after repeated infections and are at relatively low risk for severe disease. In areas where malaria is endemic, groups at high risk for severe malaria and its consequences include young children (6 to 36 months) and pregnant women. Older children and adults develop partial immunity after repeated infection and are at relatively low risk for severe disease. Travelers to areas where malaria is endemic generally have no previous exposure to malaria parasites and are at very high risk for severe disease if infected with *P. falciparum.* The incubation period for P. falciparum infection is usually 12 to 14 days. Longer incubation periods are more likely in semi-immune individuals and individuals taking inadequate malaria pro-phylaxis at the infection time. The relapsing malarias (*P. vivax* & *P. ovale*) can cause clinical illness several weeks or months after the initial infection due to presence of hynozoites in the liver. Malaria should be suspected in patients with any febrile illness after exposure to a region where malaria is endemic. Initial symptoms of malaria are nonspecific and may also include tachycardia, tachypnea, chills, malaise, fatigue, diaphoresis, headache, cough, anorexia, nausea, vomiting, abdominal pain, diarrhea, arthralgias, and myalgias. Complicated or severe malaria is generally defined as acute malaria with hyperparasitemia (≥ 5 to 10% of RBCs infected) and/or major signs of organ dysfunction. Features of complicated malaria may include cerebral malaria, hypoglycemia, acidosis, renal impairment, noncardiogenic pulmonary edema, hematologic abnormalities, liver dysfunction and concomitant infection. Common manifestations among children with severe malaria include convulsions, coma, hypoglycemia, metabolic acidosis, severe anemia, and neurodevelopmental sequelae, more frequently among adults than children include severe jaundice, acute renal failure, and acute pulmonary edema. Malaria differential diagnosis includes viral infection, meningitis, pneumonia, bacteremia, leptospirosis, typhus, and enteric fever. Malaria can coexist with such entities, with HIV, malnutrition, and intestinal geohelminths. Compared to non-pregnant women, pregnant ones experience more severe disease, more hypoglycemia, and more respiratory complications as pulmonary edema, acute respiratory distress syndrome (Saeed *et al*, 1990). Hypoglycemia was in 58% of gravid women vs. 8% of non-pregnant ones (White, 1996). In holo-endemic regions, splenomegaly was 10 to 23% of pregnant women than controls (Espinoza *et al*, 2005).

Anemia is a common complication of malaria in pregnancy; approximately 60% of pregnant women presenting with malarial infection are anemic (Whitty *et al*, 2005) and anemia may be one of the few signs of the disease. However, anemia in resource poor countries can be due to one or more other etiologies, including nutritional deficiency, intestinal parasites (especially hook worms), and thalassemia trait. In one review, 5 to 10% of pregnant African women developed severe anemia and one-quarter of these cases were attributed to malaria. Some experts believe that malaria is a sufficiently common and serious cause of anemia in pregnant women in endemic areas that it is prudent to treat for malaria unless other causes of the anemia can be ascertained and respond to therapy (Whitty *et al*, 2005). Iron deficiency may protect against placental malaria. A study of pregnant Tanzanian women found the prevalence of placental malaria was lower in iron deficient primigravidae than in primigravidae without iron deficiency; 8.5 vs. 47.3%, $p<0.0001$ (Kabyemela *et al*, 2008). After first pregnancy, reduction in malaria prevalence with iron deficiency was maintained but attenuated secundigravidae (10.7 vs. 31.6%, $p<0.01$) multigravidae (5.1

vs. 12.8%, P<0.08). Also, some studies in which iron supplements were given to primigravidae and children in areas where malaria and malnutrition are common have reported this intervention increased the rate of malaria. Given that iron supplementation is routinely recommended during pregnancy, these findings highlight the need for large interventional trials evaluating the risks and benefits of iron supplementation in pregnant women who live in malarious areas (Oppenheimer *et al*, 1986).

Prevalence of anemia: Severe malarial anemia (SMA) is seen most frequently in areas of very high malarial transmission and most commonly in young children and pregnant women (Greenwood, 1997). The prevalence of anemia, defined as a hematocrit <33 percent, in malarial endemic areas of Africa varies between 31 and 91% in children, and between 60 and 80% in pregnant women. In a typical study of children living a malarial endemic area in southern Cameroon, among those who were monitored for both asymptomatic and symptomatic malaria, the prevalence of anemia (hemoglobin <11 g/dL) was the highest in six-month-old age group (47%), 42% in children <3 years of age and 21% in those 3 to 5 years of age (Schellenberg *et al*, 2003). Placental malarial infection was the primary risk factor for anemia in the six-month old children.

In individual cases, it may be difficult to attribute anemia to a single cause, although randomized placebo-controlled trials of malaria chemoprophylaxis and iron supplementation in infants have shown that malaria infection was the main etiologic factor underlying anemia (Schellenberg *et al*, 2003). The precise etiology of anemia is often complex in endemic areas since nutritional deficiencies, genetic traits, and intercurrent infection may all contribute to the anemia. The etiology of SMA in endemic areas is likely to be multifactorial and variable in both time and place. This was illustrated in a case control study of severe anemia in hospitalized children in Malawi, in which severe anemia was associated with: Malarial infection (odds ratio (OR) 2.3; 95% CI 1.6-3.3) HIV infection (OR 2.0; 95% CI 1.0-3.8) Hookworm (OR, 4.8; 95% CI 2.0-12) Bacteremia (OR 5.3; 95% CI 2.6-11) G6PD deficiency (OR 2.4; 95% CI 1.3-4.4) Deficiencies of vitamin A (OR 2.8; 95% CI 1.3-5.8) and vitamin B12 (OR 2.2; 95% CI 1.4-3.6). In this population, folate deficiency and sickle cell disease were uncommon, iron deficiency was not prevalent and not associated with bacteremia (Lamikanra *et al*, 2007).

