Royal College of Obstetricians & Gynaecologists

The diagnosis and treatment of malaria in pregnancy

Green–top Guideline No. 54b

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This is the first edition of this guideline.

1. Purpose and scope

The aim of this guideline is to provide clinicians with up-to-date, evidence-based information on the diagnosis and treatment of malaria in pregnancy, in situations that are likely to be encountered in UK medical practice. For initial rapid assessment and management, see Appendix 1.

2. Background

Malaria is the most important parasitic infection in humans and is the tropical disease most commonly imported into the UK, with approximately 1500 cases reported each year and rising, apart from 2008.[1] Approximately 75% of cases are caused by *Plasmodium falciparum* and there is an average of 5–15 deaths a year (mortality rate approximately 0.5–1.0%).[1] Immigrants and second- and third-generation relatives returning home assuming they are immune from malaria are by far the highest risk group. They may take no prophylaxis or may be deterred by the cost, may not adhere to advice, may receive poor advice or some combination of these factors.[2,3] Prevention of malaria is covered in Green-top Guideline No. 54A.[4]

In the UK, the prevalence of imported malaria in pregnancy is unknown. A review of the burden of malaria in pregnancy estimated that about one in four women in sub-Saharan Africa in areas of stable transmission has malaria at the time of birth.[5] Online and telephone enquiries with the Health Protection Agency (www.hpa.org.uk) and Eurosurveillance archives (www.eurosurveillance.org) and reviews of published reports failed to uncover a report of maternal death from malaria in UK for the past 10 years.[6] Maternal deaths from malaria are unlikely to be reported when they occur in endemic countries.

Malaria in pregnancy is detrimental to the woman and her fetus and collective data demonstrate that the risk of adverse effects from untreated malaria in pregnancy outweigh those of treatment.[5,6–10] The protozoan parasites *P. falciparum*, *P. vivax*, *P. malariae* and *P. ovale* (extremely rarely *P. knowlesi*),[11] are transmitted by the bite of a sporozoite-bearing female anopheline mosquito. After a period of pre-erythrocytic development in the liver, the blood stage infection, which causes the disease, begins. Parasitic invasion of the erythrocyte consumes haemoglobin and alters the red cell membrane. This allows *P. falciparum* infected erythrocytes to cytoadhere (or stick) inside the small blood vessels of brain, kidneys and other affected organs. Cytoadherence and rosetting (adherence of uninfected red blood cells) interfere with microcirculatory flow and metabolism of vital organs. The hallmark of falciparum malaria in pregnancy is parasites sequestered in the placenta. Sequestered parasites evade host defence mechanisms: splenic processing and filtration. Sequestration is not known to occur in the benign malarias due to *P. vivax*, *P. ovale* and *P. malariae*. In pregnancy, the adverse effects of malaria infection result from:

- the systemic infection, comparable to the effects of any severe febrile illness in pregnancy: maternal and fetal mortality, miscarriage, stillbirth and premature birth
- the parasitisation itself: fetal growth restriction and low birth weight, maternal and fetal anaemia, interaction with HIV, susceptibility of the infant to malaria.

P. falciparum causes greater morbidity (maternal and fetal, principally low birth weight and anaemia) and mortality than non-falciparum infections[5,7–10] but there is mounting evidence that *P. vivax* is not as benign as had been previously thought.[12–14] Response to antimalarial treatment is multifactorial but is associated with the degree of prior immunity acquired from repeated exposures in childhood and the background level of drug resistance. The higher the transmission of malaria, the greater the degree of prior immunity and the more likely the woman will respond favourably to a drug treatment.[15,16]

3. Identification and assessment of the evidence

A literature search was performed using Medline (November 2009). Keywords used were 'severe malaria', 'uncomplicated malaria', 'burden malaria', 'congenital malaria', 'anaemia malaria', 'pregnancy', 'treatment', 'antimalarials' 'artesunate', 'artemether', 'artemether-lumefantrine', 'atovaquone-proguanil', 'chloroquine', 'clindamycin', 'dihydroartemisinin-piperaquine', 'mefloquine', 'quinine', 'primaquine', 'UK', 'epidemics', 'maternal mortality', 'pharmacokinetic' and 'pregnancy'. Reference lists of the articles identified were hand searched for additional articles. Other sources used in the development of this guideline included UK malaria treatment guidelines, published[3] and online at the Health Protection Agency, international guidelines from the World Health Organization[17] and websites covering malaria and pregnancy. Areas lacking evidence are highlighted and annotated as 'good practice points'. Articles on intermittent preventive treatment were specifically excluded, as this practice is not recommended in the UK.

4. Limitations of the data used in this guideline

There is no published evidence of treatment efficacy for malaria in pregnant women in the UK or any other non-endemic country.[18,19] There are no randomised controlled trials of antimalarials in the first trimester of pregnancy.[18] The evidence for best treatment in pregnancy is gained from endemic areas[17,19,20] and is not supported by the availability of drugs or licensing regulations within the UK. Treatment response in UK pregnant women can only be extrapolated from, and is likely to be worse than, treatment responses in semi-immune women. Treatment responses are likely to be closest to those observed in areas of low and unstable malaria transmission, where malaria in pregnancy is usually symptomatic. Data on malaria in pregnancy, especially epidemic malaria, where the severe effects on pregnant women were recorded, is historical.[21,22] In this guideline, the best available evidence for treatment in pregnancy is published in parallel with UK treatment guidelines,[3] with comments on the guidelines. Availability of drugs within the UK can change and this guideline promotes the use of evidence-based prescription choices in this vulnerable group.

Overall, 13 randomised controlled trials on the treatment of uncomplicated *P. falciparum* in pregnancy were completed in the past 20 years in eight different countries (Africa and Asia) and have included 2254 women from high and low transmission areas and a total of 16 different antimalarial drug regimens.[23–35] Seventy-seven percent (10/13) of the trials followed the women post-treatment until delivery but 46% (6/13) attempted to evaluate the infants at 1 year of life. A 2009 Cochrane meta-analysis concluded that data on uncomplicated malaria in pregnancy were scant and, while some combinations appeared effective, data on safety were lacking.[36]

5. Definition of terms used in this guideline

5.1 Severe and complicated malaria

The severe signs of malaria are non-specific and other causes must be excluded before assigning the signs and symptoms to malaria (Box 1). The parasitaemia of severe malaria can be less than 2%. Pregnant women with 2% or more parasitised red blood cells are at higher risk of developing severe malaria and should be treated with the severe malaria protocol.[3]

5.2 Uncomplicated malaria

Uncomplicated malaria in the UK is defined as fewer than 2% parasitised red blood cells in a woman with no signs of severity and no complicating features.[3]

5.3 Congenital malaria

Congenital malaria in the very young infant or newborn results from the passage of parasites or infected red blood cells from the mother to the newborn while in utero or during delivery and not by the bite of the female anopheline mosquito.

Box 1. Clinical and laboratory findings of severe or complicated malaria in adults (reproduced with permission from the World Health Organization)[16]

Clinical manifestations

- Prostration
- Impaired consciousness
- Respiratory distress (acidotic breathing, acute respiratory distress syndrome)*
- Pulmonary oedema (including radiological)*
- Multiple convulsions
- Circulatory collapse, shock (blood pressure < 90/60 mmHg)
- Abnormal bleeding, disseminated intravascular coagulopathy
- Jaundice
- Haemoglobinuria (without G6PD deficiency)

Laboratory tests

- Severe anaemia (Haemoglobin < 8.0 g/dl)
- Thrombocytopaenia
- Hypoglycaemia (< 2.2 mmol/l)*
- Acidosis (pH < 7.3)
- Renal impairment (oliguria < 0.4 ml/kg body weight/hour or creatinine > 265 μmol/l)
- Hyperlactataemia (correlates with mortality)
- Hyperparasitaemia (> 2% parasitised red blood cells)
- 'Algid malaria' - Gram-negative septicaemia*
- Lumbar puncture to exclude meningitis

* Common features in pregnant women with severe or complicated malaria

5.4   Artemisinin combination therapy

Artemisinin combination therapy is a combination of artemisinin or one of its derivatives with an antimalarial or antimalarials of a different class.

5.5   Resistance

Resistance is defined as the ability of a parasite strain to survive and multiply despite the administration and absorption of a medicine given in doses equal to or higher than those usually recommended but within the tolerance of the subject, with the caveat that the form of the drug active against the parasite must be able to gain access to the parasite or the infected red blood cell for the duration of time necessary for its normal action.[37]

6. Diagnosis of malaria in pregnancy

6.1   Why is malaria diagnosis difficult?

There are no specific symptoms or signs and malaria infection may present with a flu-like illness.   ☑

A history of travel to a malaria endemic area should be sought in a pregnant woman with pyrexia of unknown origin.   ☑

Suspicion of malaria requires prompt confirmation by malaria blood film (Appendix 2), as there are no clinical algorithms that permit accurate diagnosis by signs and symptoms (see Section 6.2). In its early stages, the symptoms and signs of malaria can mimic influenza and other common viral infections (Box 2).

