Fever of unknown origin in pregnancy: the need for a full history

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SUMMARY

A 26-year-old woman with 29 weeks gestation presented with headache, photophobia and fever. She had deranged liver function tests and low platelets on admission. Blood film, performed to look for haemolysis, revealed she had *Plasmodium vivax* malaria, despite not having travelled to an endemic malaria area for over 1 year. The diagnosis was confirmed on PCR test performed in the HPA malaria reference laboratory in London and she was treated with chloroquine. She delivered a healthy baby at 33+3 weeks gestation, and once the patient and the baby had both tested negative for glucose-6-phosphate dehydrogenase deficiency, she was given primaquine to clear the hypnozoite phase in the liver. This case highlights the importance of an extended travel history in a patient with fever of unknown origin and the difficulties of treating non-falciparum malaria in pregnancy.

BACKGROUND

In areas where malaria is endemic, the death rate from malaria in pregnancy is high. It is estimated that each year, 50 million women living in malaria-endemic areas become pregnant and death rates, as a result of malarial infection in pregnancy, are of the order of 10 000 women and 20 000 infants annually. Although in endemic areas, pregnant women and children are the most at risk group for severe malaria (eg, coma and renal failure), the actual incidence is low in these areas compared with that in women from non-endemic areas.¹ Complications are especially prevalent when infection occurs during the first trimester.²⁻³ Meta-analyses of intervention trials suggest that successful prevention of these infections reduces the risk of severe maternal anaemia by 38%, low birth weight by 43% and perinatal mortality by 27% among paucigravidae.² These studies, however, largely describe infection with *Plasmodium falciparum* and there are no published cases of imported non-falciparum malaria in pregnancy in the UK.

CASE PRESENTATION

A 26-year-old UK-born Caucasian primigravida woman presented at 29 weeks gestation with a 4-day history of headache with mild photophobia. This was associated with fever and sweats, lethargy and generalised myalgia. She had been otherwise well throughout her pregnancy and her antenatal examinations had been normal to date. She had had no contact with anyone who had been unwell. She had not travelled abroad in the previous 3 months.

Her only medical history was of depression for which she was taking citalopram. She worked as a nursery school teacher and lived with her husband.

She had never smoked and had taken no alcohol since the start of her pregnancy. She had no significant family history.

On examination, she was warm to touch and had a spiking temperature of up to 38.6°C. Her pulse was 101 bpm, blood pressure 88/43 (normal for patient), SpO₂ 96% on air and respiratory rate 18/min. Neurological examination was normal and she was Kernig's sign negative. Her heart sounds were pure and her chest was clear. Abdominal examination revealed a gravid uterus with fundal height appropriate for gestational age. Fetal HR was 154 bpm.

INVESTIGATIONS

At the time of presentation, the patient's cardiography was normal with no evidence of fetal distress or uterine contractions. Fetal ultrasound was performed which showed no abnormality.

Full blood count on admission showed mild thrombocytopenia ($112 \times 10^9/l$), which subsequently dropped to $67 \times 10^9/l$ 48 h later. She had no anaemia. Blood film on admission showed reactive changes only.

Her liver function was deranged (α -1-antitrypsin 133 U/l, Alkaline Phosphatase 123 U/l, γ -glutamyltransferase 26 U/l, bilirubin 29 μ mol/l). Further investigation into the cause of her deranged liver function tests (LFTs) revealed negative Monospot and Cytomegalovirus serology, evidence of past infection with Epstein-Barr virus, negative hepatitis A, B & C serology and abdominal ultrasound scan showed no liver abnormalities. She had a mildly elevated C reactive protein at 62 mg/l. Blood cultures were negative and viral PCR from a throat swab was negative.

DIFFERENTIAL DIAGNOSIS

At this stage, our differential diagnosis included haemolysis, elevated liver enzymes and low platelets syndrome; cholestasis of pregnancy or a viral infection.

In view of the above differential, lactate dehydrogenase was examined and found to be normal (386 units/l). We also requested a further blood film to look for evidence of haemolysis and abnormal platelets. This second blood film showed a few malarial parasites at gametocyte stage, with no ring forms identified, probably *Plasmodium ovale* or *Plasmodium vivax* infection. No parasite count was given at the time.

Further travel history was therefore obtained. She had travelled to Northern India and Goa 1 year back. She had been well while travelling and on her return. She had taken doxycycline 100 mg once daily for malaria prophylaxis while away and had not missed any doses.

