Malaria in Pregnancy

See also separate Malaria article.

This is a notifiable disease in the UK. See the Notifiable Diseases article for more detail.

Pregnant women are more susceptible than the general population to malaria: they are more likely to become infected, have a recurrence, develop severe complications and to die from the disease. Malaria contributes very significantly to maternal and fetal mortality (see 'Epidemiology', below).

Regardless of symptoms, the presence of plasmodial parasites in a pregnant woman’s body will have a negative impact on her own health and that of her fetus. Restricting treatment to symptomatic pregnant women is an inadequate strategy to reduce the morbidity and mortality associated with malaria.[1] Subclinical infection is common in areas where natural immunity is high (eg, sub-Saharan Africa), whereas symptomatic cases are more common in areas with low immunity (eg, the Asia-Pacific region, and South Africa).[2]

Malaria in pregnancy is different to the disease in the non-pregnant state. The severity of malaria in pregnancy is thought to be due to general impaired immunity plus a diminution of acquired immunity to malaria in endemic areas. Placental malaria occurs where Plasmodium falciparum-infected erythrocytes accumulate in the intervillous space of the placenta but may be rare or absent in the peripheral circulation. Diagnosis by light microscopy of blood films is more difficult.[2]

Treatment can be more difficult due to restrictions on anti-malarial agents. Many are unlicensed in pregnancy, due to lack of clinical trials involving this important population, for fear of damaging the fetus. There is frequently a lack of good post-marketing surveillance where these drugs are routinely used in pregnancy. However, data support the safety of artemisinin-combined drugs (ACDs) and their advent has provided a useful therapeutic option. With regard to chemoprophylaxis, recent World Health Organization (WHO) recommendations and a large meta-analysis support the use of intermittent prophylactic treatment during the second and third trimester.[3] Dihydroartemisinin-piperaquine is being evaluated as an option to replace sulfadoxine-pyrimethamine for intermittent preventive treatment.[4]

Concurrent HIV infection worsens this scenario significantly: HIV increases susceptibility to malarial infection and the presence of malaria causes an increase in HIV viral load.[5]

Epidemiology

Producing good estimates of the global burden of malaria is difficult due to poor numerator (number of women affected by malaria in pregnancy) and denominator (population at risk) data. However:

- Globally, 125 million women are at risk of malaria every year.
- In sub-Saharan Africa, the area most burdened by malaria, the disease is thought to cause as many as 10,000 cases of malaria-related deaths in pregnancy, mainly due to severe maternal anaemia.
- Between 75,000 and 200,000 infants (children under the age of 12 months) are estimated to die annually as a result of malarial infection during pregnancy.
- Approximately 11% (100,000) of neonatal deaths are due to low birth weight resulting from P. falciparum infections in pregnancy.
- Use of intermittent preventative treatment in pregnancy and using nets resulted in an estimated 94,000 newborn deaths being averted between 2009 and 2012 in 25 African countries. If these interventions had been applied to 80% of the at-risk population, it is estimated that 300,000 deaths could have been prevented.
- Preventing malaria in pregnant women:
  - Reduces severe maternal anaemia by 38%.
  - Reduces low birth weight by 43%.
  - Reduces perinatal mortality by 27%.

- Scaling up coverage and access to preventative measures is clearly the way forward.
- A review of studies, carried out in sub-Saharan Africa between 2000 and 2011, reports that prevalence of malaria in pregnant women attending antenatal clinics was 29.5% in East and Southern Africa and 35.1% in West and Central Africa.[2]
- Malaria in the Asia-Pacific region requires special consideration and it cannot be assumed that data deriving from Africa will be relevant to this area. Further studies of mortality and morbidity in pregnant women resident in this region are required. The high incidence of Plasmodium vivax and the spread of drug-resistant P. falciparum are proving challenging.[7]

Preventing and treating malaria in pregnancy can be a key intervention to improving maternal, fetal and child health globally and are linked to three of the Millennium Development Goals (MDG-3 Maternal Health, MDG-4 Child Health, MDG-5 Combating Infectious Disease).[8]
Risk factors\textsuperscript{[2]}
- Primigravidae are at highest risk of malarial infection and serious complications. Pregnant women with one previous birth are also at higher risk.
- The effect of gravida status on complication risk is negated by concurrent HIV infection.\textsuperscript{[9]}
- Younger maternal age (particularly adolescence) carries a higher risk of infection and adverse effects.
- Second trimester carries the highest risk of infection.
- Some studies suggest the increased risk disperses quickly after delivery, others that the first two months postpartum continue to carry an increased risk of infection.