Box 2. Symptoms and signs of malaria
Symptoms
● Fever/chills/sweats
● Headache
● Muscle pain
● Nausea
● Vomiting
● Diarrhea
● Cough
● General malaise
Signs
● Jaundice
● Elevated temperature
● Perspiration
● Pallor
● Splenomegaly
● Respiratory distress

Misdiagnosis has been reported to occur when the leading symptoms are jaundice or respiratory[38–40] and possibly gastrointestinal (certainly in children) in nature. Misdiagnosis and delay of treatment are the most common reasons cited for death from malaria in Europe[41,42] and the USA.[43] For the non-falciparum malarias, the history of travel may be more than 1 year before the onset of symptoms[3,43] and, for any woman who has taken prophylaxis, compliance does not rule out the diagnosis of malaria. In the only case series of imported malaria in pregnant women in Europe (Marseille, France), the majority (14 of 18) had fever and the four women who did not, had thrombocytopenia or anaemia associated with splenomegaly.[44]

A history of travel to the tropics and the non-specific nature of the symptoms and signs will lead clinicians to consider investigating other travel-related diagnoses, according to the region visited; for example, influenza-like illnesses including H1N1, severe acute respiratory syndrome, avian influenza, HIV, meningitis/encephalitis and viral haemorrhagic fevers, hepatitis, dengue fever, scrub and murine typhus and leptospirosis. However, for malaria diagnosis a blood film is vital.

6.2   How should malaria in pregnancy be diagnosed?

Microscopic diagnosis allows species identification and estimation of parasitaemia, so that appropriate antimalarials can be prescribed.

A

Rapid detection tests may miss low parasitaemia, which is more likely in pregnant women, and rapid detections tests are relatively insensitive in *P. vivax* malaria.

C

Microscopy and rapid diagnostic tests are the standard tools available. The diagnosis of malaria in pregnancy, as in non-pregnant patients, relies on microscopic examination (the current gold standard) of thick and thin blood films for parasites (Appendix 2) or the use of rapid diagnostic tests which detect specific parasite antigen or enzyme. Rapid diagnostic tests are less sensitive than malaria blood film.[45,46] A positive rapid diagnostic test should be followed by microscopy to quantify the number of infected red blood cells (parasitaemia) and to confirm the species and the stage of parasites. The rapid diagnostic tests should not replace blood films, which should always be prepared, even if they cannot immediately be read (assistance can be provided in the UK; Box 3).

> **Box 3.** Assistance for reading malaria blood films sent urgently by courier or taxi
>
> **HPA Malaria Reference Laboratory**
>
> Website: www.hpa.org.uk/HPA
>
> For advice on laboratory diagnosis: tel: 020 7927 2427
>
> Send in the risk assessment template by fax and receive results within 3 days; fax: 020 7637 0248
>
> **Patient data requirements (risk assessment template 'Malaria Request Form') available to download as a PDF file:**
> www.hpa.org.uk/HPA/ProductsServices/InfectiousDiseases/LaboratoriesAndReferenceFacilities/1200660023262/
>
> **Send samples to:**
> HPA Malaria Reference Laboratory, London School of Hygiene and Tropical Medicine, Keppel Street, London WC1E 7HT
>
> For advice for health professionals over the phone, please contact the National Travel Health Network and Centre: tel: 0845 602 6712
>
> **Hospital for Tropical Diseases, London**
>
> Website information for doctors: www.thehtd.org/Fordoctors.aspx
>
> General practitioners or hospitals requiring information or clinical advice should telephone: 0845 1555 000 ext. 5414/5418
>
> **Send films by courier or cab to:**
> Hospital for Tropical Diseases, Department of Parasitology, Mortimer Market Centre, Capper St, London WC1E 6AU
>
> After 17:00 or at the weekend, the sample should be addressed to:
> SHO on call, T8, University College Hospital, 253 Euston Road, London NW1 2BU
>
> Tel. 08451555000 bleep 5840
>
> **Liverpool School of Tropical Medicine, Liverpool**
>
> **Patient data requirements (HPA risk assessment template 'Malaria Request Form') available to download as a PDF file :**
> www.liv.ac.uk/lstm/travel_health_services/diagnos_lab.htm
>
> **Sample requirements:** original (EDTA) blood sample plus two unstained thick films and two unstained, methanol fixed, thin films. Samples should be sent by first class mail, or courier to:
> Clinical Diagnostic Parasitology Laboratory, Liverpool School of Tropical Medicine, Pembroke Place, Liverpool, L3 5QA
>
> or, if in the Hays DX scheme:
> Liverpool School of Tropical Medicine, Diagnostic Laboratory, DX 6966301, Liverpool 92L
>
> A charge is made for all laboratory services; for current prices please telephone laboratory staff on 0151 705 3220. Please note that the laboratory opening hours are 08.30–17.00 Monday to Friday. The laboratory is closed at weekends and on Bank Holidays. For technical advice regarding samples/tests and for interpretation of results please contact the Diagnostic Laboratory 0151 705 3220/3290

In a febrile patient, three negative malaria smears 12–24 hours apart rules out the diagnosis of malaria. `C`

In a case series of pregnant women from France, all women were identified as positive for malaria by microscopy.[44] There are occasions for suspicions to remain high and expert advice should be sought in such circumstances. Women who have taken prophylaxis may have their parasitaemia suppressed below the level of microscopic detection (total biomass 108 parasites) and details of prophylaxis (name, where it was bought – in case of fake drug – dosing and adherence) should be sought. Stop prophylaxis on admission to hospital. Pregnant women with a high background immune level may have negative peripheral blood thick films but parasites sequestered in the placenta (for example, a recently arrived woman from a high malaria-endemic country with an unexplained anaemia).[47]

Other important prognostic factors that should be reported on a peripheral blood smear result are:

- the presence and count of mature trophozoites and schizonts of *P. falciparum*
- finding malaria pigment in more than 5% of the polymorphonuclear leucocytes in the peripheral blood film.[48,49]

6.3   Is the severity of malaria a useful aid in managing the infection?

Women with malaria in pregnancy should have the severity of their condition assessed and documented as an aid to management. ✓

The clinical condition is the most important indicator of severity and should be assessed promptly (Box 1). A helpful summary of the key points for use in the emergency department has been made available via the British Infection Society website (www.britishinfectionsociety.org). The severity of malaria determines the treatment and predicts the case fatality rate. In uncomplicated malaria, fatality rates are low: approximately 0.1% for *P. falciparum*. In severe malaria, particularly in pregnancy, fatality rates are high (15–20% in nonpregnant women compared with 50% in pregnancy).[17,38,50,51] Brabin estimated mortality to be 2–10 times higher in pregnant women than in non-pregnant women in endemic areas.[52] The non-falciparum species are rarely fatal but caution should still be observed.[12,53]

Once the disease has been classified as severe/complicated (as defined in Section 5.1 and Box 1 of this guideline) or uncomplicated malaria (as defined in Section 5.2 of this guideline) prompt treatment should be instituted.

7.   How is malaria infection treated during pregnancy?

Treat malaria in pregnancy as an emergency. B

Admit pregnant women with uncomplicated malaria to hospital and pregnant women with severe and complicated malaria to an intensive care unit. A

Intravenous artesunate is the treatment of choice for severe falciparum malaria. Use intravenous quinine if artesunate is not available. A

Use quinine and clindamycin to treat uncomplicated *P. falciparum* (or mixed, such as *P. falciparum* and *P. vivax*). B

Use chloroquine to treat *P. vivax*, *P. ovale* or *P. malariae*. A

Primaquine should not be used in pregnancy. D

Seek advice from infectious diseases specialists, especially for severe and recurrent cases. ✓

Do not persist with oral therapy if vomiting is persistent. ✓

Treat the fever with antipyretics. B

Screen women with malaria for anaemia and treat appropriately. A

Write a management plan for follow-up, to ensure detection of relapse. B

7.1   Drug treatment

Delay in diagnosis and treatment is associated with death from severe malaria.[42,54-56] Use the treatment guidelines shown in Table 1. For a summary of the published evidence see Appendix 3.