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A blood sample was sent for PCR to exclude mixed infection with *P falciparum* to the HPA Malaria Reference Laboratory in London. This confirmed *P vivax* infection alone.

TREATMENT

Initial treatment was with oral quinine, with close monitoring of her blood sugar levels. Once *P vivax* was confirmed on PCR; this was changed to chloroquine (620 mg chloroquine base at 0 h, followed by 310 mg chloroquine base at 6, 24 and 48 h).

Owing to the risk of neonatal haemolysis and methaemoglobinemia were she or her baby to have glucose-6-phosphate dehydrogenase (G6PD) deficiency, she was not given Primaquine, to clear the hypnozoite phase in her liver and prevent relapse. Being Caucasian, the risk was low; however, guidelines do not differ for different ethnic groups. She was therefore given a dose of 310 mg chloroquine base once a week for the remainder of her pregnancy, as recommended by the Royal College of Obstetricians and Gynaecologists guidelines.⁴ She was negative for G6PD deficiency. As she planned to breast-feed, plans were in place to test the baby for G6PDH deficiency after delivery as there is a risk of Primaquine being excreted in breast milk and causing haemolysis in the baby.

OUTCOME AND FOLLOW-UP

Over 3 days, her symptoms improved and her fever settled. Her platelet count fell to $67 \times 10^9/l$ initially but rose to $129 \times 10^9/l$ at the time of discharge. Her LFTs were still deranged at this time, but were improving and, by clinical review at 1 month, were entirely normal.

Blood films on the patient were performed daily during admission until negative. The first positive malaria film was on day 2 of admission. Films on days 3, 4 and 5 continued to be Quantitative Buffy Coat test (QBC) positive with gametocytes; trophozoites seen on 'wide scanning'. By day 7, the film was negative for QBC testing, and no parasites were seen. At no stage was there sufficient parasitaemia to estimate a parasite load. She had further films done at clinical follow-up at 2 and 4 months, both of which were negative.

She delivered a live female baby at 33 weeks+2 days gestation. Birth weight was 2050 gm which is in the 75th centile for her gestation and head circumference was 30 cm (50th centile for her gestation). Her Apgar score at 1 and 5 min was 9 and she briefly required CPAP support. In contrast to guidance from the Royal College of Obstetrics and Gynaecology,⁴ which suggests blood films at birth and every week until 28 days, the baby had blood films performed on days 2, 3, 7 and 14 postdelivery and no malarial parasites were seen in any of these films. The baby therefore, received no treatment.

The baby tested negative for G6PD deficiency and therefore it was safe for the patient to receive primaquine treatment and continue to breastfeed. The patient was treated with primaquine 30 mg once daily for 2 weeks with no adverse effects.

Her placenta was sent for histology and showed evidence of an ascending bacterial infection with a neutrophil infiltrate. No sequestration of malarial parasites was noted. It is therefore unlikely that preterm delivery was a direct result of her malarial infection.

DISCUSSION

This case highlights the importance of an extended travel history in a patient with fever of unknown origin. Although, at admission, she was asked about travel in the last 3 months, this

was clearly not adequate. In our patient, had an extended history been taken, we may have reached a diagnosis earlier and therefore been able to start treatment sooner. This case also highlights that the diagnosis of *P vivax* malaria in pregnancy potentially carries additional complications for mother and baby compared with a non-pregnant individual.

She had been given doxycycline for malaria prophylaxis when travelling to India. Current UK guidelines⁵ advise chloroquine and proguanil as prophylaxis but many patients prefer to take doxycycline as this is to be taken once daily and is less expensive. Although doxycycline has an excess of 90% efficiency against *P falciparum*, it may not protect against hypnozoite-induced episodes of *P vivax* malaria. This may have been relevant in this case.

