

Case reports: scrub typhus during pregnancy in India

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Abstract

Scrub typhus, caused by *Orientia tsutsugamushi*, is a rural zoonosis endemic in the Asian Pacific region. Doxycycline and chloramphenicol, the recommended drugs for treating this infection, may not be safe during pregnancy. We report on 5 patients with scrub typhus during pregnancy who were seen in India between October 2001 and February 2002. Four of the 5 women were treated initially with ciprofloxacin. Three women had stillbirths, 1 an abortion and 1 a low birthweight baby, which suggests that ciprofloxacin should not be used for treating pregnant women and that scrub typhus leads to severe adverse effects during pregnancy. Randomized controlled trials are urgently needed to ascertain the optimal drug choice, given that currently recommended drugs are contraindicated in pregnant women.

Keywords: scrub typhus, *Orientia tsutsugamushi*, Weil–Felix, chemotherapy, ciprofloxacin, pregnancy, India

Introduction

Scrub typhus, caused by *Orientia tsutsugamushi*, is an acute febrile rural zoonosis endemic in the Asian Pacific region in Australia, Japan, and India (Mathai *et al.*, 2001). Scrub typhus may account for up to 23% of all fever in the endemic regions of Asia. In India, the presence of scrub typhus and other types of rickettsial infection has been documented for several decades. A recent report based on serology suggested that human rickettsial diseases and scrub typhus continue to occur in southern India and that the magnitude of the problem is not recognized (Mathai *et al.*, 2001). Symptoms occur usually 2–10 d after being bitten by a mite and may be associated with an eschar, fever, lymphadenopathy, rash, headache, and myalgia. The severity of the disease varies from asymptomatic to fatal. In untreated cases, mortality may be as high as 30%. There is a paucity of information on the prevalence and effects of scrub typhus during pregnancy. Reports from other parts of the world suggest that this infection may be associated with increased fetal loss (Watt *et al.* 1999). However, there is no consensus on the choice of antibiotics to be used during pregnancy since tetracycline and chloramphenicol, currently the drugs of choice to treat scrub typhus, are preferably avoided during pregnancy. We report on 5 patients with scrub typhus during pregnancy who were seen at the Christian Medical College Hospital, Vellore, India between October 2001 and February 2002.

Materials and Methods

Sera from patients were tested using the Weil–Felix reaction with a positive cut-off titre of 1:80 for the OX-19 and OX-2 strains of *Proteus mirabilis* and the agglutinated variant strain OX-K (Mathai *et al.*, 2001). Serum samples were then sent to the Unité des Rickettsies Marseille, France for specific microimmunofluorescence (MIF) assay using whole cell antigens of *O. tsutsugamushi* serotypes Karp, Kato, Gilliam, and Kawasaki (Amano *et al.*, 1993). Sera were also tested with other antigens including *Bartonella henselae*, *Rickettsia typhi*, *Francisella tularensis*, *Coxiella burnetii*, *R. felis*, *R. japonica*, *R. helvetica*, *R. conorii*, *R. hone*, and *R. heilongjiangi*. The MIF assay was conducted as previously described for other rickettsiae (Fournier *et al.*, 2002). Positive cut-off titres were $\geq 1:128$ for immunoglobulin (Ig) G and $\geq 1:64$ for IgM.

Results

The Table summarizes the clinical and serological data of the 5 pregnant women reported in this study. All had significant antibody titres against *O. tsutsugamushi* and sera did not react with spotted fever or typhus group rickettsiae.

All 5 women tested negative by Venereal Disease Research Laboratory slide tests. In addition, blood films were negative for malarial parasites, urine cultures did not show significant growth, and blood cultures and Widal test results were negative. *Proteus* spp. were not isolated from any of the cultures.

Case 1

A 17-year-old primigravida from Tiruvannamalai district presented at 28 weeks gestation with high-grade fever of 15 d duration associated with chills, dry cough, and breathlessness. She appeared malnourished and ill. She was febrile and had bronchial breath sounds in the left subscapular area. Fundal height was 23 cm and fetal heart sounds were heard. She was given ciprofloxacin 750 mg twice a day but remained febrile. Fetal demise occurred during this period. On the twelfth day after starting ciprofloxacin treatment, the fever subsided and a macerated stillborn male baby weighing 1.2 kg was delivered.

