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ORIGINAL ARTICLE

Clinical Profile of Scrub Typhus in Pregnancy in Sub-Himalayan Region

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Abstract

Background Scrub typhus is rare in pregnancy, but it has now become an important cause of febrile illness in pregnancy in sub-Himalayan region of India. Only a few case reports have been published so far, and they show adverse maternal and fetal outcomes. No consensus has been reached till now regarding treatment.

Methodology All the pregnant patients irrespective of period of gestation admitted with febrile illness with positive IgM ELISA for scrub typhus with or without eschar were included. The clinical profile was observed using a detailed history of symptoms, travel, recreation, agricultural activities, treatment record prior to admission, and a detailed examination, and the treatment outcome was noted. Fever workup including cultures, CXR, CSF analysis, serology for scrub was done. IgM scrub typhus was done by kit method manufactured by InBios Intertational, Inc.

Results We observed in total 14 pregnant patients out of which eight were in the the second trimester and six were in the third trimester. The clinical features of the disease observed for pregnant females were the same as for

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nonpregnant females. There was no difference in the severity of scrub typhus between pregnant and nonpregnant women. No mortality was found in these patients. On follow-up, they had normal peripartum and postpartum periods. All were treated with azithromycin 500 mg once a day for 5 days.

Conclusion Although rare, scrub typhus should be considered in differential diagnosis of fever in pregnant patients especially in scrub season. Azithromycin should be the drug of choice in pregnancy as it has no adverse effect on fetus and pregnancy outcome.

Keywords Scrub typhus · Pregnancy · Outcome · Azithromycin · Mortality

Introduction

Scrub typhus is a rickettsia borne zoonosis which has emerged as an important cause of febrile illness in sub-Himalayan region of India. It is transmitted to humans 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 [1, 2]. The clinical manifestations of the disease vary in severity from mild and self-limited to fatal, and the case-fatality rate can be as high as 30 % if untreated [3]. Scrub typhus during pregnancy is quite rare. Only few case reports and case series have been published so far. Diagnosis of scrub typhus during pregnancy is the same as in nonpregnant women There has been reports that scrub typhus may lead to spontaneous abortion, stillbirth, preterm delivery and small for gestational age infants but still exact impact in final maternal and fetal outcome is still unclear [4, 5]. Doxycycline continues to be the standard therapy for scrub typhus in nonpregnant adults; however, being a class D drug according to the U.S. Food and Drug Administration (FDA), it is contraindicated in pregnant women. Azithromycin has been reported to effectively cure scrub typhus in pregnant women and showed favorable pregnancy outcomes [5–7]. Till date, no other study based on IgM ELISA from sub-Himalayan region has described the clinical profile and outcome of scrub typhus in pregnant females.

Methodology

In the present study, we observed the profile of subgroup of pregnant patients from the larger observational study which included all the patients more than 18 years of age. All the pregnant patients irrespective of period of gestation admitted with febrile illness with positive IgM ELISA for scrub typhus with or without eschar were included. This was a prospective observational study conducted in the Department of Medicine and Microbiology,IGMC, Shimla from July 2012 to June 2013. The clinical profile was observed using a detailed history of symptoms, travel, recreation, agricultural activities, treatment record prior to admission, and a detailed examination, and the treatment outcome was noted. Fever workup including cultures, CXR, CSF analysis, serology for scrub was done. IgM scrub typhus was done by kit method manufactured by InBios Intertational, Inc. This was qualitative ELISA for the detection of IgM antibodies to *O. tsusugamushi* in serum. Statistical analysis was done using EPI info 2000 (Center of Disease Control and Prevention, Atlanta, GA, USA) and SPSS student version 16.0 (SPSS Inc, Chicago, US). Later, all the patients were followed up for pregnancy outcome and perinatal complications.

