Scrub typhus in pregnancy: Maternal and fetal outcomes

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Abstract

Scrub typhus is an important unrecognized cause for undifferentiated acute febrile illness in India associated with poor fetal outcomes. Maternal and fetal outcomes among pregnant patients with scrub typhus presenting to a tertiary care university teaching hospital from January 2010 to July 2012 were studied. Scrub typhus was diagnosed by clinical criteria along with scrub ELISA positivity or an eschar. In total, 33 of 738 patients (4.5%) who were diagnosed with scrub typhus were pregnant; 57.6% were in the third trimester, 27.3% in the second, and only 15.2% in the first trimester; 69.7% required admission to intensive care. Mortality was low (3%, $n = 1$) compared to 12.2% mortality reported previously. All patients were treated with Azithromycin. Poor fetal outcome was observed in 51.5% of these pregnancies with fetal loss occurring in 42.4% and preterm childbirth in 9.1%. Scrub typhus complicating pregnancy is associated with a poor fetal outcome despite treatment with Azithromycin. A majority require intensive care treatment for survival.

Keywords

Scrub typhus, pregnancy, infectious complications

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Introduction

Scrub typhus, caused by Gram-negative intracellular coccobacilli *Orientia tsutsugamushi*, was first isolated and identified in 1930 in Japan.¹ This disease affects close to a million people a year in an endemic area called as the “tsutsugamushi triangle,” which extends from northern Japan and far-eastern Russia in the north, to northern Australia in the south, and to Pakistan in the west.^{2,3} This disease occurs commonly through the semi-arid regions covering most of the Indian subcontinent and is emerging zoonosis in the tropics with increasing urbanization of rural areas. Scrub typhus is transmitted by the bite of the chigger (larval stage) of trombiculid mites. The bite presents as an eschar (Figure 1), usually single, that is used for diagnosis of the disease. It is painless ulcer with a necrotic center that scabs resembling a cigarette burn usually found in the axilla, groin, genitalia, and neck. The disease presents with a spectrum of clinical manifestations ranging from self-limited to death, with untreated case fatality reaching as high as 30%.⁴ It is also an important unrecognized cause for undifferentiated acute febrile illness in India with a high case fatality rate and has been found to be associated with poor fetal outcomes among affected pregnant women.^{5,6}

Methods

The medical records of patients admitted to medical units between January 2010 and June 2012 at the 2700 bed university teaching hospital in South India were reviewed. Those diagnosed with scrub typhus based on modified World Health Organization (WHO) criteria as response to tetracycline was not feasible, given that tetracyclines are contraindicated among pregnant women (Table 1) were recruited if they were pregnant at the time of developing symptoms of illness.⁴ Gestational age was determined by ultrasound confirmation. Data on fetal and maternal outcomes among these patients were obtained by review of hospital records and from the labor room database. Mean with standard deviations were calculated for continuous variables. Student's *t*-test was used to compare means between the patients who had good and poor fetal outcomes. Multivariate analysis was done using three variables to identify independent risk factors for poor fetal outcome.

Results

A total of 16,860 patients were admitted into the medical wards during the study period, of whom 738 (4.3%) were diagnosed to have scrub typhus based on clinical presentation along with an eschar or typical clinical presentation with scrub ELISA positive or a combination of all the above. There was a slight preponderance of women 410 (55.6%). Of these, 33 of 738 (4.5%) were pregnant when they developed the disease; 19 (57.6%) of them had developed the disease in the third trimester while the remaining 9 (27.3%) and 5 (15.2%) in their second and first trimester, respectively. Clinical presentation and laboratory findings are summarized in Table 2; 23 (69.7%) women required intensive care which included assisted ventilation and inotropes support. All patients received Azithromycin, and 33% of the patients also received Doxycycline (post-delivery or abortion) as treatment. Mortality was reported in one patient (3%).