Table 1. UK treatment guidelines in pregnancy[3]

Severity	Indication	Drug and dosage
Severe or complicated malaria[a]	Any species (for specific cases after expert consultation; see Table 2)	Artesunate IV 2.4 mg/kg at 0, 12 and 24 hours, then daily thereafter. When the patient is well enough to take oral medication she can be switched to oral artesunate 2 mg/kg (or IM artesunate 2.4 mg/kg) once daily, plus clindamycin. If oral artesunate is not available, use a 3-day course of Riamet® (GSK) or atovaquone-proguanil (Malarone®, Novartis) or a 7-day course of quinine and clindamycin at 450 mg 3 times a day 7 days.
		ALTERNATIVELY
	Any species	Quinine IV 20 mg/kg loading dose (no loading dose if patient already taking quinine or mefloquine) in 5% dextrose over 4 hours and then 10 mg/kg IV over 4 hours every 8 hours plus clindamycin IV 450 mg every 8 hours (max. dose quinine 1.4 g). When the patient is well enough to take oral medication she can be switched to oral quinine 600 mg 3 times a day to complete 5–7 days and oral clindamycin 450 mg 3 times a day 7 days (an alternative rapid quinine-loading regimen is 7 mg/kg quinine dihyrochloride IV over 30 minutes using an infusion pump followed by 10 mg/kg over 4 hours).
		Note: quinine dosing should be reduced to 12-hourly dosing if IV therapy extends more than 48 hours or if the patient has renal or hepatic dysfunction.[56] Quinine is associated with severe and recurrent hypoglycaemia in late pregnancy.[57]
Uncomplicated malaria[b]	*P. falciparum*	Oral quinine 600 mg 8 hourly and oral clindamycin 450 mg 8 hourly for 7 days (can be given together) **or** Riamet® 4 tablets/dose for weight > 35 kg, twice daily for 3 days (with fat) **or** atovaquone-proguanil (Malarone®) 4 standard tablets daily for 3 days.
	Vomiting but no signs of severe or complicated malaria	Quinine 10 mg/kg dose IV in 5% dextrose over 4 hours every 8 hours plus IV clindamycin 450 mg every 8 hours. When the patient is well enough to take oral medication she can be switched to oral quinine 600 mg 3 times a day to complete 5–7 days and oral clindamycin can if needed be switched to 450 mg 3 times a day 7 days.
Non-falciparum malaria[c]	*P. vivax*, *P. ovale*, *P. malariae*	Oral chloroquine (base) 600 mg followed by 300 mg 68 hours later. Then 300 mg on day 2 and again on day 3.
	Resistant *P. vivax*	As for uncomplicated malaria *P. falciparum*
	Preventing relapse DURING pregnancy	Chloroquine oral 300 mg weekly until delivery
	Preventing relapse AFTER delivery	Postpone until 3 months after delivery and G6PD testing
	P. ovale	Oral primaquine 15 mg single daily dose for 14 days
	P. vivax	Oral primaquine 30 mg single daily dose for 14 days
	G6PD (mild) for *P. vivax* or *P. ovale*	Primaquine oral 45–60 mg once a week for 8 weeks

[a] Severe and complicated malaria published evidence, see Appendix 3.1;
[b] Uncomplicated malaria published evidence, see Appendix 3.2;
[c] Non-falciparum malaria published evidence, see Appendix 3.3; IM = intramuscular, IV = intravenous

7.2 Who should prescribe treatment for malaria infection in pregnancy?

In the UK, treatment prescription is limited to physicians. Treatment in pregnancy, particularly of severe and recurrent malaria, is best given with expert advice (Table 2).

7.3 Where should treatment of uncomplicated malaria infection take place?

In the UK, it is advisable to hospitalise all pregnant women with *P. falciparum*, as the clinical condition can deteriorate rapidly.[3,59–62] Blood films are usually monitored every 24 hours but clinical deterioration is an indication for a repeat blood film.

Table 2. Contact details for intravenous artesunate or specialist advice in cases of severe malaria

Organisation	Contact details
Hospital for Tropical Diseases, London [http://www.thehtd.org/Emergencies.aspx] HTD will send artesunate to other hospitals dealing with severe cases if there is going to be a delay in transferring the patient to HTD (do not delay IV treatment in the interim)	FOR ADVICE/IV ARTESUNATE Ask for the on-call tropical medicine registrar (24-hour service). Use the University College London Hospital switchboard; tel: 08451 555000
Oxford Hospital for Tropical Diseases	FOR ADVICE/IV ARTESUNATE Ask for the infectious diseases consultant on call at the John Warin Ward. Use Churchill Hospital Switchboard; tel: 01865 741841 Note: the drug can be sent during the daytime and services at the weekend are limited.
Liverpool School Tropical Medicine Tropical Medicine Services for Health Professionals [www.liv.ac.uk/lstm/travel_health_services/health_profs.htm]	FOR ADVICE/IV ARTESUNATE Tropical doctor on call in working hours; tel: 0151 705 3100, 0151 706 2000 (at other times ask for the infectious disease/tropical doctor on call at the Royal Hospital)
Birmingham Heartlands Hospital Infectious Diseases Unit	Department of Infection and Tropical Medicine Birmingham Heartlands Hospital Birmingham B9 5ST Tel: 0121 424 1137 Outside working hours tel: 0121 424 2000 for the switchboard
Idis Pharma [www.idispharma.com] Despite the fact that artesunate has not achieved good manufacturing practice certification, it has received the orphan medicinal products designation from the European Medicines Agency.[132] Product details: oral artesunate guilin, 50-mg tablets 1 x 12; IV artesunate 60-mg powder/solution for injection 1 x 8	FOR IV or ORAL ARTESUNATE Contact details in the UK: tel: 01932 824100; fax: 01932 824300; email: globalsales@idispharma.com

The 7-day course of quinine has significant adverse effects, principally cinchonism,[19] which includes tinnitus, headache, nausea, diarrhoea, altered auditory acuity and blurred vision. This can lead to non-compliance, which frequently leads to failure.[16,63–66] For this reason, hospitalisation can be useful, as compliance with each dose of quinine and clindamycin can be observed and this may lead to improved cure rates.[65,67]

While non-falciparum malaria can be managed on an outpatient basis, admission ensures compliance and any risk of vomiting or rapid deterioration is minimised and allows time for planning post-treatment prophylaxis.

7.4   What happens if the patient vomits?

Vomiting is a symptom of malaria and a known adverse effect of quinine.[68–70] It is associated with antimalarial treatment failure.[16]

Evidence level 2+

If the patient vomits, use an antiemetic. There are no studies of their efficacy in malaria[17] but metoclopramide is considered safe, even in the first trimester.[71] After the antiemetic has had time to take effect, repeat the dose. Repeat vomiting after antiemetic is an indication for parenteral therapy.

7.5   What other medication should be provided alongside treatment of uncomplicated malaria infection?

The fever of malaria has been associated with premature labour[53,72] and fetal distress.[73] Prompt treatment with antipyretics (paracetamol at the standard dose) is fundamental to the treatment of fever from malaria in pregnancy. Evidence for the efficacy of paracetamol arises mostly from studies in children.[74–78]

Evidence level 1

An estimated 400 000 pregnant woman developed severe anaemia as a result of malaria in sub-Saharan Africa in 1995.[79] Despite the massive burden of malaria-related anaemia in pregnancy, there are very few studies that

have directly addressed the question of routine iron and folate supplementation as part of uncomplicated malaria treatment. In *P. falciparum* malaria treatment trials in women with low premunition, 90% of women developed anaemia (haemoglobin less than 10 g/dl), either on admission or during follow-up.[80] Premunition is the degree of naturally acquired host immunity to malaria. It depends on repeated exposure to infectious anopheline bites, so most UK-based residents will have low or no premunition. Mild and moderate malaria-associated anaemia is treated with ferrous sulphate and folic acid at the usual doses.

7.6 Does pregnancy affect the efficacy of malaria treatments?

Treatments in pregnancy may have lower efficacy than in non-pregnant patients but this apparent effect could result from lowered concentrations of antimalarials in pregnancy.[26,30,32] Women should be advised of the risk of recurrence and a suitable follow-up plan devised; for example, if symptoms or fever return, a repeat blood film is necessary. Alternatively, weekly screening by blood film can provide early detection and treatment of malaria. This has been shown to reduce maternal death from malaria in Thailand.[10] There is no evidence of weekly blood film use in the UK but Thailand is a low endemic area so immune levels would not be much higher than those in women from the UK who were not immune.

Malaria in pregnancy is unique and the ability of *P. falciparum* to sequester in the placenta challenges the normal way antimalarial drug efficacy is assessed.[37] Polymerase chain reaction (PCR)-confirmed prolonged submicroscopic carriage with subsequent recurrence has been reported in pregnant women for months following drug treatment for uncomplicated *P. falciparum*. Most recurrence is around day 28–42 but late-reported recurrence, so far unique to pregnancy, has been reported to occur at 85 days with quinine,[28] 98 days with artesunate, 63 days with artemether-lumefantrine[30] and 121 days with mefloquine.[81] Weekly screening by blood film until delivery allows these women to be detected positive before becoming symptomatic.[10]

7.7 How should recurrence be treated?

The treatment efficacy of antimalarials for recurrent malaria in pregnancy has been described in only a hand-ful of trials.[30,82–84] The cure rates for uncomplicated malaria with quinine fell from 77.0% to 61.0% ($P = 0.03$) and for mefloquine from 72.0% to 62.5% ($P > 0.05$) when these drugs were used to treat primary and recurrent infections.[82] The alternative regimen for recurrent malaria at that time (1995–1997) was artesunate monotherapy, which had a cure rate of 84%. In another study, the PCR-confirmed cure rates of women treated in the second and third trimesters of pregnancy were highest when the infection on admission to the study was primary (the first for the pregnancy) and lowest when the infection was recrudescent (failure of previous drug treatment in pregnancy).[82] Infections that recur following treatment are likely to be intrinsically less sensitive to the drugs used against them. A highly effective 7-day treatment has more chance of curing the patient. All the trials of recurrent malaria in pregnancy rely on artemisinin derivatives.

