Case Report: Rocky Mountain Spotted Fever and Pregnancy: Four Cases from Sonora, Mexico

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Abstract. We present a series of four pregnant women with Rocky Mountain spotted fever (RMSF) that occurred in Sonora, Mexico, during 2015–2016. Confirmatory diagnoses were made by polymerase chain reaction or serological reactivity to antigens of *Rickettsia rickettsii* by using an indirect immunofluorescence antibody assay. Each patient presented with fever and petechial rash and was treated successfully with doxycycline. Each of the women and one full-term infant delivered at 36 weeks gestation survived the infection. Three of the patients in their first trimester of pregnancy suffered spontaneous abortions. RMSF should be suspected in any pregnant woman presenting with fever, malaise and rash in regions where *R. rickettsii* is endemic.

INTRODUCTION

Rocky Mountain spotted fever (RMSF) is a life-threatening tick-borne disease caused by *Rickettsia rickettsii*.^{1,2} Several states of Mexico, including Sonora, have experienced a resurgence of RMSF beginning the 21st century, with case-fatality rates between 20% and 33%.³

This disease can be extremely difficult to diagnose during the first days of symptoms.⁴ This challenge can be accentuated in pregnant women, because some severe manifestations such as respiratory distress and acute renal failure are similar to other diseases of pregnancy including preeclampsia, hemolysis, elevated liver enzymes level, low platelet level syndrome, and toxic shock syndrome.⁵ Additionally, the administration of antibiotics with efficacy against *R. rickettsii*, namely doxycycline and chloramphenicol, are usually contraindicated in pregnancy.^{2,5,8–13}

Few cases of RMSF in pregnancy have been described.^{5–8} Although Sonora is a region where RMSF is endemic, little is known about its clinical profile in pregnant women. Herein, we describe a series of four patients diagnosed with RMSF during pregnancy and review issues related to the diagnosis and pharmacological treatment.

Case 1. A 24-year-old woman (gravida 3, para 2) presented to an emergency room with 4 days of self-reported fever, headache, abdominal pain, gingival and vaginal hemorrhage, and a petechial rash involving her palms and soles. Physical examination revealed a febrile hypotensive woman with thrombocytopenia, leukocytosis, hyponatremia, and elevated hepatic transaminase levels (Table 1). Her pregnancy had been previously uneventful. She reported amenorrhea of approximately 8 weeks duration preceding the onset of her symptoms. The initial diagnosis included dengue, chikungunya, and Zika virus infections. An abdominal ultrasound identified a fetus with a gestational age of 8.5 weeks. Within 8 hours of admission the patient developed respiratory distress and was admitted to an intensive care unit (ICU). On hospital day 3, the patient experienced a spontaneous abortion. On hospital day 6, her mean arterial pressure increased from 50 to 85 mmHg;

nonetheless, she developed digital necrosis of her toes and left thumb (Figure 1A), which required surgical amputation. A history of tick exposure 1 week prior to symptom onset was elicited and doxycycline started on hospital day 7. RMSF was confirmed retrospectively by evaluation of a whole blood specimen collected on hospital day 2, using a polymerase chain reaction (PCR) assay to target a 401-base pair segment of the *gltA* gene of *R. rickettsii* (Table 2).^{14,15} She was discharged after 13 days of hospitalization.

Case 2. An 18-year-old-woman (gravida 1, para 0) presented with a 7-day history of abdominal pain, self-reported fever, vaginal bleeding, and a 3-day history of diffuse petechial rash (Figure 1B). Physical examination revealed a febrile and normotensive woman with thrombocytopenia. She was hospitalized due to threatened abortion. An abdominal ultrasound revealed a dead fetus estimated at 8.5 weeks gestational age. Cervical dilatation and instrumented curettage was performed on hospital day 2. She presented vaginal bleeding on hospital day 3 and was admitted to an ICU where developed respiratory distress. Presumptive diagnoses included dengue or Zika virus infection, and atypical pneumonia caused by influenza. PCR tests were negative for each of these agents. Further investigation revealed a history of contact with ticks. RMSF was suspected on the 13th day of illness and doxycycline was initiated. The case was confirmed by a 4-fold rise in titer of IgG antibodies reactive with *R. rickettsii* using indirect immunofluorescence antibody (IFA) assay (Table 2). The patient was discharged after a hospital stay of 28 days with no documented sequelae.

Case 3. A 15 year-old-woman (gravida 1, para 0) with 6 weeks of amenorrhea presented to a hospital with a 14-day history of self-reported fever, myalgia, arthralgia, headache, and a generalized petechial rash (Figure 1C). Physical examination revealed a febrile and normotensive woman with thrombocytopenia (Table 1). A history of contact with a tick-infested dog was elicited. RMSF was suspected and doxycycline was initiated. A transvaginal ultrasound revealed a blighted ovum. Dilatation and instrumented curettage was performed. A serum sample was obtained on day 15 of her illness and demonstrated an anti-*R. rickettsii* IgG antibody titer of 1:4,096 when tested by using an IFA assay. The patient was discharged on hospital day 7 with no sequelae.