Features of malarial anemia: The spectrum of the clinical presentation and severity of *P. falciparum* infection is broad. In endemic areas many malarial infections present in semi-immune and immune children and adults as an uncomplicated febrile illness. Fever develops with the release of merozoites from ruptured, infected red cells. Anemia, thrombocytopenia, splenomegaly (occasionally massive), hepatomegaly, and jaundice can develop, and splenic rupture can occasionally occur. However, the clinical setting of SMA is varied and complex. Not only may acute infection present with anemia and/or cerebral malaria, respiratory distress and hypoglycaemia, but chronic, repeated malarial infection may also lead to severe anemia (Calis *et al*, 2998).

Severe malarial anemia: New malarial infections are often associated with an sudden drop in hemoglobin concentration associated with increased hemolysis and bone marrow suppression. Non-immune patients may exhibit a number of clinical syndromes including anemia, coma, respiratory distress, and hypoglycemia, and may have a high frequency of concurrent bacteremia. Children may present with mild, moderate or severe anemia with or without other syndromes of severe disease as malaise, fatigue, dyspnea, or respiratory distress as metabolic acidosis supervenes (Bedu-Addo and Bates, 2002).

The age distribution of the syndromes of severe disease is striking, but poorly understood. Children born in endemic areas are largely protected from severe malaria during

the first 6 months of life by the passive transfer of maternal immunoglobulins and by presence of fetal, rather than adult hemoglobin. Fetal hemoglobin is relatively resistant to digestion of malarial proteases and slows parasite growth can be found elsewhere. Disease presentation changes from severe anemia in children aged between 1 & 3 years in areas of high transmission to cerebral malaria in older children in areas of lower transmission (English, 2000).

Chronic anemia: Anemia is also present in those with chronic malarial infection. Many children may present with severe anemia and a blood smear negative for malaria parasites, but will respond to antimalarial treatment. In Indian children with chronic falciparum malaria, those with moderate to severe anemia and hepatosplenomegaly had a greater degree of hemolysis, neutropenia, atypical lymphocytosis, and thrombocytopenia, but a lower level of parasitemia than with acute malaria (Snow *et al*, 1997).

Hematologic *P. falciparum* anemia is typically normocytic and normochromic, with a notable absence of reticulocytes. Microcytosis and hypochromia may be present due to very high frequency of thalassemia trait and/or iron deficiency in many, but not in all endemic areas (Roberts *et al*, 2005).

Black-water fever: A less common form of anemia in malaria is "Blackwater Fever" (BWF) characterized by intravascular hemolysis, the sudden appearance of hemoglobin in the urine, and renal failure, classically associated with irregular use of quinine. Disseminated intravascular coagulation and red cell fragmentation may accompany this presentation. An important clinical point is that BWF is sometimes difficult to relate to malarial infection, because parasitemia can be missed due to synchronous lysis of all infected red cells. Series of cases of BWF in Africa and South-East Asia have shown that sudden hemolysis is associated with malarial infection, glucose-6-Phosphate dehydrogenase deficiency, and use of quinine (Naqvi *et al*, 1996). BWF virtually disappeared after 1950, when chloroquine superseded quinine. But, in European expatriates living in Africa, BWF has been associated with use of the antimalarial agents halofantrine, quinine, and mefloquine (Delacollette *et al*, 1995).

Anemia in *P. vivax* malaria: Although most work describes the association of P falciparum malaria with anemia, infection with *P vivax* may cause severe disease, including anemia and severe hemolysis. *P. vivax* malaria has been clearly associated with anemia during pregnancy, along with low birth weight of the children of these infected mothers (Rodriguez-Morales *et al*, 2006).

Postpartum infection: The increased risk for acquiring an infection and developing more severe disease persists for at least 60 to 70 days postpartum. Puerperal infection can also be caused by a new infection, rather than by parasites trapped in the placenta and released into the maternal blood at delivery (Ramharter *et al*, 2005). The reason for the high susceptibility to infection postpartum may be related to postpartum changes in the maternal immune system, maternal behavioral changes, or other undefined factors**.**

HIV-Co-infection: From the standpoint of malarial disease, a seropositive HIV status increases the morbidity and mortality associated with the malaria infection (Kublin *et al*, 2005). Mothers with HIV may be at higher risk for malaria acquisition, placental malaria, higher parasite densities, and more severe clinical disease. After delivery, women with HIV and malaria are at increased risk for anemia compared to HIV seronegative women with or without malaria. Dual infection with malaria and HIV also leads to an increased risk of adverse perinatal outcomes. HIV and malaria infections often coexist in patients in many parts of the world due to geographic overlap of these two diseases. This is true in sub-Saharan Africa, where an estimated 40 million people are living with HIV and more than 350 million episodes of malaria occur yearly. There is also evidence of a negative interaction between these two infections. HIV increases

the risk of malaria infection and developing clinical malaria. Conversely, malaria increases HIV replication (Hewitt *et al*, 2006).

Presently, most data on HIV interaction with malaria are derived from *P. falciparum* endemic regions of sub-Saharan Africa. However, as HIV spreads to areas endemic for *P. vivax*, similar important interactions may be identified.