Unfortunately, the options for treatment of recurrent infection in pregnancy in the UK are limited but, if quinine and clindamycin has failed as first-line treatment, an alternative should be considered. Atovaquone-proguanil-artesunate[83] and dihydroartemisinin-piperaquine[84] have been used in pregnant women with multiple recurrent infections with good effect. Atovaquone-proguanil (Malarone®, GlaxoSmithKline) is available in the UK and, as noted earlier, was highly effective against uncomplicated *P. falciparum* malaria even when it was not combined with artesunate.[85] Note that oral artesunate can be obtained from IDIS Pharma (Table 2). The World Health Organization recommended regimen of 7 days of artesunate (2 mg/kg/day or 100 mg daily for 7 days) and clindamycin (450 mg three times daily for 7 days) could be given.

8. How are pregnancy-related complications of severe malaria managed?

Monitor for hypoglycaemia regularly, as it can be profound and persistent in malaria in pregnancy and can be exacerbated by quinine.

<div style="text-align:right">B</div>

Prevent mortality from pulmonary oedema and acute respiratory distress syndrome by clinical assessment of jugular venous or central venous pressure, aimed at keeping right arterial pressure less than 10 cm H2O. | B |

Women who are severely anaemic should be transfused slowly, preferably with packed cells and intravenous frusemide 20 mg. Alternatively, exchange transfusion may be considered in centres where this can be performed safely. | B |

Secondary bacterial infection should be suspected if the patient becomes hypotensive. | C |

Severe malaria in pregnancy is a medical emergency and women should be treated in a high-dependency or intensive care unit, according to their condition and without delay. The World Health Organization's 2006 malaria treatment guidelines detail the treatment of severe malaria and do not need to be repeated here.[17] Common clinical manifestations and management of severe malaria have been summarised (Table 3).[17,50] While hypoglycaemia, pulmonary oedema, severe anaemia and secondary bacterial infection can occur in severe malaria in non-pregnant patients, they are more common and severe in pregnant women.[3,39,40,50,86]

Hypoglycaemia is commonly asymptomatic, although it may be associated with fetal bradycardia and other signs of fetal distress. In the most severely ill women, it is associated with lactic acidosis and high mortality.[68] In patients who have been given quinine, abnormal behaviour, sweating and sudden loss of consciousness are the usual manifestations. The hypoglycaemia of quinine is caused by hyperinsulinaemia and remains the most common and important adverse effect of this drug.[87] The hypoglycaemia may be profound, recurrent and intractable in pregnancy[73,87,88] and regular monitoring of glucose is required while under quinine treatment. It may present late in the disease when the patient appears to be recovering. Quinine at treatment doses does not induce abortion or labour.[73,89]

Evidence level 2

Table 3. Supportive clinical care in severe malaria

Manifestation or complication	Management
Coma (cerebral malaria)	Monitor using Glasgow Coma Score. Maintain airway, place patient on her left side, exclude treatable causes of coma (e.g. hypoglycaemia, bacterial meningitis)
Hyperpyrexia	Administer tepid sponging, fanning and antipyretic drugs
Convulsions	Maintain airway; treat promptly with intravenous or rectal diazepam
Hypoglycaemia (blood glucose < 2.2 mmol/l or < 40 mg/100 ml)	Check blood glucose regularly, correct hypoglycaemia and maintain with glucose-containing infusion. Quinine induced hypoglycaemia can occur quite late in the course even after the patient appears to be recovering
Severe anaemia (haemoglobin < 8 g/100 ml or packed cell volume < 24%)	Transfuse with packed red cells
Acute pulmonary oedema (possible overlay of acute respiratory distress syndrome)	Prevent by monitoring jugular venous pressure(JVP)/central venous pressure (CVP) to keep right arterial pressure < 10 cm H2O. Treat by propping patient up at an angle of 45 degrees, give oxygen, give a diuretic, stop intravenous fluids, intubate and add positive end-expiratory pressure/continuous positive airway pressure in life-threatening hypoxaemia
Renal failure	Exclude pre-renal causes, check fluid balance and urinary sodium; if in established renal failure, add haemofiltration or haemodialysis or, if unavailable, peritoneal dialysis. The benefits of diuretics/dopamine in acute renal failure are not proven
Spontaneous bleeding and coagulopathy	Transfuse with screened fresh whole blood (cryoprecipitate, fresh frozen plasma and platelets if available); give Vitamin K by injection
Metabolic acidosis	Prevent by careful fluid balance; observation of JVP/CVP by central venous access helps optimise fluid balance and avoids overfilling. Exclude or treat hypoglycaemia, hypovolaemia and septicaemia. If severe, add haemofiltration or haemodialysis
Shock	Suspect septicaemia, take blood for cultures; give parenteral broad-spectrum antimicrobials, correct haemodynamic disturbances

Pulmonary oedema may be present on admission or may develop suddenly and unexpectedly. It may develop immediately after childbirth.[38] Pulmonary oedema is a grave complication of severe malaria, with a high mortality of over 50%.[39,40,86,90-93] The first indication of impending pulmonary oedema is an increase in the respiratory rate, which precedes the development of other chest signs. Ensure that the pulmonary oedema has not resulted from iatrogenic fluid overload and monitor the central venous pressure and urine output. In some women, acute respiratory distress syndrome can occur in addition to the pulmonary oedema. Once this syndrome develops, the patient needs fluid restriction.

Evidence level 2+

Severe anaemia is associated with maternal morbidity, an increased risk of postpartum haemorrhage and perinatal mortality.[8,39,51,52,90,93-96] Women who go into labour when severely anaemic or fluid-overloaded may develop acute pulmonary oedema after separation of the placenta. Monitor haemoglobin and transfuse as necessary. Exchange transfusion may be considered but there is no clear evidence base.[97]

Evidence level 2++

Secondary bacterial infection, principally Gram-negative septicaemia, has been reported; the patient is collapsed with a systolic blood pressure less than 80 mmHg in the supine position.[55,98,99] Blood cultures should be taken if the patient shows signs of shock or fever returns after apparent fever clearance, Broad-spectrum antibiotics (such as ceftriaxone) should be started immediately. Once the results of blood culture and sensitivity testing are available, give the appropriate antibiotic.

Evidence level 3

9. Obstetric management specific to malaria infection in pregnancy

9.1 Common obstetric problems with acute symptomatic malaria

Preterm labour, fetal growth restriction and fetal heart rate abnormalities can occur in malaria in pregnancy.

D

In severe malaria complicated by fetal compromise, a multidisciplinary team approach (intensive care specialist, infectious disease specialist, obstetrician, neonatologist) is required to plan optimal management of mother and baby.

C

Stillbirth and premature delivery in malaria in pregnancy are best prevented with prompt and effective antimalarial treatment.

B

Uncomplicated malaria in pregnancy is not a reason for induction of labour.

A

Pharmacological thromboprophylaxis should be weighed up against the risk of haemorrhage and should be withheld if the platelet count is falling or less than 100, indicating thrombocytopenia.

C

Peripartum malaria is an indication for placental histology and placenta, cord and baby blood films to detect congenital malaria at an early stage.

D

Inform women of the risk of vertical transmission and, in the presence of positive placental blood films, that fever in the infant could indicate malaria; a blood film from the baby is required for confirmation.

C

Commonsense obstetrics applies to the management of the adverse effects of malaria in pregnancy. Efficacious and prompt treatment of malaria in the woman reduces the systemic effects of parasitaemia and reduces the adverse effects on the fetus, such as fetal distress.

In severe malaria, cardiotocograph monitoring may reveal fetal tachycardia, bradycardia or late decelerations in relation to uterine contractions, indicating fetal distress, particularly in the

Evidence level 4

presence of fever.[72] Paracetamol 1 g every 4–6 hours (to a maximum of 4 g/day) is safe and effective and should be prescribed. Maternal hypoglycaemia should be excluded as the cause of fetal distress, particularly if treatment is with quinine. Tocolytic therapy and prophylactic steroid therapy at the usual obstetric doses should be considered if there are no contraindications.[100]

<div align="right">Evidence
level 4</div>

Historic records indicate a high fetal loss rate with malaria in pregnancy.[101,102] In a more recent study from the Kenyan coast, Dorman *et al*.[103] found that the risk of preterm delivery in women with histological evidence of past placental malaria infection compared with women without infection was more than twice as high (relative risk [RR] 2.33; 95% confidence interval [CI] 1.31–4.13; $P = 0.004$).