There are very few case reports of imported non-falciparum malaria in pregnancy, and we were able to find none in the UK. The only evidence we have for the complications of malaria in pregnancy relate to studies from endemic areas which may or may not be transferrable to the traveller from a non-endemic area. We found one case series of imported *P falciparum* malaria in pregnancy in France.⁶ A case report of *P falciparum* in pregnancy in Aberdeen, Scotland discusses the rise in the prevalence of malaria due to the increased number of travellers to endemic areas. Non-immune pregnant women are particularly prone to *P falciparum* malarial infection, with infection in the second and third trimester carrying a bad prognosis. The fact that most patients with malaria present with minimal or non-descript symptoms (eg, fever and headache) makes misdiagnosis (eg, with influenza) common.⁷

Studies in high-transmission areas have shown that primigravidae are at greatest risk of infection but this effect is less obvious in areas of low transmission. A further independent risk factor for malarial infection in pregnancy in areas of high transmission is young maternal age—particularly adolescence. This suggests that there is some immunity acquired with age and subsequent pregnancies. Last, the risk of maternal infection has been found to be highest during the second trimester.²

Presentation in endemic areas is often asymptomatic; however, in non-endemic areas, presentation in pregnancy does not differ from that in non-pregnant individuals with febrile illness, myalgia and headache, although the symptoms may be more severe.

The complications of malaria in pregnancy include maternal anaemia, low birth weight, preterm labour and/or miscarriage and congenital infection. It is thought that cytoadherence of the parasite to the placenta is the underlying cause for low birth weight and preterm labour in *P falciparum*.^{1 3 8} However, there is no evidence for this in our patient who had *P vivax*. A study from the northwestern border of Thailand⁹ compared the rates of low birth weight and maternal anaemia in a cohort of pregnant women with both *P vivax* and *P falciparum* malaria. They undertook pathological studies of the placenta postpartum and found rates of these complications were similar in the two groups. This is despite the finding of a high placental density of parasites in the *P falciparum* cohort and evidence of placental changes including increased inflammatory cells, fibrin deposition, cytotrophoblastic prominence and syncytial knotting, not found in women with *P vivax*. This suggests that there is another mechanism behind these complications other than placental dysfunction. Certainly, outcomes in either infection have been found to be worse in patients who present with fever. In contrast to previous studies, they found no evidence of parasite cytoadherence to the placenta in either group.

A study from Papua, Indonesia,¹⁰ further suggests that *P. vivax* has a significant impact on outcomes of pregnancy. In 2570 women, there was a 16.8% parasitaemia at the time of delivery with either *P. falciparum* or *P. vivax* mono-infection. *P. falciparum* malaria was associated with a significant decrease in birth weight (198 g) and an increase in the OR (2.8) for severe anaemia (Hb<7 g/dl). *P. vivax* was also associated with a lower birth weight (108 g) and increased OR for severe anaemia (1.8). Therefore, although the outcomes for *P. falciparum* are more severe those for *P. vivax* are significant.

As discussed earlier, the treatment of *P. vivax* infection in pregnancy in the UK is to prescribe chloroquine 310 mg base weekly after treatment of the acute infection to prevent relapse before birth. The use of primaquine during pregnancy is not recommended owing to the theoretical risk of haemolysis in the unborn baby from the drug crossing the placenta. After birth, if the mother chooses to breastfeed, current UK guidance is for the use of 30 mg primaquine daily for 2 weeks assuming that the baby and the mother test negative for G6PD deficiency. If the baby is to be bottle fed, only the mother requires a negative test to receive treatment. As with the use of many drugs during lactation, there is little known about the quantity of the drug excreted in breastmilk and so the risks of other potential side effects such as rash, abdominal pain, vomiting, leucopaenia and methaemoglobinaemia are unknown. In each individual case, the risk and benefit to both mother and baby should be considered.

The reported prevalence of congenital malaria varies from 8–33%. In one of the largest studies of congenital malaria carried out in a non-endemic area, *P. vivax* was found to be the predominant species. Congenital malaria can occur if malarial infection is close to delivery and presents within the first 2 weeks of life often despite appropriate treatment of the mother during pregnancy. Current guidelines suggest that placental histology and cord and baby blood films should be carried out to detect congenital malaria. A negative placental blood film significantly reduces the risk of congenital malaria. It is important to educate the mother regarding the risk of vertical transmission and that if the baby presents with fever, a blood film will be required.⁴

Learning points

- Importance of extended travel history in a patient with fever of unknown origin.
- Awareness of additional complications (low birth weight, anaemia and preterm delivery) of malaria in pregnancy
- The risks of *Plasmodium vivax* malaria in pregnancy are significant.
- Non-falciparum malaria in pregnancy can be controlled by weekly chloroquine.
- Need to avoid primaquine in pregnancy because it is not known if baby has glucose-6-phosphate dehydrogenase (G6PD) deficiency and therefore risk of haemolysis.
- Need to examine both mother and baby for G6PD deficiency, especially if intending to breastfeed.

Competing interests None.

Patient consent Obtained.

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