Results

We observed total 14 pregnant patients out of which eight were in the second trimester and six were in the third trimester. Profile of patients has been tabulated in Table 1. All the patients were from rural background and were engaged in active outdoor agricultural work. Fever was present in 14 (100 %) patients, shortness of breath: 5 (35.71 %), abdomen pain: 4 (28.56 %), vomiting: 2 (14.28 %) and altered sensorium in 1 (7.10 %) patient. Tachycardia was present in 14 (100 %) patients, temperature >100 °F: 14(100 %), tachypnea: 5 (35.84 %), hypotension: 6 (42.81 %), pallor: 11 (78.28 %), icterus: 1 (7.10 %), lymphadenopathy: 4 (28.56 %), eschar: 3 (21.42 %), and rash in 2 (14.28 %) patients (Table 1). Low hemoglobin (<11 g) in 11 (78.56 %), increased TLC (>12,000 mm^3) in 3 (21.42 %), increased ESR (>20) in 13 (92.56 %), low platelets (<1.5000 lakh) in 3 (21.42 %), increased blood urea (>40 mg) in 5 (35.70 %), increased bilirubin (>2.5 mg) in 3 (21.42 %), low serum protein (<5 gm) in 5 (25.71 %), low albumin (<3.5 g) in 7 (49.98 %), increased SGOT/SGPT in 12 (92.30 %), increased S. Alkaline phosphatase in 4 (28.56 %) patients (Table 2). Hepatic dysfunction was present in 11 (49.98 %), sepsis: 10 (71.48 %), severe sepsis: 5 (35.70 %), renal dysfunction: 5 (35.70 %), ARDS: 4 (28.56 %), MODS: 4 (25.80 %), and septic shock in 5 (35.70 %) patients (Table 3). All patients were treated with azithromycin 500 mg for 5 days and survived (Table 1). Average period of deference was 48–72 h. The hospital stay was <7 days in 8 (56.10 %) patients, 7–14 days in 5 (35.71 %) patients, and >14 days in 1 (7.14 %) patient. Pregnancy outcome was favorable in all patients with normal term delivery on follow-up.

Table 1 Clinical profile of patients

		P 1	P 2	P 3	P 4	P 5	P 6	P 7
1	Age(y)	18	23	29	24	26	27	35
2	POG(weeks)	34	15	26	29	30	31	22
3	Fever (days)	6	4	3	3	9	4	3
4	Shortness of breath	−	+	−	−	−	−	−
5	Vomiting	−	−	−	+	−	−	−
6	Abdomen pain	−	+	−	+	−	+	−
7	Altered sensorium	−	−	−	−	+	−	−
8	Tachycardia (>90/min)	+	+	+	+	+	+	+
9	Temperature (>100 °F)	+	+	+	+	+	+	+
10	Tachypnea (24/min)	−	+	−	−	−	−	−
11	Hypotension (<90 mm of Hg)	−	+	−	−	+	+	−
12	Pallor	+	+	+	+	+	+	−
13	Icterus	−	−	−	−	−	+	−
14	Lymphadenopathy	−	−	Axillary	Generalizedised	−	Axillary	−
15	Eschar	−	Inguinal	−	−	−	Axilla	−
16	Rash	Trunk	−	−	−	Trunk	−	−
17	Stay in hospital (days)	12	>14	5	6	10	12	5
18	Pregnancy outcome/birth weight (kg)	Term delivery/2.8	Term delivery/NA	Term delivery/3.2	Term delivery/NA	Term delivery/NA	Term delivery/NA	Term delivery/3
19	Treatment given	Azithromycin	Azithromycin	Azithromycin	Azithromycin	Azithromycin	Azithromycin	Azithromycin
20	Outcome	Survived	Survived	Survived	Survived	Survived	Survived	Survived
		P 8	P 9	P 10	P 11	P 12	P 13	P 14
1	Age(y)	28	22	25	25	24	33	20
2	POG(weeks)	26	32	34	20	26	21	24
3	Fever (days)	8	5	8	8	5	3	9
4	Shortness of breath	+	−	−	+	−	+	+
5	Vomiting	−	−	−	−	+	−	−
6	Abdomen pain	−	+	−	+	−	−	−
7	Altered sensorium	−	−	−	−	−	−	−
8	Tachycardia (>90/min)	+	+	+	+	+	+	+
9	Temperature (>100 °F)	+	+	+	+	+	+	+
10	Tachypnea (24/min)	+	−	−	+	−	+	+
11	Hypotension (<90 mm of Hg)	−	−	−	+	−	+	+
12	Pallor	−	+	−	+	+	+	+
13	Icterus	−	−	−	−	−	−	−
14	Lymphadenopathy	−	Cervical	−	−	−	−	−