<div align="right">Evidence
level 2-</div>

Abnormalities in fetal and placental circulation have been noted on Doppler studies. In one study, 23 women with acute malaria reported that the umbilical artery resistance index increased by 5 to 20% ($P < 0.05$), with evidence of cerebral redistribution.[103,104] In the second observational study in Kenya, malaria infection at 32–35 weeks of gestation was associated with abnormal uterine artery flow velocity waveforms on the day of blood testing (RR 2.11; 95% CI 1.24–3.59; $P = 0.006$).[103]

In women with severe malaria, obstetric advice should be sought at an early stage. The paediatrician should be alerted and the mother's blood glucose checked frequently, particularly when intravenous quinine is administered. Fetal distress is common and has been related to malaria fever: late (type II) decelerations of the fetal heart rate were recorded in six women before treatment but, in most women, signs of fetal distress diminished as the maternal temperature fell.[73] Standard obstetric principles apply: the life of the woman comes first. There are no formal studies but instrumental birth in the second stage of labour in the presence of maternal or fetal distress is indicated, if there are no contraindications. In severe malaria, the role of early caesarean section for the viable fetus is unproven.

<div align="right">Evidence
level 3</div>

Acute malaria can cause thrombocytopenia in pregnancy.[105] Two studies have examined the effects on postpartum haemorrhage, which was reported to be higher in malarious areas compared with non-malarious areas of Papua New Guinea.[106] One further trial found an increased mean blood loss in women with malaria but no increased risk of postpartum haemorrhage.[107]

In more than 3000 pregnant women who have participated in uncomplicated malaria treatment trials[7,24,26–29,43,53,80,82–84,108–121] and have been prospectively followed from diagnosis of malaria through treatment and birth, no routine induction of labour occurred unless it was indicated on obstetric grounds.

<div align="right">Evidence
level 1++</div>

There is usually no need for pregnant women with malaria infection to receive thromboprophylaxis. Acute malaria causes thrombocytopenia[105] and, in severe malaria, can cause disseminated intravascular coagulation.[50] Thrombocytopenia recovers with treatment: 90% by day 7 and 100% by day 14, irrespective of the type of antimalarial treatment.[105]

<div align="right">Evidence
level 3</div>

Antimalarial drugs can clear peripheral parasitaemia more quickly than from the placenta.[122] Maternal malaria close to delivery can result in congenital malaria, which can cause significant mortality.[123] Congenital malaria may present in the first weeks to months of life. A negative placental blood film at delivery in a woman who has had malaria in pregnancy eliminates the risk of congenital malaria significantly. Placenta- and cord-positive blood films result in a higher chance of congenital malaria than placenta-positive, cord-negative blood films. Send the placenta for histopathology, as it is more sensitive than microscopy for detection of placental parasites.[124,125]

<div align="right">Evidence
level 2+</div>

9.2   What antenatal care after recovery from an episode of malaria in pregnancy is advised?

Regular antenatal care, including assessment of maternal haemoglobin, platelets, glucose and fetal growth scans, is advised following recovery from an episode of malaria in pregnancy.   ✓

Regular fetal growth assessment is advised and, if growth restriction is identified, routine obstetric management for this condition applies (See RCOG Green-top Guideline No. 31: *Investigation and Management of Small-for-Gestational-Age Fetus*).[126]   ✓

Inform the woman about the risk of relapse, try to prevent it and develop a clear plan with the woman in the event of symptom recurrence.   ✓

In endemic settings, malaria in pregnancy is responsible for over 50% of fetal growth restriction but most babies born to women with infection during pregnancy will be of normal birth weight.[5] No additional fetal surveillance will prevent the growth restriction. If growth restriction is identified, routine obstetric protocols for this condition apply. Effective antimalarial treatment which clears the placenta of parasites is the most important step in preventing this complication (Table 1) followed by prophylaxis to prevent relapse (Appendix 3), such as weekly chloroquine for *P. vivax*. The chances of recurrence are low when a woman has completed an effective course of antimalarials. Nevertheless, it is useful for women to be aware that malaria can recur (and is more likely with *P. vivax* or *P. ovale*). Should symptoms return, prompt screening by malaria blood film, preferably at the same hospital where treatment was first given, is essential.

The post-malaria treatment course for women treated for malaria can be complicated by anaemia, which will be detected in routine antenatal screening. There are malaria-endemic countries where the risk of pre-eclampsia is increased significantly in women with placental malaria.[127] The situation for women in these countries is different from that of a pregnant woman treated for malaria in the UK because malaria is endemic, diagnosis and case management tends to be weak, impregnated bed nets and prophylaxis are the main stay of malaria control in pregnancy and the risk of reinfection is high. The risk of pre-eclampsia in UK pregnant women treated for malaria is not known but may be lower than in malaria endemic countries.

Evidence level 3

10.   What is the risk of vertical transmission of malaria infection to the baby?

Vertical transmission to the fetus can occur particularly when there is infection at the time of birth and the placenta and cord are blood film positive for malaria (Appendix 2).   **B**

All neonates whose mothers developed malaria in pregnancy should be screened for malaria with standard microscopy of thick and thin blood films at birth and weekly blood films for 28 days.   **D**

Vertical transmission of malaria occurs when malaria parasites cross the placenta, either during pregnancy or at the time of birth (Appendix 4).[128] In a non-endemic country, congenital malaria can be diagnosed by finding parasites in the neonate if they have not travelled in an endemic area.[128–132] The reported prevalence of congenital malaria varies from 8% to 33%.[5] One or the largest series of congenital malaria in a non-endemic country comes from the USA.[133] *P. vivax* was the predominant infecting species and the most common error in the treatment of these infants was the administration of primaquine, which is unnecessary in this group. Infection of the newborn can occur despite appropriate treatment in the mother during pregnancy. If the placenta is positive for parasites, weekly screening of the newborn for 28 days is useful to allow early detection and treatment of congenital malaria.

Evidence level 3

11. Disease reporting

Does a case of malaria in pregnancy in the UK need reporting?

In the UK, malaria in pregnancy must be reported to the public health authorities and the Health Protection Agency (www.hpa.org.uk) and slides, plus a blood aliquot, should be sent to the Malaria Reference Laboratory for confirmation, which is performed free of charge.[3]

Health Protection Agency Central Office   **OR**

7th Floor
Holborn Gate
330 High Holborn
London, WC1V 7PP
Tel: 020 7759 2700 / 2701
Fax: 020 7759 2733
Email: webteam@hpa.org.uk

Health Protection Agency Centre for Infections

61 Colindale Avenue
London NW9 5EQ
Tel: 020 8200 4400
Fax: 020 8200 7868
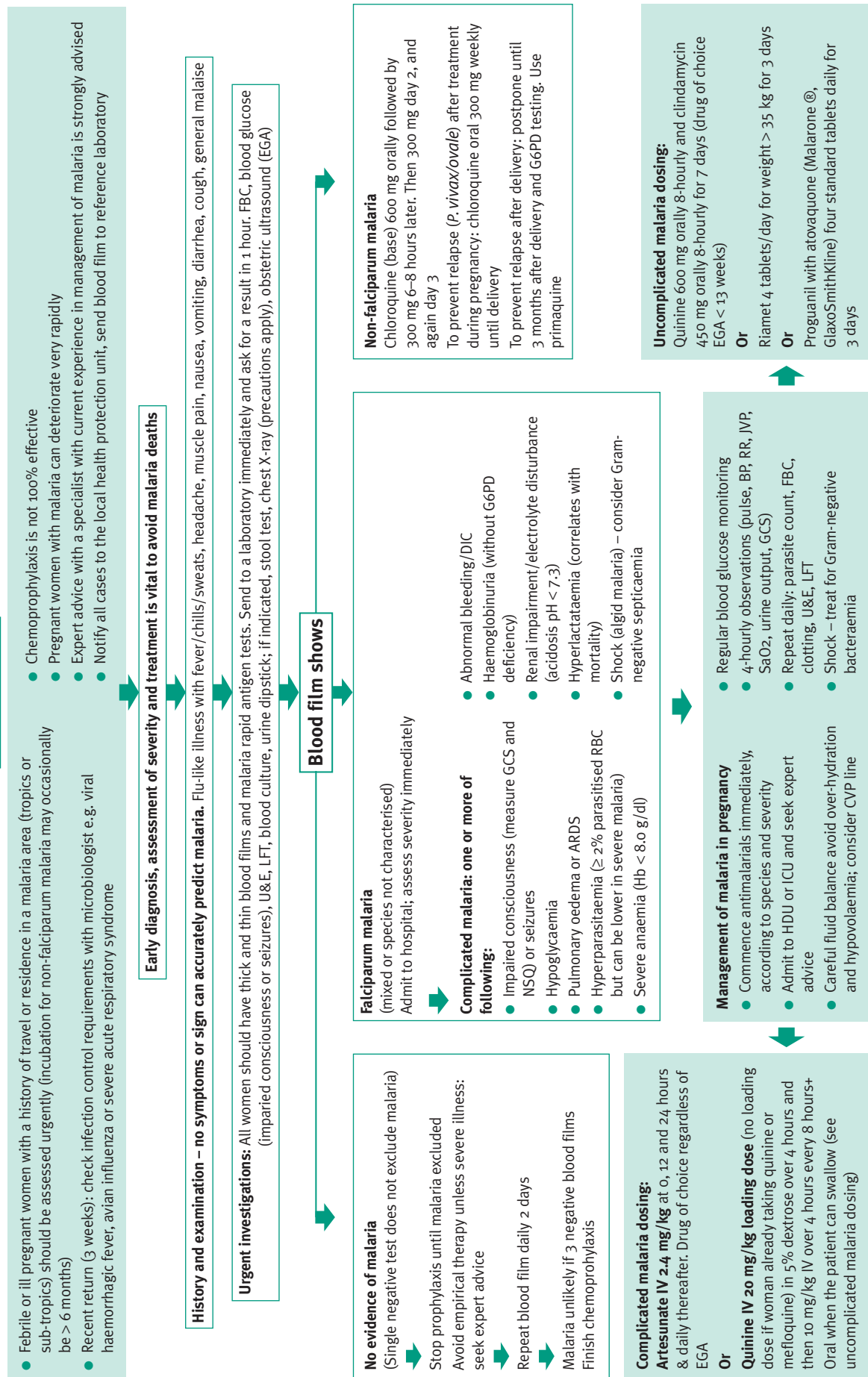Email: infections@hpa.org.uk

