OXFORD MATERNAL AND PERINATAL HEALTH INSTITUTE

Maternal Health Task Force

THE GLOBAL HEALTH NETWORK
Enabling research by sharing knowledge

Malaria in pregnancy

The Geneva Foundation for Medical Education and Research

On successful completion of this module you should be able to know:

- The burden of malaria and public health challenges posed by malaria.
- The transmission of malaria.
- Maternal malaria.
- Symptoms of malaria.
- Diagnosis of malaria.
- Treatment of malaria during pregnancy and postpartum.
- Prevention of malaria in the community and during pregnancy.

Introduction

Malaria is a life-threatening disease caused by the protozoan plasmodium that is transmitted to people through the bites of infected Anopheles mosquitoes, called “malaria vectors” which bite mainly between dusk and dawn

There are four protozoan species that cause malaria in humans:

Plasmodium falciparum
Plasmodium vivax
Plasmodium malariae
Plasmodium ovale.

Plasmodium falciparum and Plasmodium vivax are the most common.
Plasmodium falciparum is the most deadly.

Some of human cases of malaria have also occurred with Plasmodium knowlesi in forested areas of South-East Asia. P. knowlesi causes malaria in monkeys.

World Health Organization. Malaria. Fact sheet N° 94. WHO. 2014.

The burden of malaria in pregnancy

Globally, an estimated 3.2 billion people in 97 countries are at risk of being infected with malaria and developing the disease, of which 1.2 billion are at high risk (WHO 2014).

Malaria primarily affects low and lower income countries and within endemic countries, the poorest and most marginalized communities. Most of malaria cases and deaths occur in Sub-Saharan Africa, but Asia, Latin America and to a lesser extent the Middle East and part of Europe are also affected. Approximately 25 million pregnant women are at risk of infection by P. falciparum annually in Africa (WHO 2014).

World Health Organization. World Malaria Report 2014. WHO. 2014.

The burden of malaria in pregnancy

A recent review of studies in East and Southern Africa found the following prevalence of malaria in women attending antenatal clinics: 32 % for peripheral malaria and 38.2% for placental malaria. (Chico RM 2012)

In areas of stable transmission in Sub-Saharan Africa, 1 in every 4 pregnant women has evidence of peripheral or placental infection with malaria parasites (Desai 2007)

In low transmission areas of the African continent, peripheral and placental parasitaemia have been shown to be 13.7% and 6.7% respectively, while in low transmission areas outside Africa, placental infection is slightly higher (9.6%) than peripheral (6.2%). (Desai 2007)

Placental infection seems to persist outside seasons of high infection. (Desai 2007)

Chico RM, Mayaud P, Ariti C, Mabey D, Ronsmans C, Chandramohan D. Prevalence of malaria and sexually transmitted and reproductive tract infections in pregnancy in sub-Saharan Africa: a systematic review. JAMA. 2012 May 16;307(19):2079–86
Desai M, ter Kuile FO, Nosten F, McGready R, Asamoa K, Brabin B, Newman RD. Epidemiology and burden of malaria in pregnancy. Lancet Infect Dis. 2007 Feb;7(2):93–104.

Complications of malaria during pregnancy

Parity and age are important determinants of risk of infection among pregnant women. Primigravidae and younger maternal age (adolescents) have poorer immunity to malaria compared to their older and multiparous counterparts. The risk of infection is also highest during the second trimester.

In Africa, a quarter of cases of **severe anemia** in pregnancy are attributable to malaria. The percentage of maternal deaths attributed directly or indirectly to malaria is approximately 10% in both hospital studies (0.5% to 23.0%) and community-based studies (2.9% to 17.6%). This does not differ much from estimates in low-transmission regions outside Africa (0.6 to 12.5%).

Desai M, ter Kuile FO, Nosten F, McGready R, Asamoa K, Brabin B, Newman RD. Epidemiology and burden of malaria in pregnancy. Lancet Infect Dis. 2007 Feb;7(2):93–104.

Complications of malaria during pregnancy

Placental malaria doubles the risk of **low birth weight.** Compared to multiparous women, primigravid women have a two- to seven times the risk of low birth weight deliveries. Low birth weight in itself is a major risk factor for neonatal mortality but Malaria-induced low birthweight is estimated to be responsible for 3 to 17 deaths per 1000 livebirths.

