

Teratogen Update: Lyme Disease

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ABSTRACT We reviewed the world literature concerning the reproductive effects of Lyme disease (LD). *Borrelia burgdorferi*, which is the etiology of LD, is a spirochete and, as such, may share the potential for causing fetal infection, which may occur in the setting of maternal spirochetemia. Information concerning the effects of gestational LD derives from case reports and series, epidemiologic studies, and experimental animal models. Although provocative, these studies fail to define a characteristic teratogenic effect. However, skin and cardiac involvement have predominated in some reports. Pregnancy wastage has been suggested primarily by animal studies. Gestational LD appears to be associated with a low risk of adverse pregnancy outcome, particularly with appropriated antibiotic therapy. Suggestions for management of clinical situations are presented. *Teratology* 64:276–281, 2001. © 2001 Wiley-Liss, Inc.

INTRODUCTION

First described in the late-1970s, Lyme disease has become the most common vector-borne illness in the United States and parts of Europe. In 1983, *Borrelia burgdorferi* was identified as the causative organism (Steere et al., '83). It is a fastidious spirochete that is transmitted to humans through the bite of a tick of the *Ixodid* species. In most cases, infection is marked by erythema migrans, an expanding annular rash with central clearing that forms at the site of inoculation. Other signs of early infection are nonspecific and include fever, myalgias, arthralgias, and fatigue. Within days to weeks of initial infection, the spirochete may disseminate to tissues throughout the body through vascular or lymphatic channels and cause severe cardiac, neurologic, and musculoskeletal symptoms.

There has been concern that *B. burgdorferi* may have adverse effects on pregnancy outcome similar to what has been observed with other spirochetes. Congenital syphilis associated with the spirochete *Treponema pallidum* has been well documented (Mascola et al., '85; Wendel, '88). Similarly, adverse fetal outcome has been documented in gestational infection with *Leptospira canicola*, the etiologic agent of leptospirosis, and other *Borrelia* spp., including *Borrelia recurrentis*, the causative agent of relapsing fever (Lindsay and Luke, '49; Coghlan, '69; Steenbarger, '82; Yagupsky, '85). This

article summarizes and discusses the current evidence for the existence of an adverse effect of gestational Lyme disease on pregnancy and the fetus.

HUMAN CASE REPORTS AND PATHOLOGIC STUDIES

Transplacental transmission of *B. burgdorferi* in humans has been documented in association with adverse fetal outcome. This was first documented in the case report of a 28-year-old mother who developed erythema migrans along with a headache, stiff neck, and arthralgias during her first trimester and was later found to have an increased antibody titer to *B. burgdorferi* (Schlesinger et al., '85). Her symptoms resolved spontaneously and she was untreated. At approximately 35 weeks she gave birth to an infant who died 39 hr after delivery. An autopsy revealed severe cardiovascular defects, including patent ductus arteriosus, coarctation of the aorta, tubular hypoplasia of the aorta and aortic arch, and marked endocardial fibroelastosis. On histologic examination, rare spirochetes compatible with *B. burgdorferi* were found in the fetal spleen, renal tubules, and bone marrow. Although spirochetes were not initially found in the myocardium, they were later demonstrated in cardiac tissue by immunohistochemical techniques (MacDonald, '89). Despite the presence of spirochetes in many tissues, there was no evidence of inflammation in any of the tissue specimens. Although the cardiac defects could not be definitively attributed to infection with *B. burgdorferi*, a teratogenic effect of the infection could not be ruled out, since primary infection occurred roughly during the period of cardiac organogenesis.

The second case report of transplacental transmission in a human was of a stillborn fetus whose mother was found to have positive antibody titers at two of three laboratories after being retrospectively diagnosed with untreated first trimester Lyme disease (MacDonald et al., '87). Autopsy findings of the infant showed an atrioventricular canal ventricular septal defect. *B. burgdorferi* was cultured only from the fetal

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liver, but immunofluorescence staining revealed spirochetes in the fetal myocardium, adrenal gland, and subarachnoid space of the midbrain. Histologic examination with silver stain showed rare spirochetes in the myocardium, placenta, liver, and brain; but no significant inflammation was found in the fetal tissues.

A third case report documented transplacental transmission of *B. burgdorferi* in an infant who had severe hypertension, metabolic acidosis, myocardial dysfunction and abdominal aortic thrombosis before his death at 8 days (Lavoie et al., '87). *B. burgdorferi* was cultured from the frontal cerebral cortex, and histologic examination with silver stain showed spirochetes in the brain and heart. The mother, who was seronegative for Lyme disease, reported a several year history of migratory arthralgias and malaise.

