SCRUB TYPHUS DURING PREGNANCY AND ITS TREATMENT: A CASE SERIES AND REVIEW OF THE LITERATURE

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Abstract. Although scrub typhus is uncommon in pregnant women, when present, it can have serious repercussions for the mother and developing fetus. Since it is uncommon, the clinical impact of scrub typhus on pregnancy has not been elucidated and an effective and safe therapeutic regimen has not been validated. The medical records of pregnant women whose scrub typhus were treated at Chungnam National University Hospital were reviewed and their clinical outcomes were evaluated. A review of the literature was also performed on pregnant women with scrub typhus and their clinical outcomes. Eight pregnant women with scrub typhus were treated successfully with a single 500-mg dose of azithromycin, and no relapses were reported. They all delivered healthy babies at term, without congenital or neonatal complications. In the reviews, azithromycin was effective against scrub typhus and had favorable pregnancy outcomes. Ciprofloxacin and cefuroxime failed to treat scrub typhus and fetal loss resulted. A single 500-mg dose of azithromycin may be a reasonable treatment regimen for pregnant women with scrub typhus. Ciprofloxacin might not be advisable for the treatment of scrub typhus during pregnancy. Scrub typhus itself seems to have serious adverse effects on pregnancy if not appropriately controlled.

INTRODUCTION

Scrub typhus (tsutsugamushi disease) is an acute febrile zoonosis caused by Orientia tsutsugamushi, which is endemic in the Asia–Pacific region.1 As many as one million people may be infected yearly in the disease-endemic area.2 This disease occurs throughout the Korean Peninsula and its incidence in Korea has been increasing, reaching 4,697 cases in 2004.3 The symptoms and signs of scrub typhus include fever, headache, inoculation eschar, and rash, which occur approximately 10 days after being bitten by a chigger.2,4 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.5

Although scrub typhus is rare during pregnancy and the impact of scrub typhus on pregnancy is unclear, some data report that scrub typhus may be associated with increased fetal loss.6–8 In addition, no regimen has been evaluated for efficacy and safety in pregnant women with scrub typhus. Doxycycline and chloramphenicol continue to be the standard therapy for scrub typhus in nonpregnant adults.9 However, doxycycline, a class D drug according to the U.S. Food and Drug Administration, is contraindicated in pregnant women because it has been associated with fetal risk.9 Chloramphenicol, a class C drug, is prescribed with caution to late trimester pregnant women because of an increased risk to the fetus at the time of delivery.10

Azithromycin, a macrolide antibiotic, has been proven to be as effective as doxycycline against scrub typhus in nonpregnant adults.11 Importantly, there is little evidence to suggest that azithromycin causes harm to the developing fetus.12 Azithromycin has been reported to effectively cure scrub typhus in pregnant women and showed favorable pregnancy outcomes.13 We retrospectively evaluated the clinical manifestations and therapeutic and pregnancy outcomes of pregnant women whose scrub typhus was treated with azithromycin. We also reviewed the literature for data on the therapeutic regimens used for pregnant women with scrub typhus and the clinical effectiveness of these regimens.

PATIENTS AND METHODS

Case series. The medical records of pregnant women with scrub typhus who had been treated at the 1,013-bed Chungnam National University Hospital (Daejeon, Republic of Korea) were reviewed. To compare the clinical manifestations of scrub typhus between pregnant and nonpregnant women, the medical records of nonpregnant women of similar ages were also reviewed. The study period was from September 2002 to December 2004. Only patients who were confirmed as having scrub typhus according to the World Health Organization (WHO) criteria were enrolled.5 Patient data were taken from medical records using a standardized case record form. Information was obtained about demographic, clinical, and laboratory characteristics of the patients at admission and their therapeutic outcomes. Information about the patients’ pregnancy outcomes was gathered through telephone inquiries or direct contact.

The patients who had been infected with scrub typhus in the fall of 2004 and expected to give birth in 2005 were requested to donate their peripheral blood and cord blood for the determination of IgM and IgG titers to scrub typhus. Blood was drawn after written informed consent was obtained in accordance with a protocol that was reviewed and approved by the Institutional Review Board of Chungnam National University Hospital.