Presentation\textsuperscript{[10]}
Atypical presentation of malaria is common in pregnancy, particularly in the second and third trimesters, so a high index of suspicion should be maintained in susceptible pregnant mothers.

- A travel history should be taken in any pregnant woman with unexplained fever or anaemia.
- Fever may be absent, low-grade or very high and may not behave in the classical quartian/tertian fashion.
- Other symptoms may include cough, malaise, headache, myalgia and diarrhoea.
- Anaemia is a common feature and may be the only clue to the illness in mature primigravidae living in endemic areas.
- Splenomegaly may occur but tends to regress in the second half of pregnancy.
- Complications (see 'Complications', below), along with features of cerebral malaria (impaired consciousness, seizures) and jaundice can be the presenting features of an acute, severe illness.

Differential diagnosis
As for malaria in general, plus:
- Rhesus incompatibility
- Cytomegalovirus infection
- Herpes infection
- Rubella
- Toxoplasmosis
- Syphilis

Investigations\textsuperscript{[11, 12, 13]}
Diagnosis of falciparum malaria in pregnancy can be particularly difficult due to placental sequestration of parasites - seek expert help.

- Thick and thin films for malarial parasites should be examined and the degree of parasitaemia determined. Parasites may not be detectable on peripheral blood films.
- FBC, U&Es, blood glucose and LFTs including bilirubin levels should also be checked.
- CXR may reveal cases of pulmonary oedema.
Polymerase chain reaction tests are available.
Concerns have been raised about rapid diagnostic tests in pregnancy as low levels of parasitaemia can occur. However, modern tests are more sensitive and studies suggest they are useful and affordable in the antenatal period.\(^{14,15}\)

**Management**

If malaria is suspected in a pregnant patient, refer immediately to secondary/tertiary care where infectious disease, obstetric and neonatal care is on hand, together with intensive care facilities, if needed.

- Drugs should be used at adequate doses and according to clinical condition and local resistance patterns:\(^{10,13,16}\)
  - Chloroquine and quinine can be used safely in any part of the pregnancy but resistance is common.
  - Studies of pregnant women with malaria in Thailand found that artemisinin-combination therapy (treatment in which artemisinin is combined with other antimalarials) was safe in the first, second and third trimesters and provided fewer treatment failures than other commonly used regimes.\(^{17,18}\)
  - Mefloquine and pyrimethamine/sulfadoxine are safe in the second and third trimesters.
  - A Gambian study recommended quinine plus clindamycin for seven days as the first-line treatment for uncomplicated malaria, and artemunate plus clindamycin for seven days if this treatment fails. Treatment, however, should not be delayed and should be started with the most readily available drug.\(^{[2]}\)
  - Primaquine, tetracycline, doxycycline and halofantrine are contra-indicated. Current UK treatment guidelines suggest the use of quinine and clindamycin in place of doxycycline.\(^{[19]}\)

- Recurrence of malaria is common in pregnancy and resistance frequently reduces the usefulness of antimalarials. The WHO recommended a regimen of seven days of artemunate (2 mg/kg/day or 100 mg daily for seven days) and clindamycin (450 mg three times daily for seven days). Atovaquone-proguanil-artemunate and dihydroartemisinin-piperaquine have been used in pregnant women with multiple recurrent infections to good effect in the UK.
- Fluid replacement needs to be very carefully monitored to prevent pulmonary oedema.
- If anaemia requires transfusion (Hb <7-8 g/dL) then packed cells are preferred to avoid fluid overload.
- The complications of malaria should be carefully and aggressively managed.
- Involve the obstetric team early in case of premature labour.

