



Pregnancy and Scrub Typhus

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Introduction

Scrub typhus (Tsutsugamushi disease) is a rickettsial infection. It is an acute febrile illness caused by *Orientia tsutsugamushi* formerly called *Rickettsia tsutsugamushi* (1-3). It is transmitted to human by the bite of trombiculid mite larvae (chiggers). Its endemic areas are northern Japan, eastern Australia, and eastern Russia that includes the Indian subcontinent, western Russia, China, Southeast Asia and the Far East (4). *Orientia tsutsugamushi* exhibits a wide heterogeneity that may lead to the defining of several species in this genus. Major serotypes have been identified and must be included in serologic tests to detect scrub typhus, including serotypes Gilliam, Karp, Kato, Boryon, and Kawazaki. *O. tsutsugamushi* is transmitted transovarially in mites and is more common in females. Seasonality of the disease is determined by the appearance of larvae. In temperate zones, scrub typhus is observed mainly in the autumn but also in the spring (4). Its current prevalence is not known, but in Thailand and Laos, along with leptospirosis and murine typhus, it is one of the two most frequent infections reported in hospitalized patients. It is also common in India but is apparently grossly underreported (4). Rickettsial infection is common in Thailand & it is the 10th most common cause for acute febrile illness in the Northern region of Thailand (5).

Scrub Typhus and Pregnancy

Scrub typhus during pregnancy is quite rare. Only 22 cases were reported in the English literature (5-12) (Table-1).

Clinical Manifestations

The clinical symptoms of scrub typhus in pregnant women are the same as in the non-pregnant (8). Normally, the incubation period is about 6-18 days after exposure (2, 3). Onset is usually sudden, but it can be insidious (3, 5). Clinical symptoms are high fever, chills, severe headache and myalgia (3). The clinical symptoms (e.g. fever, headache, myalgia and cough) are not helpful in distinguishing scrub typhus from other infections (5, 13). Generalized lymphadenopathy is found in about 85% of patients 8 days after exposure (3, 5). A maculopapular rash is mostly observed by the end of the first week of illness (3, 5). Other common manifestations include splenomegaly (43%), conjunctivitis (29%), pharyngitis (28%), and

hepatomegaly (13%) (14). A necrotic eschar is a typical skin lesion that develops in 60% of patients in the primary infection and less frequently in the secondary one. Generally, it is found in lower extremities (2). Compared to murine typhus, scrub typhus more commonly presents with eschar & lymphadenopathy (15).

Diagnosis

Diagnosis of scrub typhus during pregnancy is same as in non pregnant women & is based on an exposure history, clinical symptoms and confirmed serological studies (8,16). Serology is the preferred diagnostic tool. *O. tsutsugamushi* serologic tests include indirect fluorescent antibody (IFA) and immunoperoxidase assays. The IFA assay is 92% sensitive with 11 days of fever (17). The Weil-Felix test detects cross-reacting antibodies to *Proteus mirabilis* OX-K. The Weil-Felix test is still used because of its low cost (4). It is, however, insensitive and non-specific. Isolation of *O. tsutsugamushi* can be done in cell culture or in inoculated mice.

The organism is visualized in the spleens of infected mice by Giemsa (or Diff-Quick) staining, not by Gimenez stain, as is used for *Rickettsia* (4). Polymerase chain reaction amplification of blood, skin, or lymph node samples is useful, but not generally available in endemic parts of the world. Usually, the primers are selected from the gene that codes for the 56-kDa protein gene (18, 19).

Differential Diagnosis

The differential diagnosis includes fever of unknown origin, enteric fever, dengue fever, other rickettsial infections, tularemia, anthrax, leptospirosis, malaria, and infectious mononucleosis.

Pregnancy Outcomes

During pregnancy, scrub typhus may lead to spontaneous abortion, stillbirth (6, 9, 10), preterm delivery (5, 8) and small for gestational age infants (9, 12). The English literature concerning scrub typhus in pregnancy was reviewed between year 1966 and 2009 on Medline. Currently, there were eight publications (5-12) and 22 cases (Table 1). Each case occurred in pregnant women aged between 17-37 years with a gestational age of 3-34 weeks. Fourteen patients were treated with azithromycin, three

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Table 1. Literature review: Cases of Scrub Typhus During Pregnancy (5-12)