It is also estimated that 11.4% of neonatal deaths and 5.7% of all infant deaths in malaria-endemic areas of Africa may be caused by malaria in pregnancy-associated low birthweight.

Malaria may lead to low birthweight through causation of **fetal growth restriction** or **preterm delivery**. In high-transmission areas, malaria-related fetal growth restriction may be twice as high as malaria-related preterm delivery. Contrastingly, in low-transmission settings, the predominant cause of low birthweight is preterm delivery.

Desai M, ter Kuile FO, Nosten F, McGready R, Asamoa K, Brabin B, Newman RD. Epidemiology and burden of malaria in pregnancy. Lancet Infect Dis. 2007 Feb;7(2):93–104.

Consequences of malaria in pregnancy

Stillbirths, spontaneous abortions, fetal anaemia may also be consequences of maternal parasitaemia.

Placental malaria diminishes fetal cellular and antibody response to P. falciparum making the infant susceptible to malaria.

Transplacental antibody transfer is also compromised, increasing susceptibility to other pathogens such as tetanus and Streptococcus pneumonia.

HIV increases the risk of placental malaria infection, high density parasitemia, febrile illness and worsens severe anaemia and low birthweight.

HIV also eliminates the gravidity specific pattern of malaria in areas with stable transmission from paucigravid to all pregnant women.

Desai M, ter Kuile FO, Nosten F, McGready R, Asamoa K, Brabin B, Newman RD. Epidemiology and burden of malaria in pregnancy. Lancet Infect Dis. 2007 Feb;7(2):93–104.

Public health challenges posed by malaria

All 4 plasmodium species can infect pregnant women but Plasmodium falciparum and Plasmodium vivax have been widely studied. Plasmodium falciparum is the most prevalent in African continent, which is responsible for most deaths from malaria.(Desai 2007)

Plasmodium vivax has wider geographical distribution (can develop in lower temperatures, survive in high altitudes, has a dormant liver stage known as hypnozoite). (WHO 2014)

Plasmodium vivax is more common in many areas outside Africa, where they are more prevalent than P. falciparum. (WHO 2014)

Compared with P. falciparum, the effect of P. vivax on birthweight may be more pronounced in multigravidae despite a higher incidence of P. vivax infection in primigravidae. (Desai 2007)

.

Desai M, ter Kuile FO, Nosten F, McGready R, Asamoa K, Brabin B, Newman RD. Epidemiology and burden of malaria in pregnancy. Lancet Infect Dis. 2007 Feb;7(2):93–104.
World Health Organization. World Malaria Report 2014. WHO. 2014.

Transmission

Malaria is transmitted exclusively through the bites of female Anopheles mosquitoes. The intensity of transmission depends on factors related to the parasite, the vector, the human host, and the environment.

There are 20 different species of Anopheles. They all breed in water with different preference, for example some prefer shallow collection of fresh water (rice fields, hoof prints).

Transmission is more intense in places where the mosquito's lifespan is longer (giving the parasite the time to complete its development inside the mosquito) and where the vector prefers to bite humans rather than other animals. These characteristics are seen in African vector species which explains the high rate (90%) of malaria deaths in Africa.

World Health Organization. Malaria. Fact sheet N° 94. WHO. 2014.

Transmission

Endemicity of malaria refers to the intensity of malaria transmission in a community or region that may be classified as follows:

Stable malaria areas, where transmission occurs all year round, though there may be seasonal variations. Older children and adults in the community have partial immunity which protects them from severe forms of malaria. Young children are susceptible to severe malaria.

Unstable malaria areas, where intermittent transmission may be annual, biannual or variable.

World Health Organization. Training module on malaria control: Case management. WHO. 2012.

Transmission

Climatic changes such as rainfall patterns, temperature and humidity may affect the number and survival of mosquitoes. In many places the transmission is highest during and just after the rainy season.

Malaria epidemics can occur when the climate changes and other conditions intensify transmission, particularly in areas where people have little or no immunity to malaria.

The epidemics can also occur when people with low immunity move to areas with intense malaria transmission (for example those who move to find work or refugees).