**Complications**

**Maternal complications**

In endemic/high-transmission areas for malaria, baseline immunity to malaria is decreased by pregnancy. Sufferers are more likely to experience severe anaemia. A non-immune pregnant woman (or one with low immunity from a low-transmission area) is likely to develop a severe form of the illness and complications.

- Anaemia tends to occur between 16-29 weeks - due to haemolysis of parasitised cells and increased demands of pregnancy ± folate/iron deficiency. In sub-Saharan Africa 23 million pregnant women are exposed to malarial infection annually and approximately 400,000 pregnant women develop moderate or severe anaemia.\(^{[23]}\) Severe anaemia eliminates any physiological reserve to cope with haemorrhage, making women more likely to die in childbirth.
- An Indian study reported that pregnant women with malaria are at increased risk of hypoglycaemia, cerebral malaria, acute kidney injury, hepatic failure and hypotension.\(^{[21]}\)
- Acute pulmonary oedema occurs much more commonly in pregnant women and may be the presenting feature. It carries a high mortality and is typically seen in the second and third trimesters.
- Disseminated intravascular coagulation can occur and carries a high mortality risk.

**Fetal complications**

Both *P. falciparum* and *P. vivax* can cause complications that affect the fetus. Fetal mortality is estimated at 15% for *P. vivax* and around 30% for *P. falciparum*. Common problems for the fetus include:\(^{[21]}\)

- Spontaneous abortion.
- Premature delivery.
- Stillbirth.
- Intrauterine growth restriction.
- Low birth weight - common.
- Intrauterine fetal death.

Maternal infection can also be associated with missed abortion, preterm labour, intrauterine growth restriction and intrauterine fetal death.\(^{[22]}\)

Neonatal and infant problems related to malaria include:

- Increased mortality rates.
- Congenital malaria.
- Anaemia.
- Increased rates of other infections.
- Undernutrition.
Congenital malaria may occur by transplacental spread but has always been considered rare in children born in endemic areas and is more common in offspring of non-immune mothers with malaria. Treatment of the mother may not eradicate parasites from the fetus, due to lower drug levels. Congenital malaria tends to present with fever, irritability, feeding difficulties, hepatosplenomegaly, anemia. It is most commonly due to infection with *Plasmodium falciparum* and can be diagnosed by blood films of cord or heel-prick blood within a week after birth. Always consider congenital malaria in the differential diagnosis of a febrile infant in the first three months of life of mothers who have travelled to or immigrated from malarial areas. [23]

Longer-term developmental problems related specifically to malaria during pregnancy are harder to unpick from those related to low birth weight. It is thought that there may be long-term consequences such as short stature and an increased risk of metabolic disease in adulthood. [24]

**Prognosis**

It is difficult to estimate exact morbidity and mortality rates, due to the heterogeneity of severity but with non-immune patients there is a high risk of acute, severe complications and death if the illness is not diagnosed and treated quickly.

**Prevention**

See separate Malaria Prophylaxis article.

**Further reading & references**

- [Malaria and Pregnancy](http://www.malaria.org.uk)
- [Malaria prophylaxis](http://www.nice.org.uk) NICE CKS, February 2012 (UK access only)
- The Millennium Development Goals Report, 2015; United Nations
- Laloo D et al; UK malaria treatment guidelines; British Infection Society, 2007
- Malaria Reference Laboratory/WBSITE; Public Health England
- The diagnosis and treatment of malaria in pregnancy. Green-top Guideline No. 54B; Royal College of Obstetricians and Gynaecologists (2010)
- Guidelines for the treatment of malaria; World Health Organization, 2015
- Malaria guidance, data and analysis; Public Health England
- Intermittent Preventive Treatment of Malaria for Pregnant Women (IPTp); Centers for Disease Control and Prevention, 2015

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