In 1988, Weber et al. reported the first case of transplacental transmission despite antibiotic treatment of first trimester maternal infection. In this report the mother received 7 days of oral penicillin for erythema migrans and her symptoms resolved. The child died 23 hr after birth as a result of perinatal brain damage, but histologic examination during autopsy revealed spirochetes in the brain and the liver that were identified as *B. burgdorferi* by monoclonal antibody testing. With the exception of the brain, there was no significant inflammation in any organ.

Another case report was of an otherwise healthy child who presented with multiple annular erythematous lesions, fever, and generalized lymphadenopathy which first appeared 3 weeks after birth and recurred throughout the first 3 years of life despite oral antibiotic treatment with josamycin and amoxicillin (Trevisan et al., '97). A skin biopsy revealed spirochetes by silver stain and was positive by polymerase chain reaction (PCR) for a sequence related to the flagellin protein of *B. burgdorferi*. In addition, serological examination by Western blot eventually revealed positive IgG antibodies. Although the mother had no clinical history of Lyme disease or tick bite, she had been involved in outdoor activities in an endemic region of northern Italy and had a weakly positive antibody titer.

Finally, a study of perinatal autopsy specimens also documented transplacental transmission of *B. burgdorferi* (MacDonald, '89). In each case, the spirochete was identified in fetal tissues with culture, indirect immunofluorescence, or immunohistochemistry. *B. burgdorferi* was found in a term stillborn with a ventriculoseptal defect who was born to a seropositive mother, was cultured from renal tissue of a 12-week abortus, and was identified in studies of 6 second-trimester abortuses born to seronegative mothers. Three of these had cardiac defects (one each of atrial septal defect, coarctation of the aorta, and intraventricular septal defect), two of which had died 1–2 weeks after the onset of toxemia in the mother. The author also identified *B. burgdorferi* in two infants who died shortly after birth: one with multiple anomalies includ-

ing hydrocephalus, omphalocele, clubfoot, spina bifida, meningomyelocele, and a ventriculoseptal defect; and another with a large ventriculoseptal defect and an absence of the left hemidiaphragm. *B. burgdorferi* was found in the placentas of two term infants who appeared to be septic, one of whom had a prenatal course complicated by toxemia.

Individual case reports of appropriately treated maternal Lyme disease have shown no association with adverse fetal outcomes. These cases have included both uncomplicated erythema migrans and neuroborreliosis in different stages of pregnancy (Mikkelsen, '87; Stiernstedt, '90; Schutzer et al., '91; Schaumann, '99; Grandsaerd et al., '00).

CASE SERIES

In addition to individual case reports, there have been several published case series investigating the relationship between gestational Lyme disease and fetal outcome. The results of these studies are summarized in Table 1.

EPIDEMIOLOGIC AND SEROLOGIC STUDIES

Several studies have investigated the relationship between seropositivity in pregnancy and pregnancy outcome. A large serological study including 2,014 women, of whom 12 were seropositive, found no increased risk of congenital malformations, low birth weight, abnormal length of gestation, or risk of fetal death among children born to seropositive mothers (Strobino et al., '93). A second study of 1,416 pregnant women, of whom 12 were seropositive at delivery, found no adverse outcomes attributable to seropositivity (Nadal et al., '89).

A study comparing 5,000 infants divided equally between a Lyme endemic area and a control area showed no significant differences in the incidence of total congenital malformations between the two groups (Williams et al., '95). There was a statistically significant increase in the rate of cardiac malformations in the endemic area, but within the endemic population there was no relationship between a cardiac malformation and a history of clinical or serological Lyme disease. Whether this finding represents an artifact or a valid difference among populations is unknown, but it does not seem to represent an effect attributable to Lyme disease.

Another epidemiologic study conducted in a Lyme endemic area has cast doubt on the connection between maternal Lyme disease and congenital heart disease (Strobino et al., '99). In this study of 796 patients with documented congenital heart disease and 704 control subjects, there was no significant association between congenital heart defects and a maternal history of a tick bite or Lyme disease within 3 months of conception or during pregnancy.