Human immunity is also an important factor in areas with intense or moderate transmission. Partial immunity is developed over years of exposure, but never provides complete protection. It however reduces the risk of severe disease. This explains the high mortality rate due to malaria among young children in Africa.

.

World Health Organization. Malaria. Fact sheet N° 94. WHO. 2014.

Maternal malaria

In areas of high and moderate (stable) malaria transmission, most malaria infections are asymptomatic, because adult women have developed immunity. (WHO 2007)

But during pregnancy, these infections can contribute to the development of severe anaemia in the mother, increasing the risk of maternal mortality and morbidity. Moreover it affects the health of the foetus during the second half of pregnancy. (WHO 2007)

Malarial infection of the placenta, and maternal anaemia due to malaria, contribute to low birth weight and preterm birth as well as impaired development of the child. (WHO 2007)

Despite the high prevalence of placental infection, congenital transmission of malaria is rare. (WHO 2012)

Stable transmission predominates in Sub-Saharan Africa. In these areas of high or moderate (stable) malaria transmission, the negative effects are particularly apparent in the first and second pregnancies exposed to malaria. (WHO 2007)

World Health Organization. Training module on malaria control: Case management. WHO. 2012.
World Health Organization, Department of Making Pregnancy Safer and Department of Reproductive Health and Research. Standards for maternal and neonatal care. WHO. 2007.

Maternal malaria

In areas of epidemic and low (unstable) malaria transmission, adult women have no significant level of immunity and will develop clinical illness if they have parasitaemia.

Pregnant women with no immunity are at risk of dying from severe malarial disease and/or experiencing spontaneous abortion, preterm delivery, low birth weight or stillbirth.

The prevalence and intensity of malarial infection during pregnancy is higher in women who are HIV-infected.

All pregnant women are at similar risk for malarial infection, irrespective of parity.

Abortion is common in the first trimester, and prematurity is common in the third trimester.

Other consequences during pregnancy commonly associated with P. falciparum infection include: hypoglycaemia, hyperpyrexia, severe haemolytic anaemia and pulmonary oedema.

World Health Organization, Department of Making Pregnancy Safer and Department of Reproductive Health and Research. Standards for maternal and neonatal care. WHO. 2007.

Symptoms

Malaria is an acute febrile illness. The incubation period is between 10-15 days after the infective mosquito bite. (WHO 2014)

The first symptoms are fever, headache, chills and vomiting that are not specific to malaria. If not treated within 24 hours, malaria due to P. falciparum can progress to severe illness that can lead to death. (WHO 2014)

Children with severe malaria can develop one or more of the following symptoms: severe anaemia, respiratory distress due to metabolic acidosis, or cerebral malaria. (WHO 2014)

In adults, multi-organ involvement is frequent. (WHO 2014)

In endemic area because of partial immunity development, asymptomatic infection can occur (WHO 2010).

Clinical relapse may occur with P. vivax and P. ovale, weeks to months after the first infection. This is because of dormant liver forms known as hypnozoites (absent in P. falciparum and P. malariae), which require special treatment.(WHO 2014)

World Health Organization. Guidelines for the treatment of malaria. Second edition. WHO. 2010.
World Health Organization. Malaria. Fact sheet N° 94. WHO. 2014.

Diagnosis

Rapid diagnostics

WHO recommends parasitological confirmation by microscopy or by Rapid Diagnostic Test (RDT) for all suspected cases of malaria before treatment is started. (WHO 2010)

Rapid malaria tests require minimal skill to perform and interpret. The rapid antigen detection test (RDTs) detects parasite proteins in finger-prick blood, but its sensitivity falls with a low level of parasitemia.(PAHO 2008)

Traditional diagnostics

Thick and thin peripheral blood smears, stained with Giemsa stain, remain the gold standard for routine clinical diagnosis that permits the identification of species and quantification of parasites. (PAHO 2008)

Malaria should not be excluded until at least 3 negative blood smears are obtained within 48 hours.(PAHO 2008)

Diagnosis should be promoted in pregnant women in endemic areas in order to ensure accurate diagnosis of malaria and to reduce unnecessary use of antimalarial in pregnancy.(PAHO 2008)

Pan American Health Organization, March of Dimes, Latin American Centre for Perinatology Women and Reproductive Health. Perinatal infections transmitted by the mother to her infant, education material for health personnel. Clap Scientific Publication. 2008.
World Health Organization. Guidelines for the treatment of malaria. Second edition. WHO. 2010.