Authors	Age (yrs)	Gravida & parity	Gestational age (wks)	Symptoms & signs	T/t	Maternal outcome	Fetal outcome
Tsui <i>et al</i> (11) 1992	34	-	32	-	Minocycline	Complete recovery	Term Delivery, Healthy
Suntarasaj <i>et al</i> (5) 1997	31	G ₂ P ₁	34	Fever, Chills, Cough Headache	IV ampicillin, gentamicin chloramphenicol	Complete recovery	Preterm Delivery by CS, Neonatal Scrub Typhus
Choi & Pai (7) 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 <i>et al</i> (6) 1999	26	G ₃ P ₀	32	Fever, Cough, Hearing Loss, Lymphadenopathy	Oral Azithromycin	Complete recovery	Abortion
	30	-	26	Fever, Cough, Hearing Loss, Lymphadenopathy conjunctiva suffusion	Oral Azithromycin	Complete recovery	Not Known
Mathai <i>et al</i> (9) 2003 Five Cases	17	G ₁ P ₀	28	Fever, Chills, Dry Cough, Breathlessness	IV Ciprofloxacin	Delay Response	Still Birth
	20	G ₁ P ₀	NA	Fever, Cough, Pedal Edema	Ciprofloxacin + Oral Doxycycline	Delay Response	Still Birth
	24	G ₁ P ₀	30	Fever, Chills, Cough, headache, jaundice, dysuria	IV Choramphenicol	Complete Recovery	Preterm & SGA
	32	G ₁ P ₀	16	Fever, Lymphadenopathy	Cefuroxime	Complete Recovery	Still Birth
	21	G ₁ P ₀	12	Fever, chills, dry cough, vomiting, bodyache	Ciprofloxacin Oral Doxycycline	Delay Recovery	Abortion
Phupong & Srettakraikul (8) 2004	33	G ₃ P ₀	29	Fever, chills, headache, Cough, Lymphadenopathy	IV Choramphenicol	Complete recovery	Preterm Delivery Died due to ARDS
Kim <i>et al</i> (12) 2006 (9 cases)	22-34	NA	12-30	Fever (7), Rash (9), headache (9), Myalgia (7)	Oral Azithromycin	Complete recovery	Term Delivery, Healthy (7) Ter Delivery & SGA (1) Not Known (1)
McGready <i>et al</i> (10) 2009	34	G ₅ P ₃	9	Fever, chills, headache, muscle, joint and back pain, dysuria, dizziness, vomiting, inguinal lymphadenopathy	Oral Azithromycin	Complete recovery	Abortion

with chloramphenicol, three with ciprofloxacin, and one each with minocycline and cefuroxime. Eleven cases ended as term pregnancy (one had a small for gestational age infant). Three cases ended with preterm delivery (one had a small for gestational age infant and one died from respiratory distress syndrome). Three cases ended with stillbirth & 3 with abortions. Another 2 did not come to follow-up.

Vertical transmission

There have been reports of vertical transmission from transplacental infection causing neonatal scrub typhus (5,

20). They occurred in mother with acute febrile illness during pregnancy (5). The other transmission was in perinatal blood-borne infection during labor from a mother with rickettsemia (20).

Treatment

Tetracycline or doxycycline and chloramphenicol remain the recommended treatment in non-pregnant cases (2). Doxycycline is usually given as 100 mg PO twice daily for 7 days but can also be given in a single dose or for short periods (3 to 7 days), although relapse can occur. Doxycycline is recommended for use in children as well.



Chloramphenicol is given as 50 to 75 mg/kg per day in four divided doses (4). The United State Food and Drugs Administration fetal risk summary list tetracycline as class D drug, meaning that it should not be used for treatment in the pregnant (21). Chloramphenicol is classified as class C drug. Clinical data indicate that chloramphenicol is safe to use in pregnancy if it is not circulating at the time of delivery where it may cause gray baby syndrome (21). Alternative drugs, include rifampicin (600 to 900 mg/day), roxithromycin (150 mg twice a day) and azithromycin (500 mg the first day and 250 mg/day later). They have been used for treatment of scrub typhus effectively (6, 7, 22, 23). So far, no evidence suggests that roxithromycin and azithromycin cause harm to either fetus or children (21). Thus, it may be a drug of choice for treatment of scrub typhus in pregnancy (7, 8, 22). Ciprofloxacin, in experience with pregnant women in India, is ineffective and should not be used (9).

Prevention

Currently, there is no vaccine for scrub typhus. Prevention is limited to the use of insect repellents during travel in rural areas of endemic countries.

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. The symptoms and signs during pregnancy are not different from non-pregnant women. Treatment with roxithromycin and azithromycin is safe during pregnancy. Chloramphenicol is an alternative drug and safe to use in pregnancy.

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