Poor fetal outcomes were observed in 17 (51.5%) pregnancies with intrauterine deaths and spontaneous abortion occurring in 14 (42.4%) cases, while 3 (9.1%) had preterm births at 36, 32, and 32 weeks of gestation. One fetal outcome was not known but the remaining 15 (45%) either progressed with pregnancy with no fetal or neonatal complications (Table 3). Longer duration of illness at presentation, low albumin, and hypotension were associated with a poor fetal outcome in univariate analysis with $p < 0.05$. Duration of illness more than seven days was an independent risk factors for a poor fetal outcome on multivariate analysis with an odds ratio of 2.46 (95% CI 1.6–85.9, $p = 0.01$).

Discussion

Scrub typhus is a common cause of undifferentiated febrile illness in South India. The common causes for an undifferentiated acute febrile

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Figure 1. An eschar: centrally black scab with surrounding erythema resembling a cigarette burn.

Table 1. WHO criteria for diagnosis of scrub typhus.³

Clinical description: acute onset fever along with headache, sweating, conjunctival injection, with dull macular popular rash over the trunks and extremities
Defervescence within 48 h following tetracycline initiation ^a
Presence of a primary “punched out” skin ulcer (eschar), where the bite occurs.
Laboratory criteria for diagnosis: isolation of <i>Orientia tsutsugamushi</i> by inoculation of patient’s blood in white mice ^a
Serology detection scrub typhus IgM
I:100 or higher by EIA by ELISA ^b
I:32 dilution or higher by IP ^a
I:10 dilution or higher by indirect IF ^a
Case classification:
Suspected: a case that is compatible with the clinical profile
Confirmed: a suspected case with laboratory confirmation

IgM: immunoglobulin M; EIA: enzyme immunoassay; IP: immunoperoxidase; IF: immunofluorescence.

^aNot used in the case definition.

^bKit used: PanBio Ltd, Brisbane, Australia.

illness as found in a study done in this region were scrub typhus, malaria, enteric fever, dengue, leptospirosis, spotted fever rickettsiosis, and Hantavirus, in the order of frequency.⁷ Awareness of this disease among primary care physicians is, however, still rudimentary. In this study, the high proportion of presentations in the third trimester probably reflected referral bias as sicker and more complicated patients tend to get referred to the tertiary care center. However, the gestation age at onset had no significant impact on maternal or fetal outcomes. Nearly 70% of the patients who were pregnant required intensive care therapy for survival.

Although all received recommended treatment with Azithromycin, half had poor fetal outcomes. This study noted a lower maternal case fatality rate compared to a previous similar study.⁵ Improved supportive treatment and increased awareness of the disease and its progression after previous studies could have been one of the factors influencing the better overall outcome in this study. Azithromycin seems to be an effective agent against scrub typhus because it efficiently penetrates polymorphonuclear leukocytes and macrophages, which are target cells for *O. tsutsugamushi*.⁸ We used a dose of 500 mg intravenously for one week. The dose of Azithromycin used to treat scrub typhus in pregnancy has varied from a single 500 mg dose to 1–2 g for three to five days.⁶

With suboptimal reproductive health services in rural areas, the burden of morbidity and mortality due to scrub typhus is bound to increase among the low- and middle-income countries. Urbanization combined with deforestation in semi-arid regions expose increasing numbers to these vectors and low level of awareness among practitioners may add to the disease burden. Although availability of effective and cheap antibiotics provides an effective and timely solution, this along with unregulated antibiotic availability over the counter may undermine its long-term effectiveness in the future. Meticulous search for an eschar in patients presenting with undifferentiated febrile syndrome can clinch the diagnosis even in a resource poor setting. Increasing awareness among practitioners is necessary to prevent fetal loss among pregnant women with scrub typhus as early diagnosis and start of appropriate therapy can prevent fetal loss as shown in this study.

Limitations of the study include incomplete follow up of the pregnant women, particularly those diagnosed in the early trimesters. The birth weight of infants born to the women was also not available. Scrub typhus complicating pregnancy is associated with a poor fetal

Table 2. Clinical profile of pregnant women with scrub typhus.

