

Scrub typhus in pregnancy - A threat to maternal and fetal outcome

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ABSTRACT

Background and Objectives: Scrub typhus is an acute febrile illness transmitted by the bite of trombiculid mite in the larval stage. Scrub typhus is rare in pregnancy and there is paucity of data on the clinical outcome of scrub typhus during pregnancy. **Material and Methods:** We present five cases of scrub typhus complicating pregnancy who were admitted in the obstetric ward at AIIMS Rishikesh, India during the antenatal period for management. **Results:** The first patient presented at term pregnancy in semiconscious state while the rest were preterm between 31 and 34 weeks period of gestation. The age at presentation was 21–31 years. All five had febrile illness of >5 days' duration along with cough. Fever investigations like blood culture, peripheral smear for malarial parasite, dengue serology, widal test, and urine culture were negative. Serology for scrub typhus was positive in all. Once diagnosis was confirmed for scrub typhus, patients were given the drug of choice azithromycin 500 mg twice daily for five days. Scrub typhus complicating pregnancy led to maternal mortality in one patient. It resulted in one preterm delivery, one intrauterine fetal death, and rest three were delivered at term with good perinatal outcome. **Conclusion:** Scrub typhus is common in endemic areas like Uttarakhand, India. It has a poor fetal outcome. If diagnosed early and treatment started, maternal and fetal prognosis can be favorable. As large case series are unavailable in literature, it is difficult to predict the course of disease which at times may be fulminant.

Keywords: Pregnancy with febrile illness, pregnancy with infectious diseases, scrub typhus

Introduction

Scrub typhus is a mite borne infectious disease caused by *Orientia tsutsugamushi*, a Gram negative intracellular coccobacilli that is endemic in Asia Pacific region.^[1] It is an acute febrile illness with variable clinical course ranging from mild self-limiting features like fever, headache, and myalgia to fatal course complicated by pneumonia, pulmonary edema, congestive cardiac failure, and central nervous system dysfunction. An eschar at the site of chigger bite is an early pathognomic feature but has a varying

frequency of 7%–97%.^[2] According to sero-epidemiological data, *O. tsutsugamushi* infection is widespread in Asia, with a seroprevalence of 9.3%–27.9% (median 22.2% inter-quartile range, IQR 18.6–25.7). Scrub typhus was the causative agent detected in 16.1%–96.9% of febrile cases presenting to hospitals in India.^[3]

Indian data show that the case fatality rate ranges from 1.3% to 30%.^[4,5] An early diagnosis is critical in managing pregnancy with scrub typhus, as most of the affected patients have nonspecific presentation which can be easily confused with other acute febrile illnesses like typhoid, dengue, and leptospirosis. Nonavailability of diagnostic modalities in rural setting often delays the management. Limitations in data collection and surveillance system often result in underreporting of such cases. As clinicians,

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a strong index of suspicion and being vigilant about these causes of fever especially in endemic areas as delay in diagnosis and treatment can lead to adverse fetomaternal outcome.

Material and Methods

We prospectively analyzed five antenatal women between 31 and 34 weeks period of gestation (POG) diagnosed with scrub typhus admitted at AIIMS Rishikesh between July and December 2018. Scrub typhus was diagnosed based on the rapid diagnostic test (SD Bioline Tsutsugamushi, Korea) detecting IgM, IgG, or IgA antibodies in human serum against *O. tsutsugamushi*. Fever investigations like blood culture, peripheral smear for malarial parasite, dengue serology, widal test, and urine culture were negative for these cases. Information was collected about the demographic profile. Details regarding the mode of delivery, neonatal outcome, need for neonatal resuscitation, and maternal intensive care admission along with medication given was noted. Ethical number: AIIMS/IEC/19/1317.