Serologic evidence has also been used to investigate the relationship between seropositivity and abortion,

TABLE 1. Case series of gestational Lyme disease

Author	No. of patients (no. treated)	Adverse outcomes		
		No.	Weeks at diagnosis	Type
Markowitz et al., '86	19 (13)	5	6 27 10 20 37	In utero fetal death at 20 weeks Cortical blindness and developmental delay diagnosed at 8 months 36-week infant with hyperbilirubinemia Syndactyly Hyperbilirubinemia with generalized petechial and vesicular rash, treated with PCN
Cieselski et al., '87	17 (17)	2	4 7	Spontaneous abortion at 13 weeks Syndactyly
Hercogova et al., '93	15 (13)	5	N/A	Patent ductus arteriosus repaired at 1 year Cryptorchidism Hypoplastic enamel (2 children) Delayed psychomotor development
Lakos, '95	N/A	N/A	N/A	Cheilognathopalatoschisis Cavernous hemangioma Dysplasia coxae
Maraspin et al., '99	105 (105)	12	6 5 6 10 7 21 26 20 29, 33, 16 6	Missed abortion at 9 weeks (mother with uterus bicornus) Spontaneous abortion at 10 weeks 6 preterm births Born at 25 weeks, died from chorioamnionitis (mother had previous surgical correction for uterus bicornus) Born at 25 weeks, died with no identified congenital malformations Induced at 33 weeks due to pre- eclampsia, normal development Born at 26 weeks due to incompetent cervix, normal development Born at 36 weeks Born at 36 weeks, had ASD and VSD but developed normally Urologic abnormalities diagnosed in first year (3 children) Syndactyly

but the evidence remains unclear. One study of 49 women who experienced a spontaneous abortion in an endemic area of northern Italy found a slightly increased rate of seropositivity (12%) as compared to a control group of women with full-term pregnancies (6%) (Carlomagno et al., '88). However, a subsequent study of 143 women found that there was not an increased rate of spontaneous abortion among seropositive, asymptomatic women. (Dlesk et al., '89).

Lastly, one study surveyed pediatric neurologists in an endemic area and were unable to find clinically significant neurologic sequelae in children of women with gestational Lyme disease (Gerber et al., '94).

ANIMAL STUDIES

Transplacental transmission of *B. burgdorferi* has been documented in studies of wild animals. The spirochete has been cultured from the fetal tissues of a coyote and white-footed mouse, *P. leucopus* (Burgess et al., '89; Anderson et al., '87). Another study used PCR analysis to confirm the presence of *B. burgdorferi* in fetal tissue of the white-footed mouse and the house mouse, *M. musculus* (Burgess et al., 1993). Further, a

newborn calf was found to have a positive blood culture for *B. burgdorferi* (Burgess 1988).

Transplacental transmission has also been documented in a more controlled laboratory animal population. *B. burgdorferi* was identified by PCR in 19 of 40 pups born to female beagles that had been intradermally inoculated with the spirochete multiple times between estrus and parturition (Gustafson et al., '93). There was no evidence of inflammation in any of the pups. Only four of these PCR-positive pups had culture-positive tissues, which may reflect either the difficulty in culturing *B. burgdorferi* or the presence of DNA from nonviable spirochetes. Not all pups of the same litter were PCR-positive, indicating that there may be different degrees of maternal transmission.

Controlled studies have not always demonstrated transplacental transmission. In one study in which female rats were inoculated at 4 days gestation by intraperitoneal injection, all samples of placental and fetal tissue of rats were culture-negative despite serologic evidence of infection in each mother (Moody et al., '91). In another study in which pregnant hamsters were infected by tick bite either before or after mating,

all offspring were culture-negative, while all mothers were culture-positive (Woodrum and Oliver, '99). Another study found that pups born to naturally infected white-footed mice were unable to transmit *B. burgdorferi* to spirochete-free larval *I. dammini* allowed to feed on them (Mather et al., '91).

Serologic evaluations in animals have documented probable in utero infection with *B. burgdorferi*. In separate studies by the same investigator, one aborted calf and a newborn foal had positive *B. burgdorferi* antibody titers (Burgess, '88, Burgess et al., '89). Since in utero transfer of maternal antibodies does not occur in cows or horses, these elevated titers likely indicate in utero fetal infection. Furthermore, IgM antibody was detected by western blot within 24 hr of birth in four beagle pups that did not receive colostrum (Gustafson et al., '93).

In addition to documenting transplacental transmission and serologic evidence of probable in utero infection, several animal studies have linked maternal *B. burgdorferi* infection during pregnancy with fetal wastage and reproductive failure. Circumstantial evidence for this association was found in a report that 36 cows with spontaneous abortions were seropositive for *B. burgdorferi*, one of which had a positive blood culture (Burgess, '88). In another study, examination of the maternal uterus of experimentally infected beagles showed more implantation sites than born pups in 3/9 of the infected mothers and none of the control beagles, which may indicate an increased rate of fetal resorption (Gustafson et al., '93).

Maternal infection with *B. burgdorferi* has also been associated with reproductive failure and severe fetal infection in horses (Burgess, '89). Of seven naturally infected pregnant mares, three fetuses were aborted or resorbed, three foals died within the first week of life with culture-positive renal tissue and histologic evidence of renal pathology, and one foal was euthanized at 1 year after exhibiting chronic, progressive neurological disease over the previous 6 months. Although primary infection may have occurred after birth, this case may be an example of chronic, nonfatal in utero infection.

