Brief Report

Lyme Disease During Pregnancy

Lauri E. Markowitz, MD; Allen C. Steere, MD; Jorge L. Benach, PhD; John D. Slade, MD; Claire V. Broome, MD

• Lyme disease is an increasingly recognized tick-borne illness caused by a spirochete, *Borrelia burgdorferi*. Because the etiologic agent of Lyme disease is a spirochete, there has been concern about the effect of maternal Lyme disease on pregnancy outcome. We reviewed cases of Lyme disease in pregnant women who were identified before knowledge of the pregnancy outcomes. Nineteen cases were identified with onset between 1976 and 1984. Eight of the women were affected during the first trimester, seven during the second trimester, and two during the third trimester; in two, the trimester of onset was unknown. Thirteen received appropriate antibiotic therapy for Lyme disease. Of the 19 pregnancies, five had adverse outcomes, including syndactyly, cortical blindness, intrauterine fetal death, prematurity, and rash in the newborn. Adverse outcomes occurred in cases with infection during each of the trimesters. Although *B burgdorferi* could not be implicated directly in any of the adverse outcomes, the frequency of such outcomes warrants further surveillance and studies of pregnant women with Lyme disease.

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LYME disease is an illness caused by the tick-borne spirochete, *Borrelia burgdorferi*.[1-3] The disease is characterized by a distinctive skin lesion, erythema chronicum migrans (ECM), that may be followed by rheumatic, cardiac, and neurologic manifestations.[4] *Borrelia burgdorferi* has been isolated from blood, skin lesions (ECM), and cerebrospinal fluid of patients with Lyme disease[2,3] and has been visualized in myocardium,[5] the eye,[6] and synovium.[7] In addition, all stages of the disease have been shown to respond to antimicrobial therapy.[8-10] Thus, it appears that many patients are bacteremic early in Lyme disease and that the later manifestations are due to tissue invasion and persistence of the organism. In a recent case report, transplacental transmission of the Lyme disease spirochete was documented, but was not linked directly to the congenital cardiac abnormalities found in the infant.[11] To assess the frequency and type of adverse pregnancy outcomes that may be associated with Lyme disease, we reviewed cases of Lyme disease in pregnant women who were identified before knowledge of the pregnancy outcome.

Methods

Case Definition.—A case was defined as (1) ECM in a woman during pregnancy; or (2) if no history of ECM, onset of neurologic, cardiac, or joint involvement of Lyme disease during pregnancy, and an antibody titer of 1:256 or higher to *B burgdorferi* by indirect immunofluorescence assay (IFA) or 1:200 or higher by enzyme-linked immunosorbent assay (ELISA); or (3) if no serologic tests were performed, onset of manifestations in two of three organ systems (neurologic, cardiac, or joint) during pregnancy. Only cases in which the outcome of pregnancy was not known were enrolled in the study. A normal outcome was defined as a full-term gestation with no anatomic or developmental abnormalities.

Case Finding.—Cases were identified by review of records at the Yale University School of Medicine, New Haven, Conn, through the Centers for Disease Control, Atlanta, surveillance system, and through inquiries to the Centers for Disease Control by private physicians and patients.

Data Collection.—All patients were interviewed by telephone to obtain information concerning obstetrical, medical, and family history, symptoms of Lyme disease, and treatment. Physicians were contacted and/or medical records reviewed to document adverse outcomes of pregnancy.

Laboratory Studies.—Available serum samples were tested by IFA or ELISA.[12,13] If possible, cord blood was obtained at the time of delivery. Placental and fetal tissues, if obtained, were cultured in BSK and BSK-K5 media[14,15] and examined by dark-field microscopy, and by IFA at the New Jersey State Health Department.

Results

Patients.—Nineteen women with onset of Lyme disease during pregnancy between 1976 and 1984 were identified (Table). Their ages ranged from 21 to 37 years (median, 30 years). Eleven were identified retrospectively and eight were followed up prospectively. The median time from delivery to interview was 15 months (range, one month to eight years). All but two of the women had ECM. Of the 17 women with ECM, 12 had only ECM or ECM with fever and myalgias, four had ECM followed by arthritis, and one had ECM followed by meningoencephalitis. In the two without ECM, one had facial palsy and arthritis, and the other had arthritis with an antibody titer of more than 1:3,200 by ELISA. Of the 17 patients with ECM, eight had the onset of illness in the first trimester, seven in the second trimester, and two in the third trimester. For cases without ECM, the trimester of onset was considered indeterminate: one developed facial palsy in the first trimester, and the other developed arthritis in the third trimester. Six patients did not receive antimicrobial therapy.

Pregnancy Outcomes.—Fourteen patients had normal pregnancies and outcomes, including seven with onset in the first trimester, four in the second trimester, two in the third trimester, and one in which the trimester of onset was not known. Five patients had an abnormal outcome.

