CASE REPORT

SCRUB TYPHUS DURING PREGNANCY: A CASE REPORT AND REVIEW OF THE LITERATURE

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Abstract. Scrub typhus is a rickettsial disease that is uncommon during pregnancy. We report a case of a 33-year-old woman, G_1P_0, 29 weeks pregnancy who presented to hospital with high fever, chill and headache for two weeks. Her diagnosis of scrub typhus was confirmed by serum immunofluorescent assay. She was successfully treated with chloramphenicol, but preterm delivery occurred. Her infant died from respiratory distress syndrome. No vertical transmission was demonstrated in this case. Scrub typhus should be listed in the differential diagnosis of acute febrile illness in pregnant women, who either live in, or return from, endemic areas. Chloramphenicol can be used safely during pregnancy if it is not circulating at the time of delivery.

Scrub typhus (Tsutsugamushi disease) is an acute febrile illness caused by *Orientia tsutsugamushi*, formerly called *Rickettsia tsutsugamushi* (Saah, 2000b; Watt and Olson, 2000). Its endemic areas are the South Pacific, Asia and Australia (Saah, 2000a; Watt and Olson, 2000). However, scrub typhus during pregnancy is quite rare. Only five cases have been reported in the English literature (Suntharasaj *et al*, 1997; Choi and Pai, 1998; Watt *et al*, 1999). We review available case reports of scrub typhus during pregnancy and present one case, which was successfully treated with chloramphenicol without maternal complication.

A 33-year-old, G_1P_0, 29-week pregnant woman had uneventful antenatal care at the primary healthcare center. She had good health during the first 26 weeks of pregnancy. She was admitted to Chiang Dao District Hospital in Chiang Mai, a northern province of Thailand, with high-grade fever, chill and headache for two weeks. Her physical examinations were body temperature 39.4ºC, pulse rate 100/minute, respiratory rate 22/minute, and blood pressure 90/50 mmHg. There was no jaundice, skin rash or eschar, but mild pale, injected conjunctiva, and cervical lymphadenopathy were noted. Her chest and heart were normal. The uterine fundus was at 2/4 above the umbilicus and the fetus was in a cephalic presentation, with a fetal heart rate of 160 beats/minute. A complete blood count showed hematocrit of 29.1%, white blood cell count 5,600 cells/mm^3 with 87% neutrophils, and platelets 101,000 cells/mm^3. Urinalysis, blood urea nitrogen, creatinine, and electrolytes were normal. The presumptive clinical diagnosis was scrub typhus. Serum was collected for scrub typhus antibody test, and then confirmed by serum immunofluorescent assay (IFA) with high IgG antibody titer of > 1:6400 and IgM titer of < 1:400. Treatment with 1 gram of chloramphenicol was given i.v. every 6 hours. Her clinical signs significantly improved, with no fever on the fourth day of treatment. Unfortunately, she had a regular uterine contraction on the second day and a female infant weighing 950 grams was vaginally delivered with Apgar scores five and five at one and five minutes, respectively. The infant died 6 hours later because of respiratory distress syndrome. The serological test for scrub typhus showed negative IgM. The patient was discharged 10 days after an uneventful recovery and was well at 2- and 6-week follow-up.

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Scrub typhus is an acute infectious disease that is transmitted to humans by the larval stage (chigger) of trombiculid mites (Saah, 2000b). Rickettsial infection is common in Thailand and it is the tenth ranked most common cause of acute febrile illness in the northern region (Suntharasaj *et al*, 1997). Scrub typhus during pregnancy is rare. Only five cases were reported in English literature (Suntharasaj *et al*, 1997; Choi and Pai, 1998; Watt *et al*, 1999). We report a case of scrub typhus that occurred in early third trimester, with subsequent preterm delivery.

The clinical symptoms of scrub typhus for pregnant women are the same as for the non-pregnant. Its clinical symptoms (*eg* fever, headache, myalgia, and cough) cannot helpfully distinguish scrub typhus from other infections (Brown *et al*, 1977; Suntharasaj *et al*, 1997). In this case, the patient had high fever and headache without rash or eschar. Rash and eschar are not often seen in Thai patients (Suntharasaj *et al*, 1997). Normally, the incubation period of the disease is about 6-18 days after exposure (Saah, 2000b; Watt and Olson, 2000). Its onset is usually sudden, but it can be insidious (Suntharasaj *et al*, 1997; Saah, 2000b). Its clinical symptoms are high fever, chill, severe headache, and myalgia (Saah, 2000b). Generalized lymphadenopathy, detected in this case, is found in about 85% of patients 8 days after exposure (Suntharasaj *et al*, 1997; Saah, 2000b). A maculopapular rash is mostly observed by the end of the first week of illness (Suntharasaj *et al*, 1997; Saah, 2000b). Other common manifestations include splenomegaly (43%), conjunctivitis (29%), pharyngitis (28%), and hepatomegaly (13%) (Hoeprich and Jordan, 1989). A necrotic eschar, a typical skin lesion, develops in 60% of primary infections and less frequently in secondary ones. Generally, it is found in the lower extremities (Watt and Olson, 2000).