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Suspect malaria

- Febrile or ill pregnant women with a history of travel or residence in a malaria area (tropics or sub-tropics) should be assessed urgently (incubation for non-falciparum malaria may occasionally be > 6 months)
- Recent return (3 weeks): check infection control requirements with microbiologist e.g. viral haemorrhagic fever, avian influenza or severe acute respiratory syndrome
- Chemoprophylaxis is not 100% effective
- Pregnant women with malaria can deteriorate very rapidly
- Expert advice with a specialist with current experience in management of malaria is strongly advised
- Notify all cases to the local health protection unit, send blood film to reference laboratory

Early diagnosis, assessment of severity and treatment is vital to avoid malaria deaths

History and examination – no symptoms or sign can accurately predict malaria. Flu-like illness with fever/chills/sweats, headache, muscle pain, nausea, vomiting, diarrhea, cough, general malaise

Urgent investigations: All women should have thick and thin blood films and malaria rapid antigen tests. Send to a laboratory immediately and ask for a result in 1 hour. FBC, blood glucose (impaired consciousness or seizures), U&E, LFT, blood culture, urine dipstick; if indicated, stool test, chest X-ray (precautions apply), obstetric ultrasound (EGA)

Blood film shows

No evidence of malaria
(Single negative test does not exclude malaria)

- Stop prophylaxis until malaria excluded
- Avoid empirical therapy unless severe illness: seek expert advice
- Repeat blood film daily 2 days
- Malaria unlikely if 3 negative blood films
- Finish chemoprohylaxis

Falciparum malaria
(mixed or species not characterised)
Admit to hospital; assess severity immediately

Complicated malaria: one or more of following:

- Impaired consciousness (measure GCS and NSQ) or seizures
- Hypoglycaemia
- Pulmonary oedema or ARDS
- Hyperparasitaemia (≥ 2% parasitised RBC but can be lower in severe malaria)
- Severe anaemia (Hb < 8.0 g/dl)
- Abnormal bleeding/DIC
- Haemoglobinuria (without G6PD deficiency)
- Renal impairment/electrolyte disturbance (acidosis pH < 7.3)
- Hyperlactataemia (correlates with mortality)
- Shock (algid malaria) – consider Gram-negative septicaemia

Complicated malaria dosing:
Artesunate IV 2.4 mg/kg at 0, 12 and 24 hours & daily thereafter. Drug of choice regardless of EGA

Or

Quinine IV 20 mg/kg loading dose (no loading dose if woman already taking quinine or mefloquine) in 5% dextrose over 4 hours and then 10 mg/kg IV over 4 hours every 8 hours+

Oral when the patient can swallow (see uncomplicated malaria dosing)

Management of malaria in pregnancy

- Commence antimalarials immediately, according to species and severity
- Admit to HDU or ICU and seek expert advice
- Careful fluid balance avoid over-hydration and hypovolaemia; consider CVP line
- Regular blood glucose monitoring
- 4-hourly observations (pulse, BP, RR, JVP, SaO2, urine output, GCS)
- Repeat daily: parasite count, FBC, clotting, U&E, LFT
- Shock – treat for Gram-negative bacteraemia

Uncomplicated malaria dosing:
Quinine 600 mg orally 8-hourly and clindamycin 450 mg orally 8-hourly for 7 days (drug of choice EGA < 13 weeks)

Or

Riamet 4 tablets/day for weight > 35 kg for 3 days

Or

Proguanil with atovaquone (Malarone ®, GlaxoSmithKline) four standard tablets daily for 3 days

Non-falciparum malaria

Chloroquine (base) 600 mg orally followed by 300 mg 6–8 hours later. Then 300 mg day 2, and again day 3

To prevent relapse (*P. vivax/ovale*) after treatment during pregnancy: chloroquine oral 300 mg weekly until delivery

To prevent relapse after delivery: postpone until 3 months after delivery and G6PD testing. Use primaquine

Expert advice/IV artesunate: local infectious unit or London 08451 555000; Liverpool 0151 706 2000; Oxford 08165 741845; IDIS pharma 01932 824100.
Useful information: www.hpa.org.uk/HPA/ProductsServices/InfectiousDiseases/LaboratoriesAndReferenceFacilities/1200660023262/ and www.who.int/malaria/publications/atoz/9241546948/en/index.html

Key: ARDS = acute respiratory distress syndrome, BP = blood pressure, CVP = central venous pressure, DIC = disseminated intravascular coagulation, EGA = estimated gestational age, FBC = full blood count, GCS = Glasgow Coma Score, Hb = haemoglobin, HDU = high-dependency unit, ICU = intensive care unit, JVP = jugular venous pressure, LFT = liver function test, NSQ = Neuroticism Scale Questionnaire, RBC = red blood cells, RR = respiratory rate, SaO2 = oxygen saturation, U&E = urea and electrolytes

APPENDIX II: Preparing a blood film for malaria and taking a section of placenta for histopatholgy.

Blood films are also commonly called 'malaria slide', 'thick and thin films', 'malaria smear' or 'blood slide'. A few drops of the patient's blood are required for the test. A brief summary is provided in Figure 1.

There are many useful websites (including videos) on how to prepare a thick and thin blood film. For detailed instructions, try: www.dpd.cdc.gov/dpdx/HTML/Malaria.htm or www.helid.desastres.net – select 'Parasitic and Vector Borne Disease' from the topic list (Basic Malaria Microscopy, Learning Unit 4) or see the laboratory handout from: www.shoklo-unit.com/lab.shoklo-unit.com/index.html.

Cord blood film or placental blood films require a few drops of blood collected from those sites.

Cord specimens can be obtained before delivery of the placenta. Hold the clamped end of the cord above the level of the umbilicus. Wipe the cord clean, puncture the cord with a syringe and needle (small gauge) and withdraw blood from the vessel (0.2 ml is plenty) and reclamp the cord above the puncture site. The blood obtained needs to go directly onto the glass slide before it clots (see Figure 1).

Placental blood can be obtained by placing the placenta maternal surface upward. Choose a site midway between the edge of the placenta and the cord, wipe it clean with gauze, make an incision about 1 cm deep and 3–4 cm in length with a scalpel blade (do not pierce the fetal surface) and use a syringe and needle (or haematocrit tube) to withdraw blood that pools in the incised area. Place this blood onto the glass slide before it clots.

Label all blood films clearly with the site from which they were obtained (for example, mother, cord, placenta or baby) before sending to the laboratory. This histopathological section can be obtained from the same site on the placenta by cutting a 1 × 1 × 1 cm (or smaller) block from the maternal surface through to the fetal surface and placing it in fixative.
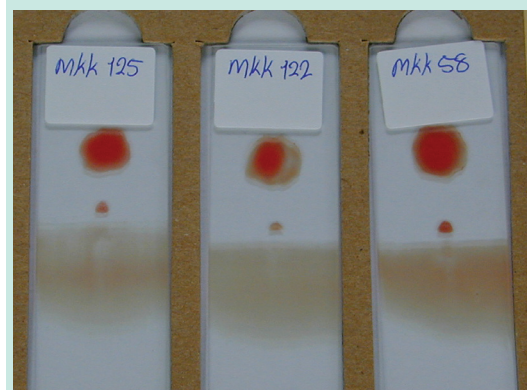

Step 1. Put 3 drops of blood onto the slide
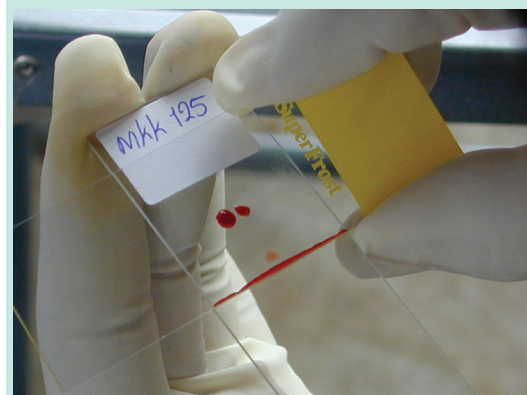
Step 2. Use another slide to spread the drop
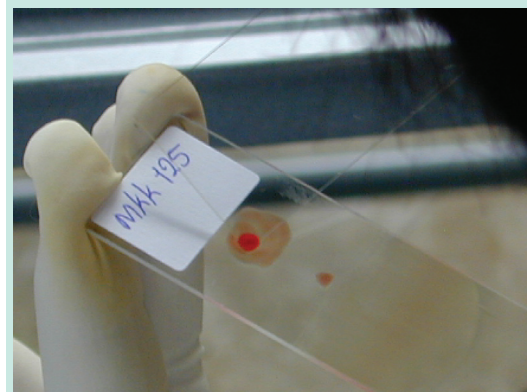
Step 3. Stir the thick drop

Step 4. Allow the slide to dry before staining

Figure 1. Summary of steps involved in making a blood film

APPENDIX III: Summary of the published evidence on pregnancy treatment recommendations

Severe and complicated malaria.