Results

The demographic profile and maternal fetal outcome of five cases are summarised in Table 1. All five cases were in third decade of their life and came from hilly region of Uttarakhand. They presented with fever of more than five days' duration. The first patient was at term pregnancy while the rest were preterm between 31 and 34 weeks POG. The first case presented in semiconscious state with breathlessness with Glasgow Coma Scale of E₁V₁M₃. History from relatives revealed that she had a sudden onset headache with fever and seizures. She was immediately intubated and admitted in an intensive care unit. As fetus was alive and

her POG was estimated as >37 weeks, decision for emergency cesarean was taken to salvage the baby. None of the cases had the characteristic eschar. Hematological parameters were normal in all cases except a high total leukocyte count (TLC) in the first case while thrombocytopenia was noted in two cases. Fever investigations like blood culture, peripheral smear for malarial parasite, dengue serology, widal test, and urine culture were negative in all. All cases received azithromycin. First case succumbed to scrub typhus complicating pregnancy despite best possible efforts. Second case had preterm-assisted breech delivery with a low birth weight baby. Pregnancy in third and fourth cases continued uneventful till term. Fifth case presented with an intrauterine fetal demise (IUID) at 27 weeks POG and delivered a stillborn baby.

Discussion

Any episode of fever complicating pregnancy should be dealt with utmost care. Common differential diagnoses include malaria, enteric fever, urinary tract infection, and dengue. In endemic areas particularly those near river banks and abandoned plantations, the diagnosis of scrub typhus should always be kept in mind. The infection is transmitted through the bite of larval mites or chiggers. Humans are accidental host. Scrub typhus can be a serious health problem owing to its high case fatality rate if not treated. Wide spectrum and nonspecific clinical course of this disease hampers diagnosis and hence there is utmost need for healthcare providers to be aware of its clinical presentation, available diagnostic tests, and treatment for it. The WHO criteria for diagnosis of scrub typhus are mentioned in Table 2.

The bite of chiggers manifests as eschar and is a pathognomic feature in scrub typhus. These are painless, punched out ulcers

Table 1: Demographic and clinical details

Parameter	Case 1	Case 2	Case 3	Case 4	Case 5
Age in years	21	22	24	24	31
Region	Tehri garhwal	Tehri garhwal	Haridwar	Pauri garhwal	Pauri garhwal
Fever (duration) in days	5	12	14	6	7
Other features	E ₁ V ₁ M ₃ , headache, respiratory distress	Cough	Vomiting	Cough	Malaise
Other obstetric complication	-	PPROM, FGR	-	-	IUID, PTL
POG in weeks	38	31	34	35	27
Hb (gm%)	10.8	9.3	8.8	9.5	9.9
TLC (per cm ³)	19,330	11,800	10,500	12,800	6430
Platelets (lakhs/mm ³)	2.04	1.55	2.36	1.28	1.1
LFT((Total bilirubin/SGOT/SGPT/alkaline phosphatase)	0.67/34/53/185	0.81/65/148/540	0.49/21/43/191	0.55/59/73/286	0.7/41/34/269
RFT (blood urea/creatinine) (mg/dl)	28/0.56	26/0.43	11/0.37	13/0.44	8/0.3
Scrub serology	Positive	Positive	Positive	Positive	Positive
Fetal affection	None	Preterm, low birth weight	None	None	IUID
Delivery	Caesarean section	Assisted breech vaginal delivery	Vaginal delivery	Vaginal delivery	Preterm delivery
Baby weight in kilograms	2.8	1	2.7	2.9	390 grams
Maternal outcome	Expired on day 14 of admission	Good	Good	Good	Good
Fetal outcome	NICU care and discharged on day 4	NICU care for 18 days	Healthy	Healthy	IUID

PPROM=Preterm prelabour rupture of membranes, FGR=Fetal Growth Restriction, Hb=Haemoglobin, LFT=Liver function test, RFT=Renal function test

Table 2: WHO criteria for diagnosis of scrub typhus^[6]**Clinical description**

Presents with a primary punched out skin ulcer (eschar), followed by fever, along with headache, profuse sweating, conjunctival injection and lymphadenopathy. Then there appears a dull maculo-papular rash initially on trunk, extending to extremities and disappearing in few days. Defervescence occurring within 48 hours of tetracycline initiation strongly suggests a rickettsial pathology

Laboratory criteria for diagnosis: Identification of *Orientia tsutsugamushi* by inoculation of patient's blood in white mice^a

- Serology detection scrub typhus IgM
- 1:100 or higher by EIA by ELISA^b
- 1:32 dilution or higher by IP^a
- 1:10 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

with a black necrotic center simulating a cigarette burn. Common sites of its presence include neck, axillae, groin, and genitalia.