Immunity to malaria is characterized by an age-related reduction in parasite burden, clinical symptoms, and prevalence of severe disease in individuals residing in an endemic area (Karp and Auwaerter, 2007). *P. falciparum* and the burden of parasitemia are often less severe in older adults than in children. Children are at increased risk since they have not yet acquired natural immunity; pregnant women transiently lose some of their acquired immunity due to the relative immunosuppression of pregnancy. The immunity degree is also related to transmission intensity, which varies geographically. HIV-related immunosuppress- ion diminishes this acquired immunity.

Clinical versus asymptomatic malaria, individuals living in endemic areas may develop partial immunity to disease following repeated infections. These "immune" individuals are not immune to infection per se. Following a bite by an infected mosquito, they would still develop parasitemia, but the severity of clinical symptoms is typically limited. This can affect estimates of clinical infection since patients who live in endemic areas are much less symptomatic and often have no symptoms.

Impact of malaria on HIV: In vitro, malarial antigens lead to T cell activation and de novo productive HIV infection (Froebel *et al*, 2004). Episodes of malaria have been associated with declines in CD4 cell counts over time compared to HIV-infected patients without parasitemia (Mermin *et al*, 2006). However, more studies are needed to confirm this observation. In a retrospective study of 190 French HIV-infected patients with imported malaria Mouala *et al*. (2008) reported that severe infection was associated with a CD4 cell count <350 cells/microL (OR = 2.58; 95% CI 1.2-5.6).

Malaria is associated with a temporary rise of HIV/RNA, although long term, this does not appear to hasten progression to AIDS (Hoffman *et al*, 1999). A cohort study performed in Malawi prospectively enrolled 348 aparasitemic patients to obtain a baseline HIV VL load and followed them over time with active surveillance for malaria infection. A near doubling of HIV RNA was demonstrated between baseline and follow-up in those patients who acquired malaria infection. Increases in viral load were greatest in patients with fever, CD4 counts >300 cells/microL and in those with a parasite density >2000/microL. This rise was temporary, with HIV viral load returning to baseline at two months after treatment of malaria (Kublin *et al*, 2005). If viral loads are being used to monitor response to HAART, testing should be delayed if the patient has had a recent malaria infection. This transient increase in viral load would be predicted to have minimal impact on long term HIV progression, unless infections were frequent or remained occult and untreated. However, from a public health standpoint, even a transient rise in HIV RNA at a population level could impact sexual transmission. Comparing rates of HIV-related survival in malaria-endemic to non-endemic countries is problematic due to the higher prevalence of additional health care problems found in these geographic regions, which may also impact morbidity and mortality. Few studies were done in malaria-endemic areas to address this question. Studies from Uganda and Malawi found a ten-year survival rate after HIV infection that was comparable to rates in developed non-malaria endemic countries in pre-HAART era (Crampin *et al*, 2002).

Studies to define the impact of HIV on malaria have been conducted to examine various malaria disease markers including susceptibility, prevalence of malaria infection, peripheral parasite burden, disease severity,

and response to treatment. HIV serostatus and immunosuppression may be associated with an increased risk of susceptibility to malaria infection as follows: A cohort study was conducted in 224 HIV-infected and 125 HIV-uninfected adults in Malawi to assess whether HIV serostatus may affect incidence of malaria (Patnaik *et al*, 2005). HIV-1 seropositivity was significantly associated with first and second episode of parasitemia. The risk of a first parasitemia episode was inversely related to baseline CD4 cell count in HIV-1-seropositive persons. In Uganda, a retrospective study was performed in 1965 patients who received treatment for an episode of malaria (Kamya *et al*, 2006). Use of molecular genotyping demonstrated that HIV-infected patients were at significantly higher risk of acquiring new infections than HIV-seronegative patients during the standard 28-day follow-up period. In Zambia, a clinical trial was performed in 971 adults with uncomplicated malaria; HIV infection was detected in 33 percent of study participants. Patients with CD4 counts <300 cells/microL were at increased risk for recurrent parasitemia, recrudescence, and new infection (Van Geertruyden *et al*, 2006).

Diagnosis: Malaria diagnosis must be considered in any febrile woman who has resided in a malarious region, or traveled to a malarious region even if briefly or only in transit. Standard methods that detect peripheral parasitemia can be used in pregnant women, and include Giemsa-stained thick and/or thin peripheral blood smears or rapid diagnostics. It is important to point out that women may have placental parasites that are not circulating in the peripheral blood, and hence, the blood film would be negative. No reliable peripheral biomarker for the presence of placental malaria has been identified; the diagnosis is made by histological examination after delivery.

Generally, malaria diagnostic tools include clinical criteria, light microscopy, rapid diagnostic tests, and molecular diagnostic techniques. There are no pathognomonic clinical signs or symptoms for diagnosis of malaria.

1- Clinical Diagnosis: History, physical exam, and routine labs can be useful to help determine whether malaria may be the cause of a patient's illness. However, symptoms may overlap with other clinical presentations (such as upper respiratory tract infection or gastrointestinal illness), which should not preclude specific diagnostic testing for malaria (Froude *et al*, 1992). Patients may present with a non-malarial illness together with a parasitemia not related to the presenting symptoms (Taylor *et al*, 2004). There are no pathognomonic clinical signs or symptoms for malaria diagnosis (Dorsey *et al*, 2000). The most predictive findings are fever without localizing symptoms, enlarged spleen, platelet count less than 150 x 109/L and bilirubin greater than 1.3 mg/dL. The presence of skin rash, skin ulcer, and eosinophilia was predictive of non-malarial disease (Bottieau *et al*, 2007).