The diagnosis of scrub typhus is based on exposure history, clinical symptoms, and serological studies (Brown *et al*, 1983). The diagnosis in this case was based on clinical symptoms: fever, chill and headache, and the serological test confirmed by a specific immunifluorescent assay titer of 1:6400 ($p<0.05$) (Brown *et al*, 1983). A specific IgM titer of greater than 1:50 is recognized as significant (Shirai *et al*, 1981). The infant had no neonatal infection from the normal IgM antibody by IFA. Vertical transmission from transplacental infection has been reported (Wang *et al*, 1992; Suntharasaj *et al*, 1997). This can be explained by acute febrile illness during pregnancy (Suntharasaj *et al*, 1997). The other transmission was perinatal blood-borne infection during labor, if the mother was in a rickettsemic status (Wang *et al*, 1992).

In this case, the patient was successfully treated with chloramphenicol. Currently, the recommended treatment for scrub typhus is either tetracycline (doxycycline) or chloramhenicol (Watt and Olson, 2000). According to the United States Food and Drugs Association fetal risk summary, tetracycline is classified as a class D drug, and should not be used to treat pregnant women (Briggs *et al*, 2002). Chloramphenicol is classified as a class C drug. Although there are no available data that indicate it is safe for pregnant women, clinical data indicate that chloramphenicol is safe for use in pregnancy if it is not circulating at the time of delivery, since the drug may cause gray baby syndrome (Briggs *et al*, 2002). As recently reported, azithromycin, a new macrolide antibiotic, has been proven for the effective treatment of scrub typhus (Choi and Pai, 1998; Watt *et al*, 1999). So far, no evidence suggests that azithromycin causes harm to either fetus or baby. Thus, it may be a drug of choice for treating scrub typhus in pregnant women (Choi and Pai, 1998).

As previously reported (Suntharasaj *et al*, 1997), the complication in this case was preterm delivery. Although the patient recovered quite well after treatment with chloramphenicol, her infant later died from respiratory distress syndrome. Further more, no sequelae were detected in the patient throughout the 6-week follow-up period.

The English language literature concerning scrub typhus in pregnancy, available from Medline between the years 1966 and 2002, was reviewed. Three publications (Suntharasaj *et al*, 1997; Choi and Pai, 1998; Watt *et al*, 1999) and 5 cases were found, including this case (Table 1). Each case occurred in pregnant women aged between 26-37 years with a gestational age of 3-34 weeks. Four of them were treated with azithromycin and the others with chloramphenicol. Two cases had no pregnancy complications, while 2 cases had preterm deliveries and 1 case had an abortion. Another one had not come for follow-up.

Table 1
Literature review: cases of scrub typhus during pregnancy (Suntharasaj *et al*, 1997; Choi and Pai, 1998; Watt *et al*, 1999).

Authors (year)	Age (years)	Gravida and parity	Gestational age (weeks)	Symptoms and signs	Treatment	Maternal outcome	Fetal outcome
Suntarasaj *et al* (1997)	31	G_2P_1	34	Fever, chill, cough, headache	Intravenous ampicillin, gentamicin, chloramphenicol	Complete recovery	Preterm delivery by C/S, neonatal scrub typhus
Choi and Pai (1998)	27	-	19	Fever, headache, skin rash, eschar	Oral azithromycin	Complete recovery	Term delivery, healthy
	37	-	24	Fever, skin rash, eschar	Oral azithromycin	Complete recovery	Term delivery, healthy
Watt *et al* (1999)	26	G_3P_0	3	Fever, cough, hearing loss, generalized lymphadenopathy	Oral azithromycin	Complete recovery	Abortion
	30	-	26	Fever, cough, hearing loss, lymphadenopathy, conjunctival suffusion	Oral azithromycin	Complete recovery	Not known
Present case	33	G_1P_0	29	Fever, chill, headache, injected conjunctiva, cervical lymphadenopathy	Intravenous chloramphenicol	Complete recovery	Preterm delivery, Death from RDS

C/S: Cesarean section, RDS: Respiratory distress syndrome

In conclusion, scrub typhus should be listed in the differential diagnosis of acute febrile illness in pregnant women who either live in, or return from, endemic areas. Chloramphenicol can be safely used during pregnancy.

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