Data on scrub typhus during pregnancy are sparse. McGready *et al.*^[7] reviewed literature extensively ranging from 1992 to 2014 on cases of both scrub and murine typhus during pregnancy. There were a total of 97 pregnancies but in 15.5% cases (15/97), the outcome was unknown. Amongst 82 cases reviewed, 2 cases (2.5%) were associated with maternal mortality. One of the women died before 24 hours of admission while the other died after three days (her preterm baby also died). Around 17.3% (14/81 cases) had miscarriage and 41.8% (28/67 cases) reported poor neonatal outcomes (still birth, low birth weight, and preterm labour).

Sengupta *et al.*^[8] in their case series of 42 cases of scrub typhus complicating pregnancy revealed that pregnancy loss with scrub typhus was significantly higher as compared to their routine obstetric data: 14 cases (33%) vs 2.8%; $P < 0.001$.

In our analysis of five cases, there was one maternal death and two had poor neonatal outcomes (one intrauterine fetal death and one preterm delivery). Similar to ours, Meena *et al.*^[9] in their study of six cases reported maternal mortality in one case but their neonatal outcome was worse as compared to ours. They had miscarriage in two cases and stillborn in one.

Yadav *et al.*^[10] reported 27 cases of scrub typhus diagnosed based on the IgM antibodies to *O. tsutsugamushi* and observed poor fetal outcome in the form of intrauterine demise (7.4%), spontaneous abortion, and still births in 3.7% cases each. There was one case (3.7%) of maternal mortality in their study. Similarly poor fetal outcome was observed in 51.5% of pregnancies affected with scrub typhus by Rajan *et al.*^[11]

Macrolide antibiotic such as azithromycin is a drug of choice for pregnancy with scrub infection owing to its safety profile during pregnancy. The optimal duration of therapy varies from

single dose of 500 mg azithromycin to a period of one week. Kim *et al.*^[12] in their study suggested that a single dose of 500 mg azithromycin can successfully treat scrub infection during pregnancy with favorable outcome. In postpartum nonlactating women, doxycycline 100 mg twice daily may be given for 14 days. Doxycycline, a tetracycline class of antibiotics, is primarily used to treat rickettsial disease during nonpregnant state as it has adverse effect on the musculoskeletal development of the fetus and can result in staining of teeth in young children. But it can be used during pregnancy also as it is relatively inexpensive compared to azithromycin,^[13] thereby making it an easy option for poor and needy patients in rural settings.

In Uttarakhand, hilly terrain and difficult roads make access to healthcare facilities often delayed. An interesting aspect in our series was that all five cases were unbooked. Four out of five antenatal women were diagnosed and treated well in time, however, the first case presented quite late with fulminate course and expired due to multiorgan failure. This series corroborates well with other studies showing increased incidence of preterm delivery and fetal deaths with scrub infection.

There is always underreporting of scrub and murine typhus cases during pregnancy owing to the dearth of diagnostic tests particularly in low resource settings leading to paucity of published literature on them. Clinical course varies with spontaneous recovery to multiple organ failure. Hence, such cases, when possible should be managed in centres with adult and neonatal intensive care units and every healthcare provider must be aware of this cause of fever. The patient should be hospitalised during the acute febrile phase. Fetal surveillance with nonstress test and fetal biophysical profile should be done based on the gestational age. As there is risk of preterm birth, when feasible, corticosteroids should be given for fetal lung maturity. The American College of Obstetricians and Gynaecologists recommends giving antenatal corticosteroid between 24 and 34 weeks of gestation. They also recommend repeating a single course of steroid in women less than 34 weeks of gestation with a risk of preterm delivery within the next 7 days, and in cases where steroid was administered more than 14 days previously.^[14] Such cases can undergo vaginal delivery with caesarean section done only for obstetric indications.

Larger prospective studies are needed to analyse the fetomaternal outcomes related to scrub infection during pregnancy.

Conclusion

Scrub typhus should be considered as an important cause of febrile illness during pregnancy, particularly in endemic areas. Timely detection and effective antibiotic course can result in favourable maternal and perinatal outcome.

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Conflicts of interest

There are no conflicts of interest.

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