Case 2

A 20-year-old primipara from Vellore district was admitted with a history of fever of 1 week duration soon after the home delivery of a fresh stillborn girl. She was reportedly diagnosed to have typhoid fever in another hospital and treated, presumably, with ciprofloxacin. At admission, she was febrile and had pedal oedema. The uterus was well contracted indicating normal involution and lochia was normal. As she continued to have high fever, rickettsial infection was suspected. The fever had started to subside by the time of diagnosis and she was sent home on doxycycline 100 mg twice daily for 2 weeks.

Case 3

A 24-year-old primigravida at 30 weeks gestation from Vellore district was referred with jaundice complicating pregnancy. She complained of high-grade fever with chills, vomiting, headache, dysuria, and cough with expectoration for 5 d. She had received penicillin, gentamicin, and chloroquine prior to referral. On admission, she was febrile (38 °C) and icteric. Liver and spleen were palpable 2 cm below the costal margins. Clinically, the lungs were normal. Fetal size corresponded to gestation and fetal heart sounds were heard. She was initially given ciprofloxacin and ampicillin while awaiting the results of investigations. After the Weil–Felix test result became available, she was given

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Table. Biological features, treatment, and outcome for five pregnant women with scrub typhus seen at the Christian Medical College Hospital, Vellore, India, October 2001 to February 2002

	Patient no.				
	1	2	3	4	5
Age (years)	17	20	24	32	21
Leucocyte count (mm ³)	9800	13900	12600	3900	16800
Neutrophils (%)	60	75	86	72	70
Lymphocyte (%)	36	22	9	26	30
Haemoglobin (g/dL)	10.2	12.2	8.9	8.4	12.0
Blood culture	Negative	Negative	Negative	Negative	Negative
Aspartate aminotransferase	30	84	133	214	NA
Alanine aminotransferase	12	456	63	217	NA
Alkaline phosphatase	31	102	304	73	NA
Serology					
Weil-Felix reaction (OX-2/OX-19/OX-K) ^a	-/-/320	160/-/1280	-/-/640	-/-/-	40/-/5120
Microimmunofluorescence assay (IgG/IgM) ^b					
Gilliam	256/512	2048/1024	64/1024	0/256	32/128
Karp	0/0	2048/1024	64/1024	0/64	32/32
Kato	256/512	0/0	0/0	0/0	0/0
Kawasaki	0/0	1024/1024	64/1024	128/64	0/0
Treatment	Ciprofloxacin	Ciprofloxacin	Chloramphenicol	Cefuroxime	Ciprofloxacin
Evolution of pregnancy	Stillbirth	Stillbirth	Low birthweight baby	Stillbirth	Abortion

NA, not available.

^aWeil-Felix reaction to the OX-2 and OX-19 strains of *Proteus mirabilis* and the agglutinated variant strain OX-K; positive cut-off titre 1:80.

^bPositive cut-off titre \geq 1:128 for immunoglobulin (Ig) G and \geq 1:64 for IgM.

chloramphenicol 500 mg for 10 d. She became afebrile within 1 d of starting treatment.

An ultrasound scan at 36 weeks showed fetal growth restriction and abnormal fetal Doppler wave forms. Labour was induced and a boy weighing 1.8 kg was delivered, 35 d after the patient finished her chloramphenicol treatment. The baby did not have grey baby syndrome. The placenta weighed 400 g, and had infarcts and lymphoplasmacytic infiltrates. The baby was negative for rubella IgM antibodies.

Case 4

A 32-year-old from Vellore district in her first pregnancy following *in vitro* fertilization and embryo transfer presented at 16 weeks with fever of 10 d duration, an eschar on the neck, and local lymph node enlargement. The fever subsided 8 d later and liver enzyme levels returned to normal. At this time, as Weil-Felix test was negative, she was treated for urinary tract infection empirically with cefuroxime. At 27 weeks she returned with complaints of decreased fetal movement of 2 d duration. Intrauterine death was diagnosed by ultrasound scan. She was delivered of a macerated stillborn baby weighing 470 g. It is possible that the fetal death occurred much earlier than 27 weeks because of the macerated baby and the fetal size corresponding to only 20–22 weeks of gestation.