The first line of treatment in the UK for severe malaria in pregnancy is intravenous quinine[1] while the World Health Organization (WHO) and an increasing number of countries throughout the world recommend intravenous (IV) artesunate as the preferred first-line drug for all severe malaria in adults including pregnant women.[2] This recommendation was based partly on two WHO informal consultations on the safety of artemisinins in pregnancy.[3] The first of these reported normal pregnancy outcomes in 124 women exposed in the first trimester. The conclusions were that there was insufficient evidence to support the use of artemisinin in the first trimester but that it should not be withheld if the life of the woman was endangered or if other antimalarials were considered unsuitable. The recommendation also relied upon a meta-analysis of artemisinins for severe malaria[4] and a large, multicentre, open-label randomised controlled trial (RCT) of severe malaria carried out mostly in adults (including pregnant women) in South East Asia, where the trial was stopped prematurely because of a significantly increased risk of mortality in the intravenous quinine group (22% compared with 15% in the IV artesunate group).[5] Mortality was reduced by 34.7% (95% confidence interval 18.5–47.6; $P = 0.002$) when IV artesunate was used or, for every 13 people treated with IV artesunate rather than IV quinine, one death was averted. In the same trial, quinine use was associated with hypoglycaemia (relative risk 3.9, $P = 0.002$). This is pertinent in pregnancy, since severe and recurrent hypoglycaemia associated with severe malaria pregnancy is exacerbated by quinine use, which stimulates insulin secretion.[6,7] These effects are more likely in the second and third trimesters of pregnancy and it is in these trimesters that the efficacy and safety data of use of artemisinin derivatives are reassuring.[8] A meta-analysis of all RCTs comparing parenteral quinine with artesunate indicated that artesunate was associated with a 35% reduction in mortality.[4] Artesunate kills circulating ring-stage parasites and so prevents sequestration, which quinine does not, and it is this mechanism of action,[9] not quinine resistance, that has been proposed for the significant reduction in mortality with IV artesunate compared when compared with IV quinine.[5] Every effort should be made to obtain IV artesunate (see Table 2 of the main report for contact details) for pregnant women with severe malaria, regardless of trimester, in an effort to prevent maternal death. Parenteral quinine should be given without delay if artesunate is unavailable but treatment should be switched to artesunate as soon as possible.

Parenteral artesunate is not currently licensed in the UK. The IV artesunate used in the multicentre study was not made to internationally recognised good manufacturing practice standards.[5] Good manufacturing practice IV artesunate is still not available and has not been licensed in the UK.[1] TropNetEurop has advocated strongly for the use of IV artesunate for severe malaria.[10] It can be made available in the UK from specialist tropical disease centres in London, Oxford and Liverpool or commercially from and Idis Pharma, who can send IV and oral artesunate to patients who need it (see Table 2 of the main report for contact details).

Treatment of malaria should never be delayed (IV quinine should be used promptly while obtaining IV artesunate). The UK guidelines explain expert consultation is required before the artesunate will be issued.[1] Severe malaria in pregnancy provides an urgent and pressing reason for artesunate to be issued (although this is not in the current guidelines).[1] IV clindamycin is a very slow-acting antimalarial and it is unlikely to add any additional value to IV artesunate, which is the fastest acting of all antimalarial drugs. In endemic countries, the treatment course when the patient is well enough to eat and drink would be any artemisinin combination therapy.[2] The only artemisinin available in the UK is Riamet® (Novartis; also known as Coartem in some countries), which can be used at standard doses, alternatively, a treatment course of atovaquone-proguanil (Malarone®, GlaxoSmithKline), four standard tablets daily for 3 days could be prescribed. Artesunate can be given intramuscularly at 2.4 mg/kg/24 hours (or oral artesunate at 2 mg/kg when available) to complete 7 days, with oral clindamycin for 7 days. Although not ideal, quinine and clindamycin can be given at the standard dose for 7 days (see Table 1 of the main report) if the preferred treatment is not available.

Uncomplicated malaria

Quinine is not thought to be teratogenic.[10-14] There is no RCT on quinine efficacy in pregnancy from Africa, where most UK patients acquire their malaria infection. Quinine is assumed to be safe and efficacious, based on historical data[15,16] and on published trials, mostly from women from South East Asia.[17] Unacceptably high failure rates have been reported with quinine monotherapy when treatment has been given in the context of an RCT. In six trials from Thailand and Burma,[18-24] in all except one,[18] there were 186 women who received quinine monotherapy and it is no longer recommended.[2] Clindamycin augments the efficacy of quinine significantly.[22] The single RCT on the effectiveness of 5 days of quinine in pregnancy resulted in failure rates greater than 30%.[24] As quinine is a rapidly eliminated antimalarial,[25] cure rates are improved with 7 day regimens, although they are poorly complied with. Note that the 5 day recommendation in the UK guidelines is for non-pregnant adults and should not be used in pregnancy.[1] Patients may deteriorate under treatment, at which point, management should be upgraded to account for severity.

The safety of clindamycin in pregnancy has been established in non-malaria studies.[26-33] It has been shown to be effective when used in combination against falciparum malaria in numerous settings,[34-36] including in pregnancy.[22,37-39]

WHO recommends artemisinin-based combination therapy in the second and third trimesters,[2,8] ahead of quinine and clindamycin, principally because of the adverse effects and risk of non-compliance with the 7-day regimen. There are now reassuring data on more than 2000 pregnancy outcomes with the use of artemisinins,[5,20-22,40,41-60] principally for uncomplicated malaria in pregnancy. Most of these studies have been RCTs in pregnant women from Africa and Asia.[20,21,40-44] This means there is now more published evidence on artemisinins in pregnancy than there is for quinine. Only one of these highly effective therapies is available in the UK (Riamet®, Novartis). For nonpregnant adults in the UK, malaria treatment guidelines prescribe three oral regimens for uncomplicated malaria, including oral quinine and doxycycline; atovaquone-proguanil, four standard tablets daily for 3 days; and Riamet, four tablets/day for weight over 35 kg. While doxycycline can be replaced with clindamycin and combined with quinine, the other two regimens have no alternatives but have been studied in the context of RCTs in the second and third trimesters of pregnancy.

Atovaquone-proguanil alone ($n = 26$)[61] and atovaquone-proguanil-artesunate ($n = 100$)[20,47,49,61] were safe and efficacious for uncomplicated *P. falciprum* in the second and third trimesters. Tinnitus was reported in 79.3% of those on quinine compared with 24.1% of those treated with atovaquone-proguanil-artesunate ($P < 0.001$) in the RCT.[20] Of the 126 women treated, most were followed through until pregnancy outcome and no adverse effects for the mother or fetus were observed. The product information sheet for Malarone® says that, while there are no adequate and well-controlled studies of atovaquone and/or proguanil hydrochloride in pregnant women, Malarone 'may be used if the potential benefit justifies the potential risk to the fetus'[62]. The same product information sheet also ignores the largest single site study ever performed on Malarone, which included 1596 nonpregnant patients randomised to receive atovaquone-proguanil, atovaquone-proguanil-artesunate or artesunate-mefloquine for uncomplicated malaria and followed-up for 42 days.[63] Adding artesunate to atovaquone-proguanil reduced the risk of failure three-fold (95% CI 1.1–8.2) although the cure rate of atovaquone-proguanil (without the addition of artesunate) was very high, 97.2% (95% CI 95.4–98.4). Atovaquone-proguanil (with or without artesunate) is likely to be a useful 3-day treatment in the treatment of *P. falciparum* in the second and third trimesters if it has not been used for prophylaxis (see Green-top Guideline No. 54A).[64]

At the time of writing, there is only one published RCT on artemether-lumefantrine treatment in pregnancy ($n = 125$) and, while the drug was well tolerated with no adverse effects on the mother or fetus, the efficacy was disappointing, with a cure rate (by delivery or day 42 if later) of 82.0% (95% CI 74.8–89.3; $P = 0.054$).[42] Pharmacokinetic data demonstrated lowered concentrations of artemether and lumefantrine in pregnancy.[57] Polymerase chain reaction confirmed that failures were as early as day 14 and 53% (9/17) had occurred at 3 weeks. Mathematical modelling has suggested an increase in the dose and length of treatment would result in

higher cure rates.[65] Two abstracts presented at the American Society of Tropical Medicine and Hygiene Annual Meeting in December 2008 analysed:

- 1001 pregnant women (artemether and lumefantrine treated, $n = 495$ and sulfadoxine-pyrimethamine treated, $n = 506$) and their fetuses or newborns (artemether and lumefantrine treated, $n = 470$ and sulfadoxine-pyrimethamine, $n = 477$) and reported no adverse effects on the fetus[55]
- preliminary results on 304 women who received artemether-lumefantrine or quinine as part of an RCT in Uganda on uncomplicated malaria in the second and third trimesters, which demonstrated high efficacy and no adverse effects on the fetus.