Patient 2 (Table) had the onset of ECM during the sixth week of pregnancy, followed by headache and stiff neck one week later. Two weeks later, serum antibody titer to *B burgdorferi* was 1:512 by IFA, and she was treated

From the Respiratory and Special Pathogens Branch, Division of Bacterial Diseases, Center for Infectious Diseases, Centers for Disease Control, Atlanta (Drs Markowitz and Broome); the Department of Medicine, Yale University School of Medicine, New Haven, Conn (Dr Steere); the New York State Department of Health, Stony Brook (Dr Benach); and the University of Medicine and Dentistry of New Jersey-Rutgers Medical School, New Brunswick (Dr Slade).

Reprint requests to Respiratory and Special Pathogens Epidemiology Branch, Division of Bacterial Diseases, Center for Infectious Diseases, Centers for Disease Control, Atlanta, GA 30333 (Dr Markowitz).

16 weeks, she had a brief episode of arthritis. On physical examination at 20 weeks, no fetal heart could be auscultated, intrauterine fetal death was documented by ultrasound, and labor was induced. At that time, maternal serum antibody titer to *B burgdorferi* was more than 1:2,048. The placenta was hypoperfused and the membranes exhibited autolytic change. There was no exudate or nodularity. The amniotic fluid was not turbid. The fetus had no congenital anomalies. Microscopic examination revealed autolysis of fetal tissues and an immature placenta with presence of syncytial and cytotrophoblastic elements. There were no inflammatory infiltrates. Culture and IFA of the placenta and fetal tissues were negative for *B burgdorferi*.

Patient 7 developed fever, headache, and facial palsy during the tenth week of pregnancy and arthritis during the 19th week. The patient received no antimicrobial therapy. At week 36, she had premature labor and was delivered of a 2,100-g infant who developed hyperbilirubinemia (18 mg/dL; indirect, 16 mg/dL) when 4 days old, but was otherwise normal. The child, now 9 years old, has had normal anatomic and functional development.

Patient 11 developed ECM during the 20th week. One week later, she experienced headache, stiff neck, and arthralgia. She was treated with erythromycin for ten days. A second course of antimicrobial therapy (oral penicillin V) was given at week 27. Her infant was normal except for syndactaly (type 1) of the second and third toes.

Patient 15, who had had a previous child with trisomy 18, developed ECM during the 27th week of pregnancy and was treated with oral penicillin V for ten days. She had no other manifestations of Lyme disease. The remainder of her pregnancy was uneventful, and she was delivered of a full-term, healthy, male infant. At 8 months of age, the child was diagnosed as having cortical blindness and developmental delay. Computed tomography, assays for antibody to toxoplasmosis, rubella, cytomegalovirus, and herpes simplex, α-fetoprotein determination, and genetic evaluation were unrevealing. At 1 year of age, the child had no serum antibodies to *B burgdorferi*.

	Symptoms		Antibiotics		
Patient/ Age, yr	Type	Onset, Week of Gestation	Type	Week of Gestation Started	Pregnancy Outcome
1/30	ECM*, fever	2	Penicillin	3	Normal
	Arthritis	4			
2/34	ECM	6	Penicillin	8	Intrauterine fetal death
	Arthritis	16			
3/27	ECM	8	Penicillin	10	Normal
4/34	ECM	8	...	...	Normal
5/21	ECM, arthralgias	9	Penicillin	10	Normal
6/38	ECM	9	Penicillin	16	Normal
	Arthritis	15			
7/32	Facial palsy, fever	10	...	...	Prematurity
	Arthritis	19			
8/25	ECM	11	Penicillin	14	Normal
9/31	ECM, fever, arthralgias	11	...	...	Normal
10/28	ECM	15	Penicillin	15	Normal
11/30	ECM, arthralgias, headache, stiff neck	20	Erythromycin Penicillin	21 27	Syndactyly
12/26	ECM, fever	23	Penicillin	23	Normal
13/37	ECM, fever, arthralgias	24	Penicillin	24	Normal
14/25	ECM, fever	25	...	...	Normal
	Arthritis	30			
15/31	ECM	27	Penicillin	27	Cortical blindness, development delay
16/31	ECM, arthralgias	27	Penicillin	40	Normal
17/30	ECM, fever, arthralgias	33	Penicillin	34	Normal
18/35	Arthritis	37	...	...	Normal
19/31	ECM	37	...	...	Rash
	Meningoencephalitis	37			

*ECM indicates erythema chronicum migrans.