Case 5

A 21-year-old primigravida at 11 weeks gestation from Tiruvannamalai district was admitted with high-grade fever of 15 d duration associated with chills, dry cough, vomiting, and bodyache. She was treated with ciprofloxacin for 1 d, amikacin for 2 d, and ceftriaxone for 5 d prior to referral to our institution. She had vaginal bleeding and lower abdominal pain suggestive of uterine contractions on admission. An ultrasound scan showed a dead fetus with a gestational age of 10 weeks. Fever settled following evacuation of the uterus. She was discharged on doxycycline.

All babies in the series were normal in appearance.

Discussion

The cases reported here indicate that scrub typhus is a cause of fever in pregnancy and perinatal loss in India. All women included in the study were seen during a short period of time. Limited previous experience has shown that there is an increase in scrub typhus incidence during the cooler months of the year. However, prospective studies are required to determine the extent of the problem in different parts of India and during different times of the year.

Specific serology remains the main method for diagnosis of rickettsial infection. All our cases were confirmed by MIF assay. Our data show that testing 4 different serotypes (namely Gilliam, Karp, Kato, and Kawasaki) is necessary since these strains are antigenically distinct (Ching *et al.*, 2001). The Weil-Felix reaction test (Mathai *et al.* 2001), the only available assay in India, is grossly insensitive to anti-*O. tsutsugamushi* antibodies. One of the 5 cases was negative by the Weil-Felix reaction test.

Doxycycline remains the antibiotic of choice for scrub typhus but chloramphenicol is commonly used in many endemic areas. While doxycycline is generally avoided in pregnancy because of its teratogenic potential, there are conflicting reports on the safety of chloramphenicol use during pregnancy (Amstey, 2000). Grey baby syndrome is seen in premature babies whose mothers were given chloramphenicol. Since there are no other proven effective alternatives, the use of chloramphenicol in pregnant women with rickettsial infection may be justified. This drug is freely available in India and relatively cheap.

In the 5 scrub typhus cases reported here, 3 women initially treated with ciprofloxacin and 1 treated with cefuroxime had fetal loss. The fifth received ciprofloxacin and then chloramphenicol, and had a low birthweight baby. Untreated rickettsial infections are known to cause abortions (Watt *et al.*, 1999), and transmission

of scrub typhus from mother to fetus may occur (Wang *et al.*, 1992). Neonatal transmission, as indicated by elevated IgM levels in the newborn, is also documented (Suntharasaj *et al.*, 1997). Ciprofloxacin has been shown to be effective *in vitro* against *O. tsutsugamushi* in mice (McClain *et al.*, 1988), and in 2 human cases from Nepal (Eaton *et al.*, 1989) and Thailand (Cracco *et al.*, 2000). In our cases, however, ciprofloxacin was ineffective. This contrasts with the effect of fluoroquinolones against rickettsial spotted fever or Q fever (Maurin & Raoult, 1996). We believe that fluoroquinolone compounds should be avoided in the treatment of scrub typhus. The same discrepancy between efficacy *in vitro* and in patients was reported for epidemic typhus also (Zanetti *et al.*, 1998).

Orientia tsutsugamushi resistance to doxycycline and chloramphenicol has been reported in northern Thailand (Watt *et al.*, 1996) and there is thus a need to find alternative drugs, especially those which are safe to use during pregnancy. Based on published preliminary *in vitro* and clinical studies, azithromycin (500 mg on the first day followed by 250 mg daily for 2–4 d) (Watt *et al.*, 1999) and rifampicin (600–900 mg/d orally for 1 week) (Watt *et al.*, 2000) are proposed as alternatives to doxycycline and chloramphenicol, especially during pregnancy. These drugs are also freely available in India and the costs are also comparable. However, prospective randomized controlled trials are required to define the optimal drug choice in pregnancy.

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Announcement

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