Symptoms	Total n = 33, n (%), mean (SD)	Good fetal outcome, n = 15	Poor fetal outcome, n = 17	p value
Duration of illness	7.0 (3.1)	5.64 (2.1)	8.16 (3.3)	<.03
Headache	11 (33)	6 (40)	5 (29)	NS
Altered sensorium	4 (12)	3 (20)	1 (5)	NS
Vomiting	9 (27)	5 (33)	4 (23)	NS
Breathlessness				
MRC grade 1–2	12 (36)	6 (40)	6 (35)	
MRC grade 3–5	21 (63)	9 (60)	11 (64.7)	NS
Heart rate (bpm)	117 (16)	119 (17)	116 (15)	NS
MAP (mmHg)	71.52 (9.12)	74 (9.8)	69.9 (8.9)	NS
SBP (mmHg)	95.7 (11.4)	101.4 (13.4)	92.1 (9.1)	NS
RR (per min)	36.71 (12.3)	32.9 (14.5)	39.6 (10.8)	
Hepatosplenomegaly	4 (12)	2 (13)	2 (11)	NS
Eschar	17 (51.5)	6 (40)	11 (64.7)	NS
Hb	9.97 (2.01)	9.6 (1.9)	9.3 (2.2)	NS

(continued)

Table 2. Continued

Symptoms	Total <i>n</i> = 33, <i>n</i> (%), mean (SD)	Good fetal outcome, <i>n</i> = 15	Poor fetal outcome, <i>n</i> = 17	<i>p</i> value
Platelet count × 10 ⁹ /L	67 (44)	87 (52)	82 (61)	NS
Leucocyte counts × 10 ⁹ /L	12.6 (4.2)	11.8 (4.7)	13.4 (3.7)	NS
Absolute neutrophil count × 10 ⁹ /L	9.7 (3.4)	9.1 (3.4)	10.3 (3.4)	NS
S. albumin g/dL	2.3 (0.48)	2.55 (0.5)	2.09 (0.3)	0.005
SGOT/AST IU/L	135.2 (85.2)	152.8 (112)	119.7 (50)	NS
SGPT/ALT IU/L	61.1 (61.5)	74.0 (86.2)	49.82 (22.7)	NS
SGOT: SGPT	2.7 (1.1)	2.8 (1.2)	2.7 (1.1)	NS
Alkaline phosphatase IU/L	254.4 (190)	211.4 (189)	292.35 (188)	NS
Creatinine mg/dL	1.01 (0.55)	1.06 (0.7)	0.98 (0.3)	NS
Urinary sediments ^a	15 (66)	6 (50)	9 (64)	NS

NS: not significant; MRC: Medical Research Council grade of breathlessness; SGOT: serum glutamic oxaloacetic transaminases; AST: aspartate amino-transferase; SGPT: serum glutamic pyruvate transaminases; ALT: alanine aminotransferase; MAP: mean arterial pressure; SBP: systolic blood pressure; RR: respiratory rate; Hb: haemoglobin.

^a>5 white or red blood cells/high power field or presence of RBC casts or coarse granular casts on microscopy.

Table 3. Maternal and fetal outcomes of pregnancy with scrub typhus.

Gestational age	<i>n</i> (%)	Fetal outcome			Maternal outcomes			
		Fetal loss	Preterm delivery	Good fetal outcome ^a	Mortality	ICU admission	Organ dysfunction	
							Single	Multiple
First trimester	5 (15.2)	4	0	1	0	4	3	1
Second trimester	9 (27.3)	2	0	7	0	4	4	0
Third trimester	19 (57.6)	8	3	7	1	15	11	4
Total <i>n</i> (%)	33	14 (42.4)	3 (9.1)	15 (45.5)	1 (3)	23 (69.7)	18 (54.5)	5 (15.2)

ICU: intensive care unit.

^aPregnancy continued or delivered normal baby.

outcome despite treatment with Azithromycin. A majority of this group require intensive care treatment for survival.

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Contributorship

SJR conceptualized, designed the study, and did the literature review, data collection, analysis and manuscript preparation, editing and manuscript review. SS and AJM were involved in conceptualization and design of the study and in the manuscript editing and review process.

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