Maternal infection occurring near the beginning of pregnancy has been associated with increased fetal loss in mice (Silver et al., '95). Maternal infection either 5 days before or 4 days after mating was associated with a loss of 12–14% of fetuses as compared with no losses in control mice. Since maternal uteri were all PCR-positive and all fetal tissues were PCR-negative in this experiment, fetal wastage in these mice may have resulted from the effect of *B. burgdorferi* effect on the maternal uterus as opposed to within the fetus itself.

DISCUSSION

Attempts to define the clinical significance of gestational Lyme disease have been limited seriously by several factors. First, the prevalence of Lyme disease in pregnant women, even in highly endemic regions, is low, making it difficult to perform statistically signifi-

cant case-control and other epidemiological based studies. Second, it is difficult to define *B. burgdorferi* infection, especially in the absence of clinical markers such as EM. Studies relying on LD seropositivity, a history of a tick bite, or even retrospective clinical history are unreliable in diagnosing LD in pregnant women and may make studies of gestational LD questionable. Third, owing to increased awareness and concern about Lyme disease, particularly in pregnant patients, most will have received antibiotic treatment. For these reasons, our understanding of the outcome of untreated gestational Lyme disease is based on a small number of case reports and pathological studies that in some instances occurred without the benefit of accurate diagnostic techniques.

Despite these limitations, it is possible to address several aspects of gestational Lyme disease. First, does *B. burgdorferi* cross the placenta and invade the fetus? Second, if there is transplacental transmission, does this have any significance for the development of the fetus? Finally, is there an overall effect on pregnancy without regard to direct fetal infection?

Studies in both human and animal models have established that *B. burgdorferi* can cross the placenta, presumably occurring during a period of spirochetemia. The clinical significance of transplacental transmission in humans remains unclear, however given the absence of a documented fetal inflammatory or immunologic response, which would be expected if the spirochetes were causing active infection.

Perhaps the most compelling argument against the teratogenicity of gestational Lyme disease is the lack of a consistent clinical outcome in affected pregnancies. Initially the most concerning potential associations involved congenital cardiac malformations and fetal loss. Subsequent epidemiologic research has cast significant doubt on this association. The relationship between gestational Lyme disease and fetal loss also remains unclear. Because gestational Lyme disease has been clearly linked to fetal loss in animal studies, the potential for a causal effect in human gestational LD exists. A connection between fetal and maternal infection in humans with other spirochetes, such as *Borrelia recurrentis* and *Leptospira canicola* has been demonstrated (Gaud et al., '47; Coghlan, '69).

Despite documentation of transplacental transmission of *Borrelia burgdorferi*, there has been no evidence for a fetal inflammatory or immune response or a consistent clinical outcome resulting from gestational Lyme disease. An analysis of current evidence, therefore, indicates that an adverse fetal outcome due to maternal infection with *B. burgdorferi* at any point during pregnancy in humans is at most extremely rare.

RECOMMENDATIONS FOR CLINICAL MANAGEMENT

Prenatal screening

Even in endemic regions, the incidence of Lyme disease in pregnant women has been shown to be low.

Since seropositivity alone has not been shown to be related to adverse fetal outcome, there is no reason to screen asymptomatic women for antibodies to *B. burgdorferi*.

Tick bite in pregnancy

No association has been found between tick bites and adverse fetal outcome in the absence of maternal clinical Lyme disease. The Infectious Diseases Society of America guidelines recommend that antibiotic prophylaxis is not advised for a tick bite, and there is no evidence to suggest that pregnant woman should be handled differently (Wormser et al., '00). Close follow-up for clinical evidence of Lyme disease is recommended.

Seropositivity in pregnancy

Clinical studies have not shown a relationship between seropositivity in pregnancy and adverse fetal outcome. No treatment is currently recommended in the absence of clinical symptoms.

Lyme disease in pregnancy

There has been some variation in the antibiotic management of Lyme disease in pregnancy over the past decade, including the use of parenteral antibiotics in pregnant women regardless of clinical stage. Evaluation of more recent literature indicates that oral antibiotics appear to be sufficient treatment for uncomplicated erythema migrans. We do, however, recommend the continual usage of parenteral antibiotics for both early disseminated and late stage Lyme disease. Tetracycline antibiotics should, of course, be avoided in the treatment of pregnant women.

Clinical signs of Lyme disease in infancy

Clinical signs of Lyme disease in infancy should be evaluated according to standard recommendations. This would include accepted clinical and serological standards for diagnosis.

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