2- Blood counts are often abnormal but are not specific. In a series of Canadian travelers, patients with malaria presented with anemia in 41% of cases. White blood cell counts were elevated above 9.8 x 109/L in 3% of patients but were less than 5.0x109/L in 48% (Kain *et al*, 1998). Platelets were low in 83% of *P. vivax*-infected patients, while 62% of *P. falciparum*-infected patients were low with mean platelet counts of 102x109/L &137x109/L, respectively.

3- Light microscopy remains the gold standard for diagnosis; it permits determination of infecting species and quantification of parasitemia, facilitating monitoring the response to therapy. But, light microscopy is also labor-intensive, time-consuming and requires substantial training and expertise. The sensitivity of microscopy can be excellent, with detection of malaria parasites at densities as low as 5 to 10 parasites/microL of blood in expert hands; approximately 0.0001% parasitemia (Moody, 2002). Diagnostic errors occur more commonly in the setting of low-density parasitemia (10 to 100

parasites/microL of blood), although errors can also occur with higher densities (Kilian *et al*, 2000). Microscopy permits determination of the infecting species as well as quantification of parasitemia, which allows monitoring the response to therapy. It remains an important tool even with the use of rapid diagnostic tests (as discussed in the subsequent sections); microscopy and RDTs should be used in parallel when feasible. Examination of blood smears by light microscopy also allows diagnosis of other infectious diseases such as filariasis, trypanosomiasis, *Borrelia recurrentis*, and babesiosis. (Saleh *et al*, 2016). Given the cyclic nature of malaria parasitemia, smears should be evaluated every 6- 12 hours for 48 hours before ruled out diagnosis (White, 1996) as the first smear is positive in 95% of cases.

Drawbacks to light microscopy include that it is labor-intensive, time-consuming, and requires substantial training and expertise (Murray *et al*, 2008). This was illustrated in an evaluation of 100 Canadian travelers; the diagnosis of malaria at presentation was missed in 59 percent of cases, and the infecting species was identified incorrectly in 64 percent of cases (resulting in therapeutic delays of 5 to 7 days). Also, clinical microscopy cannot reliably detect very low parasitemia (<5 to 10 parasites/microL).

4- Rapid diagnostic tests (RDT) for malaria were introduced in the early 1990s; most employ immunochromatographic lateral flow technology for antigen detection (Makler *et al*, 1998). In these assays, a blood sample migrates across the surface of a nitrocellulose membrane by means of capillary action. The membrane contains stripes of antibodies specific for different epitopes of a target antigen (one of which is conjugated to an indicator), along with a control antibody specific for an indicator-labeled antibody complex. The characteristics of the malaria antigen target and the detection antibodies are paramount to understanding the assay performance. Antibodies may be monoclonal (relatively specific) or polyclonal (relatively sensitive). The source of the antigen is also variable (purified native protein, recombinant proteins, or peptides). Diagnostic targets include malaria antigens conserved across the human malarias as well as antigens specific to individual *Plasmodium* species. Targets conserved across all human malarias include *Plasmodium* lactate dehydrogenase (PLDH) and aldolase enzymes (Forney *et al*, 2003). Diagnostic targets specific for *P. falciparum* include *P. falciparum* lactate dehydrogenase (pfLDH) and histidine-rich protein-2 (HRP-2). Both pLDH and aldolase fall to undetectable levels rapidly after initiation of therapy. There was limited evaluation of a proprietary *P. vivax*-specific antigen (Brown *et al*, 2004).

The first antigen used in a commercial assay was HRP-2, a P. falciparum specific water-soluble protein localized in the parasite cytoplasm and expressed on the erythrocyte membrane (Rock *et al*, 1987). It is present in the asexual stages, which permits detection at relatively low parasitemia. It is also present in young gametocytes, which can callow detection beyond 28 days following clinical response to therapy and clearance of parasites (Mueller *et al*, 2007). There is an extensive diversity in HRP-2 sequences observed among parasites around the world. Therefore, assays utilizing this antigen may have variable sensitivity depending on local sequence variation (Lee *et al*, 2006). *Plasmodium* lactose dehydrogenase (PLDH), the terminal enzyme in the malaria parasite's glycolytic pathway, is an enzymatic antigen target employed to detect sexual and asexual stage malaria parasites. Monoclonal antibodies have been developed that can target a conserved element of PLDH on all human malaria species or specific regions unique to *P. falciparum* or *P. vivax*. .Similar to peripheral parasitemia, in holo-endemic regions placental malaria is higher in primigravidas (16 to 63%) than in multigravidas (12 to 33%). Overall, prevalence of placental malaria in primigravidas was 30 to 40%, twice rate in multigravidas.

Outcome: Adverse maternal and perinatal outcomes associated with malaria during pregnancy include (McGready *et al*, 2012): 1- Miscarriage, 2- Fetal growth restriction/ small for gestational age (SGA) infant, 3- Preterm birth (<37 weeks of gestation), 4- Low birth weight (LBW) (<2500 g at birth), 5- Perinatal death, 6- Congenital infection, 7- Maternal anemia, and 8- Maternal death

In regions of unstable endemism, or when malaria is acquired in a nonimmune individual, malaria is more likely to result in severe maternal disease, preterm birth, and death of mother or fetus. In endemic malaria areas, women have usually acquired sufficient immunity to prevent febrile illness, and they are less likely to experience preterm birth and the severe maternal complications of malaria. Asymptomatic mothers remain at risk for anemia, and their fetuses remain at risk for impaired growth. In a review of 117 studies between 1985 and 2000 from endemic areas in sub-Saharan Africa, the population attributable risks for adverse birth outcomes associated with malaria were marked: anemia;3 to 15%, LBW; 8 to 14%, growth restriction; 13 to 70%, and infant mortality; 3 to 8% (Steketee *et al*, 2001). Also, in endemic areas about 19% of LBW infants result from maternal malaria infection, and 6% of infant deaths have been attributed to malaria-related LBW, and that 100,000 infant deaths each year could be due to LBW caused by malaria during pregnancy in areas of malaria (Guyatt and Snow, 2004).