Treatment

Pregnant women with symptomatic acute malaria are a high-risk group, and they must promptly receive effective antimalarial treatment.

First trimester (treatment of uncomplicated Falciparum malaria)

Despite a limited number of prospective studies, antimalarial medicines considered safe in the first trimester of pregnancy are quinine, chloroquine, clindamycin and proguanil.

Quinine plus clindamycin to be given for 7 days (artesunate plus clindamycin for 7 days is indicated if this treatment fails).
An ACT (artemisinin-based combination therapy) is indicated only if this is the only treatment immediately available, or if treatment with 7-day quinine plus clindamycin fails, or if there is uncertainty about patient compliance with a 7-day treatment.

Second and third trimesters

ACT known to be effective in the country/region or artesunate plus clindamycin for 7 days
or
Quinine plus clindamycin for 7 days. If clindamycin is unavailable or unaffordable, then the monotherapy should be given.

World Health Organization. Guidelines for the treatment of malaria. Second edition. WHO. 2010.

Treatment of severe malaria in pregnancy

WHO definition of severe malaria

Clinical features:	**Laboratory findings:**
• impaired consciousness or unrousable coma • prostration, i.e. generalized weakness so that the patient is unable to walk or sit up without assistance • failure to feed • multiple convulsions – more than two episodes in 24 h • deep breathing, respiratory distress (acidotic breathing) • circulatory collapse or shock, systolic blood pressure < 70 mm Hg in adults and < 50 mm Hg in children • clinical jaundice plus evidence of other vital organ dysfunction • haemoglobinuria • abnormal spontaneous bleeding • pulmonary oedema (radiological)	• hypoglycaemia (blood glucose < 2.2 mmol/l or < 40 mg/dl) • metabolic acidosis (plasma bicarbonate < 15 mmol/l) • severe normocytic anaemia (Hb < 5 g/dl, packed cell volume < 15%) • haemoglobinuria • hyperparasitaemia (> 2%/100 000/µl in low intensity transmission areas or > 5% or 250 000/µl in areas of high stable malaria transmission intensity) • hyperlactataemia (lactate > 5 mmol/l) • renal impairment (serum creatinine > 265 µmol/l).

World Health Organization. Guidelines for the treatment of malaria. Second edition. WHO. 2010.

Treatment of severe malaria in pregnancy

In treatment of severe malaria, saving the mother's life is the primary objective. Intravenous artesunate reduces more deaths related to severe malaria than intravenous quinine. WHO therefore recommends treatment of severe malaria in pregnancy with intravenous artesunate in the second and third trimester.

World Health Organization recommendations for the treatment of severe malaria in pregnancy

	First trimester	Second to third trimester
P. falciparum	Either IV artesunate or quinine can be used	IV artesunate should be used in preference to quinine
P. vivax	Either IV artesunate or quinine Suppressive prophylaxis with chloroquine until delivery Post-delivery, women should receive radical treatment with primaquine	IV artesunate should be used in preference to quinine Suppressive prophylaxis with chloroquine until delivery Post-delivery women should receive radical treatment with primaquine
All severe malaria	Treatment must not be delayed. If only one of the drugs artesunate, artemether, or quinine is available, it should be administered immediately	

Kovacs SD, Rijken MJ, Stergachis A. Treating severe malaria in pregnancy: a review of the evidence. Drug Saf. 2015 Feb;38(2):165-81.

Treatment

Lactating mothers (recommendation for uncomplicated falciparum malaria)

Lactating women should receive the recommended antimalarial treatment (including ACTs), except for primaquine and tetracycline.

Infant and young children

Careful clinical monitoring is required for children as their condition may deteriorate rapidly.

ACTs should be used with appropriate dosing as first-line treatment for infants and young children with uncomplicated malaria.

Referral to a health centre or hospital for young children who cannot swallow antimalarial medicines.

Use of rectal artesunate if the time to reach the referral centre is more than 6 hours.