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TABLE 1
Selected features at time of hospital admission in pregnant patients with Rocky Mountain spotted fever, Sonora, Mexico, 2015–2016

Characteristic	Reference values	Patient 1	Patient 2	Patient 3	Patient 4
Blood pressure (mmHg)		70/40	115/70	110/70	90/50
Heart rate (beats/minutes)		134	60	75	120
Breath rate (breaths/minutes)		23	18	19	27
Temperature (°C)		39	38	38	39
Leukocytes ($\times 10^6/\mu\text{L}$)	4.6–10.2	16	7.3	6.3	8.9
Neutrophils ($\times 10^6/\mu\text{L}$)	2.8–5.2	6.6	6.6	5.1	7.3
Lymphocytes ($\times 10^6/\mu\text{L}$)	1.4–3.1	0.4	0.4	0.9	1.2
Platelets ($\times 10^6/\mu\text{L}$)	139–450	35	131	81	97
Serum Sodium (mEq/L)	136–145	130	137	134	NA
Aspartate aminotransferase (U/L)	0–32	133	62	NA	NA
Alanine aminotransferase (U/L)	10–35	73	37	NA	NA

Case 4. A 17-year-old pregnant woman (gravida 1, para 0) at 36 weeks gestation determined by abdominal ultrasound, presented with a 6 days of fever, myalgia, arthralgia, a generalized petechial rash, and premature rupture of membranes. Physical examination revealed a febrile hypotensive woman with thrombocytopenia (Table 1) Supportive treatment was initiated and an emergency delivery by cesarean section was performed. A female infant was delivered successfully weighing 2.95 kg, with Apgar scores of 9/9. Immediately after surgery the mother developed respiratory distress and was admitted to an ICU. RMSF was suspected due to documented

history of contact with tick-infested dogs and doxycycline was initiated on day 7 from onset; diagnosis was confirmed via PCR assay.^{14,15} The patient was discharged after a hospital stay of 10 days, without documented sequelae. The baby remained healthy and was discharged to home with the mother.

DISCUSSION

RMSF is an infrequently documented infectious disease in pregnancy.^{5,8} In Table 2, we summarize and compare the

FIGURE 1. (A) Case 1 on her sixth day of hospitalization showing necrosis of the toes to metatarsal level. (B) Case 2 on her 13th day of evolution showing Petechial rash on thorax and left arm. (C) Case 3 at her hospital admission petechial rash on her left hand and forearm. (D) Case 4 on her 8th day of evolution showing petechial rash on her left hand. This figure appears in color at www.ajtmh.org.

TABLE 2
Clinical course of pregnant patients with Rocky Mountain spotted fever

Author's reference	Location/year	Patient age (years)	Weeks gestation at illness onset	Indicator			
				Diagnostic test result	Treatment	Maternal outcome	Fetal outcome
Gallis and others ¹⁷	North Carolina, 1983	19		<i>Proteus</i> OX 19 1:640	Chloramphenicol	No sequelae	No abnormalities
Markley and others ⁶	Pennsylvania, 1997	33	28	IgM = 1:1024/ IgG = 1:256*	Ceftriaxone/ chloramphenicol	No sequelae	No abnormalities
Stallings and others ⁵	North Carolina, 2001	22	35	latex agglutination titer 1:256	Doxycycline	No sequelae	Transient hyperbilirubinemia
De Lemos and others ¹⁶	Sao Paulo, Brazil, 1993	37	8–10	IHC staining positive†	Chloramphenicol	Fatal	Fatal
Hidalgo and others ⁸	Cundinamarca, Colombia, 2003	32	26	PCR and sequencing positive‡	Amoxicillin	Fatal	Fatal
Tribaldos and others ⁷	Panama city, Panama, 2007	22	23	PCR and sequencing positive§	Amoxicillin	Fatal	Fatal
Current study							
Patient 1	Sonora, Mexico, June, 2015	24	8.5	PCR positive¶	Doxycycline	Toes/tumb amputation	Abortion
Patient 2	Sonora, Mexico, March, 2016	18	8.5	IgG = 1:4096	Doxycycline	No sequelae	Abortion
Patient 3	Sonora, Mexico, May, 2016	15	7	IgG = 1:4096*	Doxycycline	No sequelae	Abortion
Patient 4	Sonora, Mexico, September, 2016	17	36	PCR positive¶	Doxycycline	No sequelae	No abnormalities

IFA = immunofluorescence antibody; PCR = polymerase chain reaction.

* Convalescent titers for Rocky Mountain spotted fever using IFA.