Factors related to increased severity of malarial infection during gestation and, therefore, an increased risk of adverse maternal and perinatal outcome include: low parity, young maternal age, nonimmune immunological status, *P. falciparum* or *P. vivax* protozoan species, a high degree of parasitemia and placental infection, as well as the patient's socioeconomic background, place of residency (rural or urban), and season of acquisition (Duffy and Fried, 2003).

P. vivax: The effects of *P. vivax* is considered less striking than those of *P. falciparum* infection, due to the lack of placental sequestration/inflammation with *P. vivax* and its moderate impact in causing anemia given that it only infects reticulocytes (Mayor *et al*, 2012). Nonetheless, *P. vivax* is also associated with a significant risk of adverse maternal and fetal outcomes as death, anemia, low birthweight (Poespoprodjo *et al*, 2008). Like *P. falciparum*, *P. vivax* infection is more common in primigravid than multigravid women (Suguitan *et al*, 2003).

Miscarriage: An analysis of pregnancy outcome in over 17,000 pregnant women attending antenatal clinics at the Thai-Burmese border included 945 women with first trimester malaria, of whom 773 were treated with chloroquine, quinine, or artesunate. After adjustment for maternal age, previous miscarriages, smoking, and non-malaria febrile illness, the odds of miscarriage in women with P. falciparum or *P. vivax* malaria were about three-fold higher than in women without malaria. The frequency of miscarriage in women without malaria, those with treated malaria, and all women with malaria (treated & untreated) was 19, 27, & 35%, respectively. The risk of miscarriage was increased for both symptomatic and asymptomatic malaria, but highest with symptomatic disease. The risk was similar for both *P. falciparum* and *P. vivax* infection (Suguitan *et al*, 2003).

Preterm birth: The increased prevalence of preterm deliveries among women who become infected with *P. falciparum* during pregnancy may be mediated by alterations in cytokine production. In particular, infected women have an increased concentration of tumor necrosis factor-alpha (TNF-alpha) in the intervillous circulation, and the concentration of TNF-alpha correlates with the density of *P. falciparum*-infected erythrocytes (Fried *et al*, 1998). Production of TNF-alpha plays a role in the pathogenesis of preterm birth and LBW. Individuals who carry the TNF 2 polymorphism in the promoter region of the TNF-alpha gene have heightened TNF-alpha production in response to

infection, which increases their risk of preterm delivery, severe infection, and cerebral malaria (Aidoo *et al*, 2001).

Low birth weight: In pregnancies complicated by malaria, both fetal growth restriction and preterm birth contribute to LBW. Distinguishing between the two is challenging in resource-poor settings where ultrasound dating of pregnancy is usually not available and maternal recall of the last menstrual period is poor. In some settings, malaria has been estimated to be responsible for up to 70%of fetal growth restriction and up to 25% of LBW. Similar birth weight reductions and attributable fractions of malaria-associated LBW have been reported from areas of stable and unstable malaria transmission.

Impaired fetal growth is correlated most strongly with evidence of parasites in the placenta and the corresponding inflammatory infiltrate. It has been hypothesized that malarial infection of the placenta leads to placental thickening and fibrin deposition, thereby decreasing placental transport of oxygen and nutrients. Doppler studies have demonstrated impaired uteroplacental blood flow (Dorman *et al*, 2002). The mean birth weight of infants born to mothers with no evidence of malarial placental infection is higher than for those newborns from infected placentas (2763 versus 2143g). A significant decrease (150g) in the average birth weight of infants of primigravidas with placental malaria has been reported, but this decrease was not significant (52g) in offspring of multigravidas (Kaushik *et al*, 1992). This is related to the observation that primigravidas are more likely to have placental malaria and heavier parasite loads and are less likely to have partial immunity. Support for this theory was illustrated in a study that showed affected multigravidas had higher plasma levels of anti-VAR2CSA IgG, gave birth to markedly heavier babies, and had a significantly lower risk of delivering LBW children than affected primigravid women in whom anti-VAR2CSA IgG levels were low and placental sequestration was increased. The level of adhesion of placental parasites to chondroitin sulfate receptors also was an important risk factor for LBW (Tuikue Ndam *et al*, 2004).

The assumption of causality is confounded by the frequent concomitant presence of anemia in primigravidas with placental malaria, which is independently associated with low birth weight. Indeed, when controlling for this confounding variable, the relationship between malaria and LBW becomes insignificant. However, since malaria is often the cause of the anemia, an association remains clinically compelling. A cohort study from Malawi including 2462 pregnant women found that an increasing number of *P. falciparum* infections during pregnancy increased the risks of both LBW and maternal anemia (Kalilani *et al*, 2010).In addition, second trimester infection increased the risk of LBW more than third trimester infection.

Perinatal mortality: A systematic review of 117 studies published between 1948 and 2002 found that perinatal mortality (PNM) and fetal mortality were higher in malaria endemic countries than in non-endemic ones (PNM 61.1/1000 versus 25.8/1000 and fetal mortality 40.1/1000 versus 20.0/1000). In a subset of nine of these studies that evaluated the correlation of fetal demise with placental malaria, presence of the latter significantly increased the risk for stillbirth, regardless of the number of prior pregnancies; OR 2.19, 95% CI 1.49-3.22 (van Geertruyden *et al*, 2004).