Patient 19 developed ECM and meningitis seven days before she was delivered of a full-term infant. The infant was healthy except for a generalized, petechial, vesicular rash and hyperbilirubinemia (18 mg/dL; indirect, 17 mg/dL) when 5 days old. Routine viral and bacterial blood and skin cultures were negative. The infant was treated with penicillin G potassium for ten days. Dermatology and infectious disease consultants recognized no other common neonatal condition. The rash faded in one week. The child, now 4 years of age, has had no other problems.

Only two of the 19 patients had had a subsequent pregnancy at the time of the interview. Both of these patients had had a normal outcome of the pregnancy complicated by Lyme disease, and subsequent pregnancies were also normal.

Antimicrobial Therapy, Manifestations, and Outcome.—Three (23%) of 13 patients who received antimicrobial therapy had an abnormal outcome, as did two (33%) of the six patients who did not receive antimicrobials. Abnormal pregnancy outcomes occurred in patients with onset of infection in each trimester. There was no significant difference in outcome by antimicrobial therapy or trimester of onset. Of the seven patients with a systemic manifestations of Lyme disease, three (43%) had an abnormal outcome, compared with two (17%) of the 12 patients with only ECM. This difference was not statistically significant either.

Serologic Studies.—Umbilical cord blood was obtained from five normal infants of patients in our study. Four were tested for IgM to *B burgdorferi*; none had an elevated titer. One infant, whose blood was tested only by polyvalent IFA, had an antibody titer of 1:512 at birth, but there was no detectable antibody seven months later. No umbilical cord blood was obtained from any of the infants with abnormalities.

Comment

Infections during pregnancy can result in abortion, fetal death, premature delivery, intrauterine growth retardation, or acute illness, malformations, or functional disturbances in the neonate. Among bacterial agents,

spirochetes, particularly *Treponema pallidum*, are well known to cause congenital infections. Syphilis during pregnancy is associated with abortion, stillbirths, and congenital abnormalities.[16] Transplacental transmission of relapsing fever due to *Borrelia* and *Leptospira* may also occur,[17-21] and maternal infection with either organism is associated with an increased risk of fetal loss.[18,22,23] In one study, 92% of women with relapsing fever aborted.[22] In addition, both infection with *Leptospira* and *Borrelia* have also been implicated in bovine abortion.[24,25] Congenital defects have not been reported with either of these infections.

In this study, we investigated cases of Lyme disease during pregnancy to detect any adverse outcomes. Five of the 19 pregnancies complicated by Lyme disease had an adverse outcome. Three adverse outcomes were not birth defects: prematurity, intrauterine fetal death, and rash illness in a newborn. One low-birth-weight infant in 18 is not unexpected, since 6.8% of births in the United States are infants weighing below 2,500 g.[26] However, one second-trimester abortion in 19 pregnancies is more than expected.[27] Although there was no evidence that the fetus was infected with *B burgdorferi*, this outcome might still have been due to maternal Lyme disease. The rash in the infant born to the mother who had Lyme disease during labor may have been due to congenital Lyme disease, but the case occurred before availability of laboratory tests for *B burgdorferi*, and microbiologic confirmation was not obtained.

The other two adverse outcomes were birth defects. Syndactyly of the second and third toes is usually a genetic defect and occurs in approximately 2% to 3% of white male infants (L. B. Holmes, MD, oral communication, May 15, 1985). Cortical blindness and developmental delay are less common, but at 1 year of age, this child did not have serologic evidence of infection with *B burgdorferi*.

No infant in our study had a congenital heart defect, as occurred in the case reported previously.[11] Since heart defects due to teratogens result from exposure in the first trimester, and since only eight women in this study had onset of Lyme disease during the first trimester, the power of our study to detect a congenital heart defect was limited. With this sample size, we had a 95% chance of observing a congenital defect only if greater than 31% of first-trimester infections resulted in this outcome.

Serologic evaluation of five normal infants did not suggest congenital infection in any of them. The elevated polyvalent antibody titer in one infant was probably due to passive transfer of maternal IgG, because a specimen from the infant tested several months later was negative.

Although five (26%) of the pregnancies in this study had an adverse outcome, several were minor and caused no permanent sequelae (prematurity and rash illness), no two adverse outcomes were the same, and none was documented to be due to Lyme disease. For no abnormality, however, was another etiology implicated. The frequency of adverse outcomes reported here warrants further surveillance and epidemiologic and laboratory studies of pregnant women with Lyme disease. In addition, we recommend that women who acquire Lyme disease during pregnancy be treated promptly with penicillin. For patients with early Lyme disease, oral penicillin V, 500 mg four times a day for ten to 20 days, is usually adequate.[8] Later in the illness, parenteral penicillin may be necessary.[9,10] Because results of serologic tests for Lyme disease are often negative during the first several weeks of infection, the diagnosis of Lyme disease should be made on the basis of clinical criteria,[28] and treatment started immediately.

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