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Borreliosis During Pregnancy: A Risk for the Unborn Child?

Ioannis Mylonas

Abstract

Little is known regarding the possible harmful effects of *Borrelia* infections in pregnancy, since such a risk analysis is difficult to perform. Transplacental transmission of *Borrelia burgdorferi* has been documented in several animal studies. Therefore, it had been thought that fetal infection and teratogenicity was possible from *B. burgdorferi*, especially considering the similarities between Lyme borreliosis and syphilis. However, several clinical, serological, and epidemiological studies have failed to confirm a causal association between *B. burgdorferi* infection and a pregnancy adverse outcome. Moreover, there have been no reported cases of transmission of *Borrelia* via breast milk. However, the therapeutic approach to pregnant women with Lyme disease should be antibiotic treatment, according to the clinical manifestation and the timing of the tick bite. An effective vaccine is not yet available and the prevention of Lyme borreliosis depends on public and physician education, and appropriate antibiotic therapy during pregnancy.

Key Words: Borreliosis—Fetal malformation—Lyme disease—Pregnancy.

Introduction

In 1975 an increased incidence of juvenile arthritis in children was observed in Lyme in the State of Connecticut in the United States. This increased incidence was anamnestically traced back to tick bites, and a common and unique pathological agent was suspected. Erythema chronicum migrans described by Afzelius (1909) and Lipschütz (1913), and Meningopolyneuritis, Lymphadenosis cutis benigna (described by Bäfverstedt [1943]), and Acrodermatitis chronica atrophicans described by Buchwald (1883) and Herxheimer and Hartmann (1902) were then collectively termed Lyme disease, along with a list of many other symptoms (Steere et al. 1986).

However, it was not until 1981 that W. Burgdorfer was able to identify the bacterial pathogen responsible for Lyme disease (Burgdorfer et al. 1982). *Borrelia* are spiral-shaped bacteria and belong, together with *Treponema* and *Leptospira*, to the spirochaetae family. Today, three *Borrelia* species are known to be pathogenic in humans, as well as eight minimally pathogenic or nonpathogenic species, which all belong to the genus *Borrelia burgdorferi sensu lato*. While the biological profile of the pathogens is very similar, significant differences exist between their antigenic structure (Friese et al. 2003, Singh and Girschick 2004). This heterogeneity must be taken into consideration when establishing a diagnosis.

Today, the most threatening *Borrelia* infection is Lyme borreliosis. While in America primarily only infections with *B. burgdorferi sensu stricto* occur, Europe experiences additional infections from *Borrelia afzelii* and *Borrelia garinii*. Meanwhile, transplacental transmission of *B. burgdorferi* has been documented in several animal studies with adverse fetal outcome and reproductive failure in cows, beetles, and horses (Shapiro and Gerber 2006). Therefore, it had been thought that fetal infection and teratogenicity was possible from *B. burgdorferi*, especially considering the similarities between Lyme borreliosis and syphilis.

In this review the impact of borreliosis during pregnancy and possible adverse effects as well as diagnosis and therapy are being reviewed. Search strategy and selection criteria for identifying relevant data were by performed by searching Medline, Current Contents, Web of Science, Embase, and references from relevant articles. The search was performed until January 31, 2010, and articles published until this date were considered. English and German gynecological and infectious diseases textbooks were also reviewed. Additionally, numerous articles were identified through searches of the extensive files of the author. Search terms were "Borrelia," "borreliosis," "Lyme diseases," "pregnancy," "neonatal infection," "epidemiology," and "adverse pregnancy outcome." English- and German-language articles were reviewed.

Division of Infectious Diseases in Gynaecology and Obstetrics, 1st Department of Obstetrics and Gynaecology, Ludwig-Maximilians-University Munich, Munich, Germany.

Transmission

Ticks (*Ixodes ricinus*) are the natural vectors of *Borrelia*. Eggs are deposited by reproducing insects, which hatch into nymphs that have limited movement and feed on blood. An insect can live up to 7 years and develop slowly into a young tick. The mature insects fall from hedges and trees onto passing animals or humans; during suction, the existing *Borrelia* can be passed on or even acquired. Of all *Borrelia* infections in humans, 90% are due to nymphs. Approximately every 10th tick in our mixed forests with low growth is infected with *Borrelia*. Postencounter, 2 h are sufficient to reach the critical bacterial mass for an infection. Only in every fourth *Borrelia*-containing tick, on average, is such a transfer seen (Friese et al. 2003).