Table 1 continued

		P 8	P 9	P 10	P 11	P 12	P 13	P 14
15	Eschar	–	–	Chest	–	–	–	–
16	Rash	–	–	–	–	–	–	–
17	Stay in hospital (days)	5	6	5	8	4	10	5
18	Pregnancy outcome/birth weight (kg)	Term delivery/NA	Term delivery/NA	Term delivery/NA	Term delivery/NA	Term delivery/2.3	Term delivery/NA	Term delivery/2.5
19	Treatment given	Azithromycin	Azithromycin	Azithromycin	Azithromycin	Azithromycin	Azithromycin	Azithromycin
20	Outcome	Survived	Survived	Survived	Survived	Survived	Survived	Survived

NA Not available

Discussion

Only a few case reports and case series (with patients <10) have been reported in the literature till now of scrub typhus with pregnancy. We here present the profiles of 14 patients which is maximum number so far. Our study is based on IgM ELISA which is more specific and sensitive test than the earlier used weil felix test. In our study, 14 patients were pregnant. Out of 14, eight patients were in the second, and six patients were in the third trimester, and none in the first trimester. The clinical features of the disease observed for pregnant females were the same as for nonpregnant females. Most of the patients had fever, headache, skin rash, and eschar, which are characteristic of scrub typhus. There was no difference in the severity of scrub typhus between pregnant and nonpregnant women. Complication rates were also similar. This is in accordance with other studies [3, 5, 8] No mortality was found in these patients. ARDS, severe sepsis, MODS, and septic shock were present more in patients presenting in the second trimester. On follow-up, they had normal peripartum and postpartum periods. They all delivered babies at term, without congenital or neonatal complications. However, exact birth weight records could not be collected for all. We treated patients with azithromycin 500 mg once a day for 5 days, and all patients responded completely including the patients with ARDS. Ventilatory support was required in two patients for 2 days. There has been no consensus regarding the antibiotics to be used in pregnant scrub typhus patients and also regarding the duration of the treatment. We followed the regimen which has been recommended in our institution. A study by Kim et al. from Korea has reported nine cases of scrub typhus in pregnancy treated with single dose of azithromycin [5]. However, it does not mention the treatment given to patient with severe complications. In the current study, patients had gestational age between 12 and 30 weeks without scrub complications. They all received oral azithromycin single dose 500 mg. Complete recovery was seen in all patients. Seven patients delivered healthy baby at term; one patient delivered small for gestational age at term. A review of 13 cases of pregnant scrub typhus patients between 17 and 37 years of age, with gestational ages of <4 to 34 weeks in the same study found that treatment with azithromycin and minocycline had favorable treatment and pregnancy outcome. Those treated with ciprofloxacin and cefuroxime did not respond, and still-births were observed. Patients receiving chloramphenicol and tetracycline responded to treatment, but adverse pregnancy outcomes in the form of still-birth and fetal loss were seen [5]. Cochrane's drug review for scrub typhus also fails to recommend treatment for this subgroup of scrub typhus patients [9]. Mathai et al. reported five

Table 2 Laboratory parameters of patients

Sr. no		P 1	P 2	P 3	P 4	P 5	P 6	P 7	P 8	P 9	P 10	P 11	P 12	P 13	P 14
1	Hb (g %)	5.9	9.6	9	11	8.5	10	11.3	9	9.8	10	7	8.8	9.5	11.5
2	TLC (mm^3)	13,400	5300	4000	6700	17,000	5600	9800	8600	5200	7100	7700	8300	15,100	9900
3	ESR (mm/h)	42	23	45	50	30	47	6	30	32	47	44	26	53	42
4	Platelets (lacs)	2.5	1.67	2.4	1.56	0.9	2.25	2.61	3.93	4.5	3.82	0.69	0.82	2.7	2
5	*S. creatinine* (mg)	0.9	0.4	1.1	1.3	2.6	3	0.8	2.2	1	0.9	3.4	1.1	4	1.2
6	*S. bilirubin* (mg)	1.2	1.1	1.2	0.9	1.9	3.5	1.8	1.9	0.9	1	2.6	1.4	6.9	1.5
7	Albumin (g)	2.7	2.2	3.4	3.6	2.9	2	3.1	3.5	3.4	3.5	2.4	3	2.1	3.4
8	SGOT (IU)	25	163	31	112	81	62	250	90	94	27	54	90	87	92
9	SGPT (IU)	30	154	29	77	152	45	256	390	202	291	81	174	316	25
10	S Alkaline phosphatase (IU)	236	145	200	227	657	581	231	247	124	755	219	210	390	193