Congenital infection: All types of malaria can be transmitted congenitally, but congenital disease is most often associated with *P. vivax* and *P. falciparum*. Placental infection is a prerequisite for, but does not predict, congenital disease. Placental infection is more common than cord blood parasitemia, which is more common than parasites on the infant's peripheral smear. In a Central African study of women who did not receive antimalarial agents during pregnancy, the rates of placental infection, cord blood para-

sitemia, and infant's peripheral smear parasitemia were 74, 6, and 3.6%, respectively (Schwetz and Peel, 1934).

In immune mothers, risk of transplacental transmission of malaria was small (0.1 to 1.5% of infants had cord blood positive for parasites and clinical disease). The rate is somewhat higher in women with overt attacks during pregnancy; 1 to 4% risk of congenital infection (Subramanian *et al*, 1992). The low incidence of fetal infection despite the known high incidence of placental infection is presumably secondary to passive immunization by transplacental acquisition of maternal antibody. Transplacental passage of malarial antigens capable of priming the neonatal immune system was reported (Metenou *et al*, 2007). But, in semi-immune or non-immune mothers, transplacental antibody transfer may be deficient, and congenital infection was 7 to 10% (Darie and, Haba, 1992). Maternal antibody levels are lower and the risk of congenital infection is higher in women who move from endemic areas to malaria-free locales where they are no longer frequently exposed to the disease.

In endemic areas, it may be difficult to distinguish malaria acquired congenitally from that acquired as a newborn, particularly in infants of asymptomatic mothers. The onset of symptoms is usually at 2 to 8 weeks of age and includes poor feeding, fever, vomiting, diarrhea, and irritability. Anemia, thrombocytopenia, and hyper-bilirubinemia are common (Lee *et al*, 1996). Splenomegaly is more common than hepatomegaly. There were five cases of congenital malaria in the United States since 2000. In one case, the infected seven-month old infant had fever and anemia. Peripheral smears revealed *P. vivax* parasites. Investigation by the public health department found that the mother had emigrated from Guatemala two years earlier and had a history of malaria with relapse while residing in her native country (CDC, 2005). Prenatal evaluation did not include any question as a prior history of malaria, which may have contributed to delay in diagnosis.

Maternal mortality: WHO estimated that 10,000 maternal deaths each year are associated with malaria infection during pregnancy (Kochar *et al*, 1999). Malaria is a leading cause of maternal mortality in regions of unstable endemism where there are periodic epidemics among nonimmune patients. A review of all pregnancy-related maternal deaths in an urban Mozambique setting identified 239 maternal deaths (320 maternal deaths/100,000 live births). In this series, 15.5 percent of the deaths were directly attributable to malaria, and 19.7% of the women who died were parasitemic with *P. falciparum.* Over one-third of deaths occurred in primigravid adolescents, primarily associated with severe anemia. Autopsies on 161 women showed that 44 (27.3%) had evidence of splenic malarial infection (Looareesuwan *et al*, 1985). At the main referral hospital in Gambia estimated that, during malaria season, there was a 168% increase in maternal mortality rate and a three-fold increase in proportion of deaths due to anemia. Malaria accounted for up to 93 maternal deaths/100,000 live births (Anya, 2004).

Younger maternal age is associated with higher rates of anemia and poorer maternal and fetal outcome. Adolescents have a significantly higher rate of anemia and SGA neonates than adults (anemia: 83 & 53%, respectively; SGA: 50 vs. 27%, respectively). Adults in rural areas at earlier gestations are at higher risk of malarial infection and this infection is strongly associated with anemia (particularly during the dry season. Control measures against malaria were targeted at younger rural women early in pregnancy (Dicko *et al*, 2003).

Treatment: Pharmacokinetics of most antimalarials in pregnancy remains largely undefined. Chloroquine is well-tolerated and did not cause harmful in pregnant women. Quinine and quinidine can be used in pregnant women with *P. falciparum* infections at recommended doses, and do not lead to more adverse pregnancy outcomes compared with the malaria infection itself. At

high doses, quinine has a weak abortifacient effect, but such levels were not achieved with recommended therapeutic doses. Quinine was associated with maternal and fetal hypoglycemia (Taylor and White, 2004). Unfounded fears of toxicity and unjustified withholding of quinine led to many fatal maternal out-comes. Quinine is not contraindicated in pregnancy-associated malaria and should be used when needed. Glucose levels should be monitored.

Mefloquine use during pregnancy showed that pregnant women who took mefloquine for malaria did not have an increased risk of adverse pregnancy outcomes compared to the background rate in general population. The US, FDA categorized mefloquine as category B (CDC, 2013).

Amodiaquine is used in Africa, where multidrug resistant *P. falciparum* is common. A randomized trial showed that amodiaquine alone or in combination with sulfadoxine-pyrimethamine (SP) was significantly more effective than chloroquine or SP (Tagbor *et al*, 2006). Amodiaquine treatment was not associated with an increased risk of preterm birth, stillbirth, or congenital anomalies, but trial was too small to conclude that it was safe for the fetus. Amodiaquine is not used by clinicians in the United States or United Kingdom due to risk of agranulocytosis.