World Health Organization. Guidelines for the treatment of malaria. Second edition. WHO. 2010.

Prevention

Vector (mosquito) control is the main way to reduce malaria transmission at community level.

At the individual level, protection against mosquito bites is the main preventive measure.

There are two forms of vector control:

Insecticide-treated mosquitos net (ITNs)

Long-lasting insecticide nets (LLINs) are the preferred form of ITNs. It offers effective protection against malaria. WHO recommends that all at-risk persons, particularly pregnant women and infants, sleep under ITNs during the night.

Indoor spraying with residual insecticides

Indoor residual spraying (IRS) refers to the spraying of all stable surfaces inside human habitations using an insecticide with residual action. IRS is a powerful way to rapidly reduce malaria transmission. It is effective for 3-6 months depending on the type of insecticide used. DDT can be effective for 9-12 months. New forms of insecticides are under development.

World Health Organization. Malaria. Fact sheet N° 94. WHO. 2014.

Chemoprevention

WHO recommends intermittent preventive treatment (ITP) with sulfadoxine-pyrimethamine for pregnant women living in high transmission areas at each antenatal visit after the first trimester.

Three doses of sulfadoxine-pyrimethamine is also recommended alongside routine vaccination of infants living in high-transmission areas of Africa.

Vaccination against malaria

There are **currently** no **licensed** vaccines against malaria or any other human parasite.

World Health Organization. Malaria. Fact sheet N° 94. WHO. 2014.

Insecticide resistance

In recent years mosquito resistance to pyrethroids (the insecticides currently recommended for ITNs or LLINs) has emerged in many countries (particularly in India and Sub-Saharan Africa) with a high prevalence of malaria.

This resistance has rarely been associated with decreased efficacy of IRS and LLINs, which remain highly effective tools.

The development of alternative insecticide is a priority and several promising products are in the pipeline.

World Health Organization. Malaria. Fact sheet N° 94. WHO. 2014.

References

- Chico RM, Mayaud P, Ariti C, Mabey D, Ronsmans C, Chandramohan D. Prevalence of malaria and sexually transmitted and reproductive tract infections in pregnancy in sub-Saharan Africa: a systematic review. JAMA. 2012 May 16;307(19):2079–86. Available from: http://dx.doi.org/10.1001/jama.2012.3428
- Desai M, ter Kuile FO, Nosten F, McGready R, Asamoa K, Brabin B, Newman RD. Epidemiology and burden of malaria in pregnancy. Lancet Infect Dis. 2007 Feb;7(2):93–104.
- Kovacs SD, Rijken MJ, Stergachis A. Treating severe malaria in pregnancy: a review of the evidence. Drug Saf. 2015 Feb;38(2):165-81. http://dx.doi.org/10.1007/s40264-014-0261-9
- Pan American Health Organization, March of Dimes, Latin American Centre for Perinatology Women and Reproductive Health. Perinatal infections transmitted by the mother to her infant, education material for health personnel. Clap Scientific Publication. 2008. Available from: http://www.clap.ops-oms.org/web_2005/BOLETINES%20Y%20NOVEDADES/EDICIONES%20DEL%20CLAP/CLAP%201567-02.pdf
- World Health Organization, Department of Making Pregnancy Safer and Department of Reproductive Health and Research. Standards for maternal and neonatal care. WHO. 2007. Available from: http://www.who.int/reproductivehealth/publications/maternal_perinatal_health/a91272/en/
- World Health Organization. Guidelines for the treatment of malaria. Second edition. WHO. 2010. Available from: http://www.who.int/malaria/publications/atoz/9789241547925/en/
- World Health Organization. Training module on malaria control: Case management. WHO. 2012. Available from: http://apps.who.int/iris/bitstream/10665/78070/1/9789241503976_eng.pdf
- World Health Organization. Training module on malaria control: Case management. WHO. 2013. Available from: http://www.who.int/malaria/publications/atoz/9789241503976/en/
- World Health Organization. World Malaria Report 2014. WHO. 2014. Available from: http://www.who.int/malaria/publications/world_malaria_report_2014/en/
- World Health Organization. Malaria. Fact sheet N° 94. WHO. 2014. Available from: http://www.who.int/mediacentre/factsheets/fs094/en/