Table 3 Complications in patients

		P 1	P 2	P 3	P 4	P 5	P 6	P 7	P 8	P 9	P 10	P 11	P 12	P 13	P 14	$N = 14$
1	Renal dysfunction	−	−	−	−	+	+	−	+	−	−	+	−	+	−	5 (35.70 %)
2	Hepatic dysfunction	−	+	−	+	+	+	+	+	+	+	+	+	+	−	11 (49.98 %)
3	ARDS	−	+	−	−	−	−	−	−	−	−	+	−	+	+	4 (28.56 %)
4	Sepsis	−	+	−	−	+	+	−	+	+	+	+	+	+	+	10 (71.40 %)
5	Severe sepsis	−	+	−	−	+	+	−	−	−	−	+	−	+	−	5 (35.70 %)
6	MODS	−	+	−	−	−	−	−	−	−	−	+	−	+	+	4 (28.56 %)
7	Septic shock	−	+	−	−	+	−	−	−	−	−	+	−	+	+	5 (35.70 %)

cases of scrub typhus in pregnancy. Gestational age was between 12 and 30 weeks. One patient received IV ciprofloxacin, two patients ciprofloxacin and doxycycline, one IV chloramphenicol, and one cefuroxime. There was delayed recovery in all patients. There was still birth in three patients, preterm and small for gestation age in one patient, and one patient aborted at 12th week [10]. Mahajan et al. reported five patients of scrub typhus in pregnancy. 3 patients received azithromycin, one patient ceftriaxone and azithromycin, one patient ceftriaxone and doxycycline. one patient died who presented with advanced disease and four patients had complete recovery. one patient had delivered a premature, low birth weight fetus 9 days back prior to hospitalization and infant died after few hours of birth [11]. Poomalar et al. reported eight patients—six pregnant and two postnatal with scrub typhus who were given azithromycin. All had favorable outcomes but for one whose baby died at 3 days of life [12]. Pregnancy outcome is closely related to the therapeutic outcome of each patient. In our study, all patients responded, and all patients had favorable outcomes even with ARDS patient requiring ventilator support. In some case reports, scrub typhus seems to have adverse effects on pregnancy as in reviewed by Kim et al. [5]. The serious adverse outcomes mainly occurred in patients whose scrub typhus was inappropriately controlled. Therefore, appropriate management of scrub typhus in pregnant women with effective regimens is critical for avoiding adverse pregnancy outcomes. Although two cases of neonatal scrub typhus have been reported, its transmission route from mother to fetus is still uncertain [13]. There are two possible routes: transplacental and perinatal blood-borne transmission, which have been postulated. In our study, infants were not followed up for scrub typhus transmission.

Conclusion

Although rare, scrub typhus should be considered in differential diagnosis of fever in pregnant patients especially in scrub season. Azithromycin should be the drug of choice in pregnancy as it has no adverse effect on fetus and pregnancy outcomes. Regimen we recommend is 500 mg per day for 5 days (including the patients with complications) against single 500 mg dose, as azithromycin has prolonged post-antibiotic effect. Clinical profile, diagnosis, and complications pattern are the same as in the case of nonpregnant patients.

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Compliance with Ethical Standards

Conflict of interest Ritesh Kumar, Surinder Thakur, Rajesh Bhawani, Anil Kanga and Asha Ranjan declare that they have no conflicts of interest.

Ethical approval Study conducted was in accordance to the ethical standards of the responsible committee on human study and with the Helsinki declaration of 1975, as revised in 2008.

Informed consent Informed consent was obtained from all the patients for being included in the study.

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