† Skin biopsy and autopsy specimens were positive for immunalkaline phosphatase staining for spotted fever.

‡ PCR for *Rickettsia rickettsii* using 17-kDa gene and 17kD1/2 Primer. Sequencing result *R. rickettsii* 100% Sheila Smith strain.

§ PCR for *Rickettsia* using a 401-bases pair *gltA* fragment of *Rickettsia* using primers CS-78f and CS-323R. Sequencing identity 100% with *R. rickettsii* (NCBI accession nos. JF739385–JF739387).

¶ PCR for *Rickettsia* using a 401-base pair fragment of the *gltA* gene using primers CS-78 and CS-323 and primers RRI1 and RRI2 for the hypothetical protein A1G_04230 for *Rickettsia rickettsii*.^{15,16}

|| Convalescent titers for Rocky Mountain spotted fever using IFA. First sample results were IgM negative and IgG 1:64.

clinical course of previously reported cases and those presented in our series.^{5–8,16,17} The lack of clinical specificity during the early phase of the disease can contribute to misdiagnosis, which may increase fatal outcomes.^{2,18,19} It should be emphasized that early diagnosis is empirical and presumptive, and physicians living in endemic regions should include RMSF in a differential diagnosis when evaluating a pregnant woman with fever, headache, and thrombocytopenia.^{2,20}

RMSF is easily suspected when the patient demonstrates petechial rash involving palms and soles; nonetheless, this feature does not generally present until several days of evolution and as many as 12–32% of cases may occur without rash.^{21,22} Clinical similarities with vector-borne diseases that include fever, headache, rash, and thrombocytopenia, may further confound the diagnosis of RMSF in regions where such diseases are endemic.²³ A careful medical assessment can help to distinguish these conditions. For example, the dengue rash is ruddy, morbilliform, and rough at the touch, is more commonly distributed on the face and chest and may be pruritic, whereas that of RMSF usually starts at the wrists and ankles as discrete, nonpruritic, pink macules that disappear with pressure approximately 48–72 hours after onset. As previously stated the identification of a petechial rash involving palms and soles may indicate a severe case.^{4,24} In regions where RMSF is endemic, the presence of fever and rash in a pregnant woman with history of contact with ticks can guide to a presumptive diagnosis.^{5,20}

There are few data regarding the pathophysiology of *rickettsial* vasculitis during pregnancy. From a series of scrub typhus in 11 pregnant women, investigators noted an abortion rate of 18% that likely resulted from circulatory impairment relating to thrombotic occlusion or coagulopathy initiated from endothelial infection with *Orientia tsutsugamushi*.²⁵ However, thrombotic occlusive events are rare in RMSF,²⁶ and it is more likely that hypotensive shock could lead to placental ischemia and fetal loss. In our series, infection with *R. rickettsii* precipitated the death of the fetus in for each of the three patients infected during the first trimester of pregnancy. Only one report has evaluated tissues microscopically for infection by *R. rickettsii* in a fetus aborted during RMSF in the mother and no evidence of direct infection of fetal tissues was noted, to suggest that infection does cross the placenta.¹⁶ The likely absence of vertical transmission is supported by reports of RMSF and Mediterranean spotted fever in pregnancy.^{5,27} Additional study of fetal tissues and placentae are needed to precisely define the pathophysiology of RMSF-induced abortion.

Doxycycline is recommended as the most effective therapy for treating all patients with RMSF, including pregnant women.^{2,28} However, medical reluctance to administer tetracycline-class antibiotics to pregnant women has been based on studies that described skeletal and dental abnormalities in children born to mothers who received extended courses of tetracycline during pregnancy.^{5,9–13} Nonetheless, evidence-based approaches suggest that therapeutic doses

of doxycycline do not pose a substantial risk of malformation or tooth staining in the fetus,²⁹ and no adverse events have been documented in pregnant women.^{2,30,31} Short cycles of doxycycline are also safe for nursing mothers.²⁹ In this context, doxycycline remains the recommended antibiotic to treat pregnant women with potentially life-threatening rickettsial infections such as RMSF.

Chloramphenicol is the only other antibiotic with efficacy against *R. rickettsii* and has been used to effectively treat RMSF in some pregnant women⁵; nonetheless, this drug can cause various adverse effects including aplastic anemia, bone marrow suppression, and gray baby syndrome. Moreover, the use of chloramphenicol has been associated with increased mortality in RMSF.¹⁸

In most regions of the western hemisphere, RMSF is a rare event in pregnant women; however, it is often related with the death of the fetus. Poor outcomes during pregnancy reflect substantial and life-threatening risks to the fetus and mother that vastly outweigh concerns linked with potential adverse effects associated with doxycycline therapy. Further studies that examine the pathophysiology for disease and death of the fetus are needed.

Received November 21, 2016. Accepted for publication May 1, 2017.

Published online June 12, 2017.

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