After transmission to humans through these vectors, *Borrelia* increase in population in the skin, and in <50% of cases this leads to inflammation. A reddening at the site of a tick bite is not evidence of a *Borrelia* infection, as the skin lesion allows for the normal skin flora to penetrate through, causing a nonspecific local inflammation. An inflamed reddening with progressive borders that increase in area points to a *Borrelia* infection. Approximately 60% of Borrelia infections develop such an erythema migrans within several days of the tick bite. At this stage of infection, nonspecific defense mechanisms can probably contain and eliminate the pathogen; however, it is still possible for the pathogen to enter the blood circulation and reach other organs at this time.

Around 60,000–100,000 cases of the disease occur every year. More than 20,000 cases are now reported annually in the United States (CDC 2004), and the actual number may be >60, 000. Similar estimations are being considered for Europe. Up to 10% of adults have an elevated antibody titer as a sign of a previous *Borrelia* infection (Friese et al. 2003).

Clinical Symptoms

Lyme borreliosis can be divided into three stages (Wilske et al. 2000, Friese et al. 2003, Mylonas and Friese 2004, Mylonas et al. 2005). Although borreliosis can play itself out similarly in children and adults, children show earlier manifestations of neurological symptoms (Table 1). The basic outlines of Lyme borreliosis are similar worldwide, but there are regional variations, since *B. burgdorferi* can be found in America, whereas *B. afzelii* and *B. garinii* are mostly located in Europe (Steere et al. 1986, Baranton et al. 2001, Steere 2001). Interestingly, *B. burgdorferi* often disseminates, being able to cause chronic and antibiotic-refractory arthritis. On the other hand, *B. garinii* does not typically disseminate but has neurotropic properties, causing encephalomyelitis. *B. afzelii* often infects only the skin, causing dermatoborrelioses (Steere et al. 1986, Steere 2001).

Stage I (early localized infection after days to weeks)

The first infection consists primarily of a local inflammation, an erythema migrans of the skin. It begins with an initial papula, followed by a sharply-contained painless erythema, which spreads centrifugally and fades in the middle. The Erythema migrans caused bei *B. burgdorferi* in North America is faster spreading, is more intensely inflamed, and demonstrates a shorter duration but with a frequent hematogenous dissemination as compared to *B. afzelii or B. garinii* infection in Europe (Steere et al. 1986, Steere 2001). Unusual symptoms such as fever, headache (meningismus), myalgia, arthralgia, swollen lymph nodes, and conjunctivitis can also appear. Lymphadenosis cutis benigna Bäfverstedt appear rarely on the skin as a red livid infiltrate. These consist of B-lymphocytes, are several centimeters wide with soft to plump/elastic consistency, and appear preferentially on the earlobes, mamilla, and scrotum. Antibodies are detected in 20%–50% of patients. Erythema migrans accompanied by itching, burning, pain, and dysesthesia is subjective and can spontaneously disappear within days to a few weeks.

Stage II (early disseminated infection after weeks to months, still in the same timeframe as stage I)

Neurological manifestations are at the forefront of the early disseminated infection (e.g., facial paresis, meningitis, encephalitis, radiculitis, and Garin Bujadoux Bannwarth Syndrome [meningopolyneuritis with burning radicular pain]), which may be related to the prior skin appearance in stage I. Initially, over 90% asymmetric flaccid palsy is observed, while sensible failures occur in 60% of cases (Steere et al. 1986, Steere 2001). Interestingly, *B. burgdorferi* infections in North America can cause meningitis, severe headache, and neck stiffness, whereas in Europe severe radicular pain and pleocytosis with less prominent headache and neck stiffness caused particularly by *B. garinii* are being observed (Steere et al. 1986, Steere 2001). Rare manifestations in the heart (myo-, peri-, and pancarditis, atrioventricular (AV)-transmission problems to a complete blockage, ST-T changes in the electrocardiogram (ECG) atrial fibrillation, ventricular extrasystole, tachycardia, and decrease in left ventricular functions to a full-blown heart failure) may also appear and antibodies are detectable in 70%–90% of all cases. This form also heals spontaneously within weeks or months, though with a tendency for recurrence.