Confirmation of scrub typhus. In the case series, scrub typhus was determined according to the WHO criteria for scrub typhus diagnosis. Tsutsugamushi disease was confirmed if specific IgM was detected at a dilution ≥ 1:10 or if a four-fold increase in IgG titers was demonstrated with paired serum specimens in an indirect immunofluorescence antibody (IFA) test. The IFA was performed for each serum specimen with Gilliam (ATCC VR-312), Karp (ATCC VR-150), Kato (ATCC VR-609), and Boryong (provided by Professor I. S. Kim,
Seoul National University College of Medicine, Seoul, Republic of Korea) strains of *O. tsutsugamushi* at the Korea Center for Disease Control and Prevention (Seoul, Republic of Korea).

**Literature review.** We searched the English-language literature for reports of pregnant women with scrub typhus, using the MEDLINE/PubMed database, which includes citations from 1966 to the present time. We used the search terms “scrub typhus” AND “pregnancy” and “scrub typhus” AND “neonate”. Pregnant women whose scrubs were confirmed by either IFA test, indirect immunoperoxidase assay, or microimmunofluorescence assay were all evaluated.

**RESULTS**

**Case series.** A total of 283 patients with symptoms suggestive of scrub typhus were admitted to the Division of Infectious Diseases at Chungnam National University Hospital during the study period. Among them, nine pregnant women were confirmed by IFA as having scrub typhus. Thirteen non-pregnant women in their twenties and thirties with confirmed scrub typhus were selected to make a comparison. Demographic, clinical, and laboratory characteristics of both groups at the time of admission are shown in Table 1. Most of the patients in each group had similar clinical manifestations. Fever (oral temperature > 38°C) was present in 7 (77.8%) pregnant and 11 (84.6%) nonpregnant women at admission, although all patients had febrile sensations before admission. No patients in either group had further complications such as comatose mental status, respiratory failure, renal failure, or shock. The laboratory data for both groups were also similar, except that the serum sodium levels decreased more in pregnant women than in nonpregnant women.

All pregnant women were given a single 500-mg dose of azithromycin, and fever abated within 16 hours after azithromycin was administered. Prenatal examination showed no fetal distress at that time. However, oligohydramnios and fetal distress were noticed at the 38th week of gestation and a caesarian section was performed. She delivered a baby weighing 1,800 g with Apgar scores 8 and 10 at 1 and 5 minutes, respectively. The cause of oligohydraminos was not determined and the baby showed no adverse reactions occurred that were related to the use of azithromycin. No relapses or complications were observed during the study period.

We succeeded in contacting by telephone five of the six patients who had been treated between 2002 and 2003. Three patients who had been seen in 2004 agreed to undergo serologic analyses of paired mother and cord sera. IgG levels for scrub typhus were persistently elevated in all mothers and IgM detected in one patient. High titers of IgG were detected in all cord sera, but scrub typhus–specific IgM was not detected.

The pregnancy outcomes of nine patients are shown in Table 2. Gestational ages at admission were variable, ranging from 10 to 29 weeks. Most of the patients delivered healthy babies weighing from 2,800 to 3,700 g at the 37th–41th week of gestation, except patient 3 of the case series. Patient 3, a 28-year-old woman with a gestational age of 21 weeks, visited this hospital with a fever that had persisted for five days. Her fever abated within 16 hours after azithromycin was administered. Prenatal examination showed no fetal distress at that time. However, oligohydramnios and fetal distress were noticed at the 38th week of gestation and a caesarian section was performed. She delivered a baby weighing 1,800 g with Apgar scores 8 and 10 at 1 and 5 minutes, respectively. The cause of oligohydraminos was not determined and the baby showed no