Data on the safety of artemisinin drugs in pregnancy, especially in the 1st trimester, are limited. WHO (2010) advised that artemisinin drugs be avoided in the first trimester unless the treatment is believed to be life saving for the mother and other antimalarial drugs are contraindicated, are likely to be ineffective (eg, for treatment of malaria acquired in regions with partial quinine resistance, such as Southeast Asia), or have previously failed. Among 773 women with 1st trimester pregnancies treated for malaria in Thailand, miscarriage risk was similar for women chloroquine quinine, or artesunate treated; 26, 27, & 31%, respectively (McGready *et al*, 2012). Also, congenital abnormalities risk in neonates was not statistically increased in treated pregnancies or different among the three drugs (0/262, 2/258, & 2/44, respectively vs. 1% in women with no malaria/no treatment). Experimentally animals given artemisinin compounds, fetal resorption early in gestation were reported (Boareto *et al*, 2008). This suggested depletion of embryonic erythroblasts may underlie artesunate-associated embryo toxicity. But, erythrocytes develop over a longer period of time in primates and therefore similar effects may not be observed in humans. Artemisinin derivatives was not harmful to fetus during pregnancy and acceptable for use (McGready *et al*, 2005)

Tetracycline, doxycycline, primaquine, & halofantrine are contraindicated in pregnancy (Nosten *et al*, 2006). Doxycycline is avoided during pregnancy because other tetracyclines have been associated with transient suppression of bone growth and with staining of developing teeth, but available data do not show teratogenic effects from doxycycline. Pregnancy is a contra-indication for primaquine therapy since it is not possible to assess G6PD status of a fetus in utero (Baird and Hoffman, 2004). Primaquine and tetracyclines must be avoided while breastfeeding (DeJulio, 2016). There are no human data on halofantrine exposure in pregnancy.

. **In Egypt**, the last malaria focus was in El-Fayoum Governorate which became free from transmission since 1998. But, there were few annual imported cases since the year 1998. The outbreak of *P. falciparum* and *P. vivax* in southern part at Aswan Governorate at May 2014 strongly supported the fact that malaria is reemerging (Kenawy, 2015). There are many factors contribute to the re-emergence of malaria, as infection of local Anopheline spp. by imported cases, continuous movement of populations between Aswan and Sudan as well as the influx of large population from Africa and Asia to Egypt for educational and religious purposes. Another risk factor was the environmental changes brought by water-sources development projects as Toshka (Shoukry

and Morsy, 2011) and El Salam canal (Hassan *et al*, 2003). El Bahnasawy *et al.* (2011) recorded *An. multicolor, An. Sergentii* and *An. algeriensis* in Toshka District, and added that the endemicity of Chloroquine resistant *P. falciparum* on the Egyptian-Sudanese border pave the way for malignant malaria transmission. El Bahnasawy *et al*, (2014) stated that travelling to different climates, cultures and environments abroad are exposed to tropical infectious diseases and health risks. They added that a rural health nursing has long been considered a subspecialty within public health nursing, albeit one that required the nurse to be a generalist, and applied an educational program for nursing staff on selected infectious disease disasters, which vectors are encountered at Egyptian Sudanese borders.

Imported cases can be traced to a known malarious area patient travelled (WHO, 2012). In Egypt, only *An. pharoensis* is mainly responsible for *P. vivax* transmission while, *An. sergenti* is responsible for *P. falcipaum* transmission in El Fayoum (Kenawy, 1988). *An. multicolor* is suspected vector (Gad *et al*, 1964; Zahar, 1974; Kenawy *et al*, 1986). *An. sergenti* is the oasis vector or desert malaria vector due to its distribution across the Saharan belt in northern Africa into the Middle East with ability to cope with extreme climate condition (Sinka *et al*, 2010). *An. sergenti* is an important vector in Al Fayoum (Farid, 1956; Morsy *et al*, 1995a,b). Also, el Said *et al*. (1986) in 2 neighboring villages in Al Faiyum Governorate monitored Anopheles populations over a year, to study factors causing differences in malaria prevalence. Both villages contained: *An. pharoensis, An. sergentii, An. multicolor* and *An. tenebrosus*. They reported that *An. pharoensis* and *An. sergentii* were the dominant species in Abheet with seasonal biting activity from May to December with a peak in November. They added that *An. pharoensis* and *An. sergentii* were incriminated vectors based upon their seasonal abundance and sporozoite positive specimens during the peak malaria season.

Bassiouny *et al*. (1999) in Al-Fayoum carried out a one-year longitudinal entomological study and found *A. sergenti* the commonest species followed by *A. multicolor* and the least was *A. pharoensis*. They concluded that the mean monthly temperature only and not relative humidity nor wind speed had a significant effect on larvae abundance, and that *P. falciparum* transmission season extended to more than eight months a year which could explain the persistence of malaria up there.

Zaher *et al*. (2007) reported 16 malaria cases in Almaza Military Fever Hospital. They were 9 imported pilgrims of *P. falciparum* and 7 cases acquired *P. vivax* locally (October 2003 to July 2004), and treated successfully by chloroquine. Fuller *et al*. (2012) stated that *A. arabiensis* is an opportunistic feeder and efficient vector of *P. falciparum* in Africa and might invade areas outside its normal range, as areas separated by expanses of barren desert. They added that while gaps between potential habitat patches remained large in the Green Nile scenario, the models reveal large areas of future habitat connectivity facilitating invasion of *A. arabiensis* from Sudan to Egypt.