The product information sheet applies the usual pharmaceutical safeguard statement that 'it should not be withheld in life-threatening situations, where no other effective antimalarials are available. During the second and third trimester, treatment should only be considered if the expected benefit to the mother outweighs the risk to the fetus', until dose optimisation studies are completed.[66] However, given the reassuring data on nearly 1000 pregnant women, and the fact that it is available in the UK, it can be recommended in second and third trimesters.

Chloroquine and sulfadoxine-pyrimethamine are no longer recommended for *P. falciparum* treatment, owing to resistance,[1] with supporting data from poor efficacy in RCTs in pregnant women.[41,43,67,68]

Non-falciparum malaria

The first step in the treatment in the UK of the non-falciparum infections *P. vivax*, *P. ovale* and *P. malariae* (and *P. knowlesi*) is chloroquine to treat the symptoms caused by blood-stage infection (see Table 1 of the main text).[1] For *P. vivax* and *P. ovale*, there is a second step: the treatment of the liver-stage hypnozoites (radical cure), which causes relapse, sometimes years later. In nonpregnant adults, a course of primaquine is normally prescribed.[69] In the UK, more than 10% of patients with imported *P. vivax* treated with chloroquine followed by unsupervised primaquine 15 mg/day for 14 days relapse[70] and higher-dose primaquine 30 mg/day for 14 days has been found to be more effective.[71,72] Hence, there are different dosing schedules for *P. ovale* and *P. vivax*. Primaquine is contraindicated in pregnancy, as it could induce haemolysis and methaemo-globinaemia in the fetus.[73,74] Therefore, radical cure in pregnancy is not recommended until after delivery. There are no data on primaquine in breast milk. Fetal red blood cells are almost entirely replaced by adult red blood cells by 6 months of life. It is advisable to wait for some replacement of fetal red blood cells with adult red blood cells, which are less sensitive to haemolysis, before radical cure with primaquine in the mother. There are no published data on the use of primaquine treatment in young infants, so a cut-off age cannot be recommended, but 3 months of age is likely to be safe. To prevent relapse of *P. vivax* or *P. ovale* before delivery, weekly chloroquine (300 mg) can be given (see Table 1 of the main report). It is safe and effective and has been studied in a large RCT involving 1000 women. Infants were followed to 1 year of life and no adverse effects for the mother or fetus were observed.[75]

Evidence from nonpregnant patients has demonstrated that chloroquine-resistant *P. vivax* should be treated in the same way as chloroquine resistant *P. falciparum*.[45,76–79] However, the UK guidelines recommend chloroquine and alternative treatment if there are persistent parasites or symptoms present. In pregnant women, this could result in the onset of premature labour, whereas effective first-line treatment can prevent this outcome. The combination of quinine and clindamycin is likely to have higher cure rates than chloroquine for women with *P. vivax* infection and a history of travel in Indonesia or Papua New Guinea.[45,78,79]

Where blood or plasma concentrations of antimalarial drugs have been measured in late pregnancy, they have usually been found to be reduced, indicating under-dosing. For artemether, dihyroartemisinin, atovaquone, proguanil and lumefantrine, the reductions have been substantial and are likely to have contributed to poor therapeutic responses.[80,81]

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APPENDIX IV: Persistence of Plasmodium falciparum in the placenta after apparently effective quinidine-clindamycin therapy

The persistence of *Plasmodium falciparum* in the placenta after apparently adequate therapy with quinine has been described.[1] This phenomenon is described in the placenta of a 19-year-old woman with falciparum malaria, who was treated with a combination of quinidine and clindamycin. Although this therapy was effective and diminished (her peripheral blood parasitemia from 3% at presentation to almost undetectable at the time of delivery) vast numbers of *P. falciparum*-infected erythrocytes were present in the maternal sinusoids of the placenta. This sequestration of infected erythrocytes produced a local parasitaemia in the placenta of 70–80%. Additionally, rare *Plasmodium*-infected erythrocytes were also seen in the fetal blood of the placenta. Malaria in pregnancy and parasitic involvement of the placenta are reviewed and it is emphasised that *Plasmodium*-infected erythrocytes may persist in the placenta even after clearance of parasites from the peripheral blood.

Reference

1.   Procop GW, Jessen R, Hyde SR, Scheck DN. Persistence of Plasmodium falciparum in the placenta after apparently effective quinidine/clindamycin therapy. *J Perinatol* 2001;21:128–30.

Clinical guidelines are: 'systematically developed statements which assist clinicians and patients in making decisions about appropriate treatment for specific conditions'. Each guideline is systematically developed using a standardised methodology. Exact details of this process can be found in Clinical Governance Advice No. 1: *Development of RCOG Green-top Guidelines* (available on the RCOG website at **www.rcog.org.uk/womens-health/clinical-guidance/development-rcog-green-top-guidelines-policies-and-processes**). These recommendations are not intended to dictate an exclusive course of management or treatment. They must be evaluated with reference to individual patient needs, resources and limitations unique to the institution and variations in local populations. It is hoped that this process of local ownership will help to incorporate these guidelines into routine practice. Attention is drawn to areas of clinical uncertainty where further research may be indicated within the appropriate health services.

The evidence used in this guideline was graded using the scheme below and the recommendations formulated in a similar fashion with a standardised grading scheme. Once adapted for local use, these guidelines are no longer representative of the RCOG.

Classification of evidence levels	Grades of recommendations
1++ High-quality meta-analyses, systematic reviews of randomised controlled trials or randomised controlled trials with a very low risk of bias	**A** At least one meta-analysis, systematic reviews or randomised controlled trial rated as 1++ and directly applicable to the target population; or A systematic review of randomised controlled trials or a body of evidence consisting principally of studies rated as 1+, directly applicable to the target population and demonstrating overall consistency of results
1+ Well-conducted meta-analyses, systematic reviews of randomised controlled trials or randomised controlled trials with a low risk of bias	
1– Meta-analyses, systematic reviews of randomised controlled trials or randomised controlled trials with a high risk of bias	**B** A body of evidence including studies rated as 2++ directly applicable to the target population and demonstrating overall consistency of results; or Extrapolated evidence from studies rated as 1++ or 1+
2++ High-quality systematic reviews of case–control or cohort studies or high-quality case–control or cohort studies with a very low risk of confounding, bias or chance and a high probability that the relationship is causal	**C** A body of evidence including studies rated as 2+ directly applicable to the target population and demonstrating overall consistency of results; or Extrapolated evidence from studies rated as 2++
2+ Well-conducted case–control or cohort studies with a low risk of confounding, bias or chance and a moderate probability that the relationship is causal	**D** Evidence level 3 or 4; or Extrapolated evidence from studies rated as 2+
2– Case–control or cohort studies with a high risk of confounding, bias or chance and a significant risk that the relationship is not causal	**Good practice point**
3 Non-analytical studies; e.g. case reports, case series	✓ Recommended best practice based on the clinical experience of the guideline development group
4 Expert opinion	

This Guideline was produced on behalf of the Guidelines Committee of the Royal College of Obstetricians and Gynaecologists by: Dr R McGready PhD Dip RANZCOG, Mae Sot, Thailand; Dr EA Ashley PhD, London; Professor F Nosten MD PhD, Mae Sot, Thailand; Dr M Rijken MD PhD, Mae Sot, Thailand; A Dundorp MD PhD, Bangkok, Thailand.

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The final version is the responsibility of the Guidelines Committee of the RCOG.

The guideline review process will commence in 2013
unless otherwise indicated

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The Royal College of Obstetricians and Gynaecologists produces guidelines as an educational aid to good clinical practice. They present recognised methods and techniques of clinical practice, based on published evidence, for consideration by obstetricians and gynaecologists and other relevant health professionals. The ultimate judgement regarding a particular clinical procedure or treatment plan must be made by the doctor or other attendant in the light of clinical data presented by the patient and the diagnostic and treatment options available within the appropriate health series.

This means that RCOG Guidelines are unlike protocols or guidelines issued by employers, as they are not intended to be prescriptive directions defining a single course of management. Departure from the local prescriptive protocols or guidelines should be fully documented in the patient's case notes at the time the relevant decision is taken. Once adapted for local use, these guidelines no longer represent the views of the RCOG.