### Table 1

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Pregnant (n = 9)</th>
<th>Nonpregnant (n = 13)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Demographic</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, median years (range)</td>
<td>30 (22–34)</td>
<td>27 (20–37)</td>
</tr>
<tr>
<td>Duration of fever before treatment, median days (range)</td>
<td>5 (3–10)</td>
<td>5 (2–14)</td>
</tr>
<tr>
<td><strong>Clinical</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maximum body temperature, median °C (range)</td>
<td>38.5 (37.0–39.0)</td>
<td>38.9 (37.4–40.4)</td>
</tr>
<tr>
<td>Time to defervescence, median hours (range)</td>
<td>15 (0–19)†</td>
<td>15 (0–54)</td>
</tr>
<tr>
<td>Eschar, no. of patients</td>
<td>9</td>
<td>12</td>
</tr>
<tr>
<td>Rash, no. of patients</td>
<td>9</td>
<td>13</td>
</tr>
<tr>
<td>Headache, no. of patients</td>
<td>9</td>
<td>12</td>
</tr>
<tr>
<td>Myalgia, no. of patients</td>
<td>7</td>
<td>7</td>
</tr>
<tr>
<td>Cough, no. of patients</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Vomiting, no. of patients</td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td><strong>Laboratory characteristics, median (range)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leukocyte count, ×10³ cells/L</td>
<td>6.6 (3.4–11.0)</td>
<td>4.7 (1.6–8.8)</td>
</tr>
<tr>
<td>Hemoglobin level, g/dL</td>
<td>11.6 (8.5–13.5)</td>
<td>12.1 (9.0–14.2)</td>
</tr>
<tr>
<td>Alanine aminotransferase level, IU/L</td>
<td>43 (29–157)</td>
<td>75 (29–395)</td>
</tr>
<tr>
<td>Na, mEq/L</td>
<td>130.3 (128.3–134.2)</td>
<td>136.5 (133.5–143.3)</td>
</tr>
</tbody>
</table>

* Interval between the time when the first dose of antibiotic was administered and the time when the oral temperature first decreased to < 37.5°C and was maintained for > 48 hours without antipyretics.
† Patient who had scrub typhus and urinary tract infection concomitantly was not included.

### Table 2

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age (years)</th>
<th>GA at onset of scrub typhus (weeks)</th>
<th>Treatment outcome</th>
<th>GA at delivery (weeks)</th>
<th>Birth weight (g)</th>
<th>Fetal outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>27</td>
<td>29</td>
<td>S</td>
<td>41</td>
<td>2,800</td>
<td>Healthy</td>
</tr>
<tr>
<td>2</td>
<td>31</td>
<td>10</td>
<td>S</td>
<td>40</td>
<td>3,200</td>
<td>Healthy</td>
</tr>
<tr>
<td>3</td>
<td>28</td>
<td>21</td>
<td>S</td>
<td>38</td>
<td>1,800</td>
<td>Healthy</td>
</tr>
<tr>
<td>4</td>
<td>30</td>
<td>29</td>
<td>S</td>
<td>40</td>
<td>3,600</td>
<td>Healthy</td>
</tr>
<tr>
<td>5</td>
<td>22</td>
<td>30</td>
<td>S</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>6</td>
<td>33</td>
<td>20</td>
<td>S</td>
<td>40</td>
<td>2,800</td>
<td>Healthy</td>
</tr>
<tr>
<td>7</td>
<td>34</td>
<td>15</td>
<td>S</td>
<td>37</td>
<td>2,800</td>
<td>Healthy</td>
</tr>
<tr>
<td>8</td>
<td>29</td>
<td>16</td>
<td>S</td>
<td>40</td>
<td>3,700</td>
<td>Healthy</td>
</tr>
<tr>
<td>9</td>
<td>34</td>
<td>16</td>
<td>S</td>
<td>39</td>
<td>3,290</td>
<td>Healthy</td>
</tr>
</tbody>
</table>

* GA = gestational age; S = success; NA = not available.
features of congenital malformation. As of January 2006, all
of the children are now, on average, 22.5 months old, ranging
in age from 10.1 months to 3 years. No developmental or
physical defects have been observed in these children and
none has ever had evidence of scrub typhus.

Literature review. We identified 13 women from 7 publica-
tions who were infected with scrub typhus during preg-
nancy.\textsuperscript{5–8,13–16} Each case occurred in women between 17 and
37 years of age, with gestational ages of < 4 to 34 weeks, and
their clinical data are shown in Table 3. The therapeutic out-
comes of pregnant women who were given azithromycin,
chloramphenicol, or tetracycline were successful. However,
ciprofloxacin and beta-lactam agents failed to relieve the
symptoms or signs of scrub typhus in pregnant women.