El-Bahnasawy *et al.* (2010) in Military Fever Hospital reported 36 patients of whom 20 diagnosed as malarial patients, who were recruited from Peace Keeping Mission Forces in Africa and 16 cases presented with prolonged fever from different Egyptian areas. Wassim (2014) reported by secondary structure and sequence of ITS2-rDNA *An. pharoensis* proven vector all over Egypt, especially in the Delta, *An. sergenti* the primary vector in the Western Desert Oases, *An. multicolor* in Al-Fayoum, *An. stephensi* in the Red Sea Coast, and *An. superpictus* in Sinai.

Dahesh and Mostafa (2015) reevaluated malaria in Al-Fayoum reported that 14/2044 (0.68%) were passive male patients who attended to El-Fayoum Malaria Units after their return from Sudan. Microscopic exam-

ination showed that 9 (64.2%) out of passive cases were positive 3 of them were *P. falciparum* (33.3%) and 6 were *P. vivax* (66.7%) The species formulas of *P. falciparum* and *P. vivax* were 33.3% & 66.7% respectively. Concerning the density class, only one *vivax* case was of low density class while the other cases were of high density class. The areas with highest number of imported cases were Abu Shanap, Aboxa and Kafr Aboud. In Al Nazla *A. sergeni* and *A. multicolor* larvae were detected, but no case.

Saleh *et al*. (2016) in a mini-review of malaria mentioned that the majority of world's population-live in areas at risk of malaria transmission. Malaria is a serious *Anopheles*-borne disease that causes symptoms like the flu, as a high fever, chills, and muscle pain also, anemia, bloody stools, coma, convulsion, fever, headache, jaundice, nausea, sweating and vomiting. Symptoms tend to come and go in cycles. Apart from Anopheles vector, malaria could be transmitted nosocomial, blood transfusion or needle-stick injury. They added that some types of malaria may cause more serious damage problems to heart, lungs, kidneys, or brain, which can be deadly. The primary factors contributing to the resurgence of malaria are appearance of drug-resistant strains, insecticide-resistant strains of mosquito and lack of licensed malaria vaccines of proven efficacy. People can get malaria if they come into contact with infected blood as blood transfusion or needle-stick injury also nosocomial and congenital malaria was reported.

Kandeel *et al*. (2016) reported that in 2014, after several years of maintaining zero malaria indigenous cases, Egypt had an outbreak of *Plasmodium vivax*: 21 confirmed cases during May-June 2014. In response to the outbreak, the Ministry of Health and Population (MoHP) launched an emergency response through early detection and prompt treatment of cases, vector control, public education and intersectoral collaboration. Twenty cases (95.2%) were residents of El-Sheikh Mostafa village, Edfu district, Aswan governorate, southern Egypt. Cases, consequent to index case were identified by house-to-house visits. One *P. falciparum* case was also identified in the same village. Treatment of all infected cases was initiated following laboratory confirmation.

Comments

1- Nursing of patient malaria: a- Avoid treatment on empty stomach, b- Must give the first dose under a doctor's supervision, c- Must repeat dose in case of vomiting within 30 minutes. d- Must submit a report; no improvement after 48 hours or for deterioration of patient condition and transfer him ICU. e- Must examine patient for presence of concomitant disease(s), f- Keep in mind nosocomial malaria; transmission by needle-stick injury and can survive in heparin and blood culture. 2- Compared to non-pregnant women, pregnant/postpartum women are at increased risk of both acquiring malaria and developing more severe disease. One of the unique malaria features in pregnancy is the ability of *P. falciparum*-parasitized erythrocytes to sequester within the placenta intervillous. Placental infection and poor pregnancy outcome decrease with successive pregnancies for women who reside in endemic areas: non-immune pregnant women, especially nulliparas, are at high risk of adverse maternal-perinatal outcome than multiparous ones. Pregnancy-associated malaria is characterized by sequestration and multiplication of a distinct population of malarial parasites in placenta, which express a specific class of variant surface antigens (VSAs) that mediate adhesion of parasite-infected erythrocytes to chondroitin sulfate A (CSA) on syncytiotrophoblast lining intervillous space. Once parasites adhere to trophoblastic villi surface, they induce inflammatory leukocytes accumulation. 3- Clinical presentation varies according to the underlying endemicity of the region. Parasitemia peaks in the second trimester in both primigravidas and multigravidas, and the increased risk for pregnancy-associated malaria persists for 60 days postpartum. Anemia and hypoglycemia

are common maternal clinical manifestations. 4- Malaria must be considered in any febrile pregnant woman who traveled to or resided in a malarious region, even if briefly or only in transit. Peripheral blood smears are used for diagnosis, but may be negative in asymptomatic women with placental malaria. 5- Adverse perinatal outcomes associated with malaria include miscarriage, fetal growth restriction/ small for gestational age infant, preterm birth, low birth weight, perinatal death, and congenital infection. 6- Pregnant travelers should be advised to defer travel to areas where risk of malaria is high, if feasible, until after delivery. For pregnant women who cannot defer travel or residence in malarious regions, chemoprophylaxis and mosquito avoidance recommended (Grade 1A). For women in areas of high and medium malaria transmission, intermittent preventative therapy with Fansidar suggested (Grade 2A), twice after onset of quickening, and monthly in 3rd trimester in HIV positive mothers. Optimal antimalarial agent, timing, dose, and frequency of intermittent preventative therapy depend upon regional issues, such as drug resistance patterns. The drug choice for active malaria depends upon the drug resistance where malaria was acquired. In chloroquine-sensitive areas, chloroquine is first-line therapy (Grade 2C). With rapid increase of chloroquine-resistant strains worldwide, quinine combined with clindamycin, artemisin-combination therapy may be used in 2nd or 3rd trimester as an alternative.

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