Stage III (persistent infection after months to years)

Neuroborreliosis manifests itself in the form of polyradiculoneuritis (Bannwarth Syndrome), with constant pain that increases at night. Subtle encephalopathy with cognitive disturbance and slight intrathecal antibody production might occur in patients infected with *B. burgdorferi*, while severe encephalomyelitis, spasticity, cognitive abnormalities, and marked intrathecal antibody production are primarily caused by *B. garinii* (Steere et al. 1986, Steere 2001). Palsies appearing within the context of radiculitis show a tendency to retreat, although with incomplete healing, evidenced for example by paresthesia. Acrodermatitis chronica atrophicans Herxheimer with atrophy of the skin (cigarette paper thin) may be seen. Manifestations of acra and stretchy skin are nowadays rarely observed. The Lyme arthritis is a relapsing or chronic mono- or oligoarticular disease where jumping joints, elbow joints, and sometimes even finger, toe, wrist, and jaw joints are affected. *B. burgdorferi*–infected patients demonstrate more frequent oligoarticular arthritis with more intense joint inflammation compared to European patients (Steere et al. 1986, Steere 2001). At this stage, a chronic encephalomyelitis with para- and tetraparesis may appear. Antibodies are detected in 90%–100% of cases. In patients with human immunodeficiency virus infection, dissemination into the central nervous system can occur.

Table 1. Clinical Manifestation of Lyme Borreliosis[a]

Stage	*Adults*	*Children*
Stage I: Early localized Infection	Erythema migrans General symptoms (flu-like) Including headache and fever Lymphadenosis cutis benigna	Erythema migrans General symptoms (flu-like) Including headache and fever Conjunctivitis Neuritis of cranialer nerves (*Nervus fascialis*) Pericarditis Lymphocytic meningitis Arthralgia und myalgia
Stage II: Early disseminated infection	Secondary erythema migrans-lesions Pericarditis Lymphocytic meningitis Myo-, peri-, and pancarditis Atrioventricular (AV) block Encephalitis Cerebral palsy Radiculoneuropathy Neuritis cranial nerves (*Nervus fascialis*) Atrial fibrillation Ventricular extrasystole Arthralgia and myalgia Arthritis	
Stage III: Persistent	Acrodermatitis chronica atrophicans Therapy-resistant arthritis Myositis Peripheral neuropathy Subacute encephalopathy Progressive encephalomyelitis Garin-Bujadoux-Bannwarth-Syndrome	Acrodermatitis chronica atrophicans (rare) Chronic arthritis Meningoradiculoneuritis (rare) Radiculoneuropathy Encephalomyelitis (rare) Conjunctivitis, uveitis, keratitis Myo-, peri-, and pancarditis

[a]Steere et al. (1986), Steere (2001), Friese et al. (2003), Mylonas and Friese (2004, 2009), Mylonas et al. (2005), and Shapiro and Gerber (2006).

Lyme Disease During Pregnancy

Little is known about the possible harmful effects of *Borrelia* infections in pregnancy, since such a risk analysis is difficult to perform. Transplacental transmission of *B. burgdorferi* has been documented in several animal studies. Therefore, it has been believed that fetal infection and possible teratogenicity could arise from *B. burgdorferi*, especially considering the similarities between Lyme borreliosis and syphilis.

Transplacental transmission—animal studies

B. burgdorferi has been cultured or identified from fetal tissues of a coyote, a white-footed mouse, a calf, a newborn foal, and four beagle pups. Several animal studies have linked infection with *B. burgdorferi* during pregnancy with fetal wastage and reproductive failure in cows, beetles, and horses (Shapiro and Gerber 2006).

B. burgdorferi was detected by polymerase chain reaction (PCR) in 19 out of 40 beagle pups born from a mother who was inoculated several times intradermally with spirochaetae (Gustafson et al. 1993). None of the pups showed evidence of inflammation. Only four of the PCR-positive pups yielded positive tissue cultures (Moody and Barthold 1991). In controlled studies, transplacental transmission was not confirmed in any of the cases. Examination on the fourth gestation day of female rats inoculated intraperitoneally with *B. burgdorferi* showed that all placental and fetal tissues were negative, although serology showed infection in the rats (Moody and Barthold 1991). Maternal infection at the beginning of the pregnancy could be correlated with an increased abortion rate in mice (Silver et al. 1995). When these were infected 5 days before and 4 days after pairing, a 12%–14% abortion rate was observed. As all uteri tested positive for the pathogen using PCR, abortions may have occurred due to the effects of *B. burgdorferi* on the cervix rather than on the fetus (Silver et al. 1995).