Pregnancy outcome was closely related to the therapeutic
outcome of each patient. Choi and others reported two preg-
nant women who were treated with azithromycin successfully
and gave birth to healthy babies at term.\textsuperscript{15} Watt and others
reported two pregnant women whose scrub typhus was
treated successfully with azithromycin.\textsuperscript{6} However, preclinical
fetal loss occurred in one patient, who had experienced two
spontaneous abortions, and the pregnancy outcome of
the other woman was not known because she was not fol-
lowed-up. Tsui and others reported a pregnant woman who
was successfully treated with minocycline.\textsuperscript{14} In that case, a
normal, healthy baby was born in the 40th week of gestation
and the Weil Felix test OXK titer of the newborn serum was
1:20 (not significant). Among the few reports of pregnant
women who had received chloramphenicol, Phupon and Sret-
takraikul reported a 29-week pregnant woman who devel-
oped high-grade fever and headache of two-week’s duration.\textsuperscript{8}
Although chloramphenicol was given to her with a presumptu-
ive diagnosis of scrub typhus, she delivered a baby weighing 950 g
on the second day after the initiation of treatment. The
neonate died within six hours because of respiratory distress
syndrome. Despite the mother’s high scrub typhus–specific
IgG and IgM titers, IgM was not detected in the neonate’s
sera.

Stillbirth and abortion were mainly observed in mothers
whose scrub typhus was poorly controlled. Mathai and others
reported four pregnant women who were given ciprofloxacin
or cefuroxime.\textsuperscript{7} Their illnesses were not controlled with those
regimens and all mothers miscarried.

There were two cases of neonatal scrub typhus.\textsuperscript{15,16} The
two neonates were born to patients who were not treated
until delivery. These neonates developed febrile illnesses sug-
gestive of scrub typhus, and elevated scrub typhus–specific
IgM titers were detected in both. After the diagnosis was
confirmed, the neonates and their mothers were given teta-
rycycline or chloramphenicol and recovered completely.

DISCUSSION

The clinical manifestations of scrub typhus in pregnant
women seem to be similar to those of nonpregnant women of
similar ages. Most of the patients had fever, headache, skin
rash, and eschar, which are characteristic of scrub typhus.\textsuperscript{4}
There was no difference in the severity of scrub typhus be-
tween pregnant and nonpregnant women. No patients in ei-
ther group presented with severe scrub typhus–related com-
plications, which include shock, comatose mental status, res-
piratory failure, or renal failure. The laboratory findings for
each group were also similar, except that serum sodium levels
increased more in pregnant women. However, considering
that the serum sodium level can decrease by 5 mEq/L during
pregnancy, the degree of serum sodium decrease did not dif-
ferr between the two groups.\textsuperscript{17}

In our case series, nine patients were treated successfully
with a single 500-mg dose of azithromycin and none relapsed.
Rapid defervescence within 19 hours was observed in all preg-
nant women except one, who had acute pyelonephritis simul-
taneously with scrub typhus. No serious adverse effects were
observed during the study period. This result is consistent
with that of a previous study of azithromycin therapy in non-
pregnant adults with scrub typhus.\textsuperscript{11} Azithromycin seems to
be an effective agent against scrub typhus because it effi-
ciently penetrates polymorphonuclear leukocytes and macro-
phages, which are target cells for \textit{O. tsutsugamushi}.\textsuperscript{18} In
addition, a long tissue half-life and the long-lasting post-
antibiotic effects of azithromycin may explain why there were
no relapses despite the use of a single dose.\textsuperscript{19}

Based on our review series, a 3–5-day course of 1,000–2,000-mg doses
of azithromycin was administered and fever was resolved within
51 hours after the first dose. Further study is required to
determine the optimal dosage of azithromycin for scrub ty-
phus during pregnancy.

\begin{table}
\centering
\caption{Treatment and pregnancy outcomes of pregnant women with scrub typhus in review series*}
\begin{tabular}{|c|c|c|c|c|c|c|c|}
\hline
Patient & Age & GA at onset & Antibiotics & Treatment outcome & GA at delivery & Birth weight & Fetal outcome & IgM titers of cord blood  \\
& (years) & of scrub typhus & & & (weeks) & (g) & &  \\
& & & & & & & &  \\
\hline
K & [16] & 31 & 34 & Chloramphenicol† & S & 34 & 2,200 & Neonatal ST & Positive  \\
\hline
\end{tabular}
\end{table}

* GA = gestational age; S = success; NA = not available; F = failure; ST = scrub typhus.† Two mothers were treated after they delivered children.
Pregnancy outcomes were also favorable in azithromycin-treated patients in our case series and reviews. Among the eight patients whose pregnancy outcomes were available in the case series, all delivered healthy babies at term. Although one patient delivered a baby with a low birth weight, there were no congenital or neonatal complications, nor any spontaneous abortions, in the case series. During the follow-up periods of 10 months to 3 years, no developmental or physical defects have been observed in these children. In the reviews, most of the women who were given azithromycin delivered healthy babies. Although one preclinical fetal loss was reported, it is unlikely that azithromycin was responsible because she had had two prior spontaneous abortions, the last of which had occurred six months before her scrub typhus infection.

Chloramphenicol and minocycline were effective against scrub typhus in both pregnant and nonpregnant women. However, clinicians may be reluctant to choose chloramphenicol for pregnant women since one neonatal death and one preterm delivery with low birth weight have been reported in chloramphenicol-treated women. Although a minocycline-treated woman delivered a normal and healthy baby, it is difficult to define the safety of its use during pregnancy from this single limited report.

Ciprofloxacin is a quinolone antibiotic that is effective against *O. tsutsugamushi* in mice and clinically in a few human cases. However, there is a substantial amount of data demonstrating that ciprofloxacin is not efficacious in the treatment of scrub typhus. There has been a case of scrub typhus being transmitted by a needle prick injury from a patient who was being given pefloxacin for scrub typhus. Seilmair and others reported that a patient who had not responded to ciprofloxacin for a presumptive diagnosis of typhoid fever showed defervescence after doxycycline was administered with confirmation of scrub typhus. In the cases reported by Mathai and others, ciprofloxacin failed to relieve symptoms of scrub typhus in three pregnant women, and resulted in miscarriage in all of them. Since the rates of spontaneous abortion or major congenital malformations did not differ between the ciprofloxacin-treated and control groups during pregnancy, poorly controlled scrub typhus may have been the probable cause of miscarriage. Therefore, we believe that ciprofloxacin should be selected with caution for the treatment of scrub typhus, especially during pregnancy.

Scrub typhus seems to have adverse effects on pregnancy; the serious adverse outcomes mainly occurred in patients whose scrub typhus was inappropriately controlled. All four patients whose scrub typhus was poorly controlled miscarried, while there were no miscarriages in patients whose illness was completely 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. There are two possible routes: transplacental and perinatal blood-borne transmission. In our cases and review series, among the neonates who were delivered by cured mothers, none had scrub typhus—specific IgM, which indicated transplacental transmission of infection. Because two cases of neonatal scrub typhus were delivered from the untreated mothers who may have been in a rickettsemic state at the time of delivery, perinatal blood-borne transmission might be more likely. There are additional data showing that the possibility of transplacental transmission of *O. tsutsugamushi* is low. Shirai and others studied 111 sets of paired mother and cord sera in an area highly endemic for scrub typhus. Although 32% of these mothers had positive IgG titers, IgM antibodies were not detected in any cord sera. Shirai and others also experimentally infected mice with *O. tsutsugamushi* before and after impregnation. They isolated the organisms from 80% of the placentas in the experimentally infected mice but not from their fetuses.

In summary, our study suggests that a single 500-mg dose of azithromycin can be an effective regimen for treatment of scrub typhus in both pregnant and nonpregnant women. Moreover, azithromycin may be the best drug for treatment of scrub typhus during pregnancy because of its favorable pregnancy outcomes. However, ciprofloxacin might not be advisable for the treatment of scrub typhus during pregnancy. Based on our limited data, it does not appear that clinical manifestations of scrub typhus differ between pregnant and nonpregnant women. However, our preliminary data should be confirmed by a larger prospective study. Scrub typhus seems to have serious adverse effects on pregnancy, such as miscarriage, if not appropriately controlled.

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