Case reports of Borrelia *infection during pregnancy*

The likelihood of a transplacental infection is probably higher at the beginning of pregnancy than in the remaining duration of pregnancy. Besides abortion (Carlomagno et al. 1988), malformations such as syndactyly, ventricular septum defect, and heart rate defects have been described (Table 2). However, some case reports of pregnant women with erythema migrans or neurological involvement were reported without any association between infection and adverse pregnancy outcome (Shapiro and Gerber 2006).

The first case was reported in 1985 of a 28-year-old mother who was suffering during her first trimester from erythema migrans, headaches, and arthralgia (Schlesinger et al. 1985). Subsequently, an increased level of antibodies against *B. burgdorferi* was recorded. The symptoms disappeared spontaneously and the baby was born at week 35 of pregnancy, and died after 39 h. An autopsy revealed severe cardiovascular defects, and *B. burgdorferi*–like spirochaetae were detected in the fetal spleen, kidney tubules, and bone marrow.

Table 2. Case Reports of Adverse Pregnancy Outcome After *Borrelia* Infection During Pregnancy

Clinical manifestation	*Reference*
Premature birth	Markowitz et al. (1986)
Intrauterine death	Markowitz et al. (1986)
Stillbirth	Schlesinger et al. (1985),
Establishment of spirochaetae in fetal tissue	McDonald (1989)
Hydrocephalus	
Sudden infant death syndrome	
Intrauterine growth restriction	Markowitz et al. (1986)
Bilateral ureterostenosis with hydronephrosis	Schlesinger et al. (1985)
Connatales exanthem	Markowitz et al. (1986)
Atrial and ventricular septum defect	Maraspin et al. (1996)
Multiple cardiovascular malformation	Schlesinger et al. (1985)
Connatal sepsis	Shirts et al. (1983)
Pale facial color	
Hepatosplenomegaly	
Petechia	
Thrombocytopenia	
Hyperbilirubinemia	
Cheilognathopalatoschisis	Maraspin et al. (1996)
Syndactyly	Markowitz et al. (1986)
Hip dysplasia	Maraspin et al. (1996)
Cavernous hemangioma	Maraspin et al. (1996)
Cortical blindness	Markowitz et al. (1986)

Despite the presence of spirochaetae in fetal tissues, inflammatory reactions were not detectable. Although the cardiac complications could not be traced back directly to the *B. burgdorferi* infection, a teratogenic effect from *Borrelia* could not be excluded.

A second case report of stillbirth by a seropositive mother followed in 1987 (MacDonald et al. 1987). An autopsy of the fetus showed a ventricular septum defect, while *B. burgdorferi* was only culturable from the liver. Immunofluorescent methods demonstrated the presence of spirochaetae in fetal myocardia, adrenal glands, and the subarachnoid space in the brain. A histological examination with silver nitrate further indicated involvement of the myocardium, placenta, liver, and brain. Interestingly, an inflammatory reaction in the tissue was not detected (MacDonald et al. 1987).

In 1988, a case was recorded of transplacental transmission of *Borrelia* despite antibiotic therapy (Weber et al. 1988). The mother received penicillin treatment for 7 days after erythema migrans was observed in the first trimester. The newborn was dead within 23 h after birth, following perinatal brain damage. The histological examinations showed the presence of spirochaetae in the brain and in the liver. With the exception of the brain, a significant inflammatory reaction was seen in all other major organs (Weber et al. 1988).

In 1989, one abortion in a pregnant woman with disseminated Lyme borreliosis insufficiently treated with oral penicillin for 5 days was observed (Hercogova et al. 1993). Although *Borrelia* was detected in the placenta, an association between the abortion and infection was unclear. In 1997 a healthy child of 3 weeks of age presented with multiple annular, erythematous patches, fever, and generalized lymphadenopathy (Trevisan et al. 1997). *B. burgdorferi* was isolated from the skin samples but, despite oral antibiotic therapy, the skin lesions recurred over the following 3 years (Trevisan et al. 1997). The authors suggested a congenital borreliosis.

A series of 105 women with erythema migrans during pregnancy was reported in 1999 (Maraspin et al. 1999). Ninety-three women (88.6%) had healthy infants delivered at term, whereas six pregnancies (5.7%) resulted in preterm birth and two (1.9%) pregnancies ended with a miscarriage. Two preterm newborns died shortly after birth, while one had cardiac abnormalities. Of the 93 deliveries at term, 4 newborns (3.8%) displayed congenital abnormalities. However, *B. burgdorferi* infection could not be directly implicated as the primary etiology of these malformations.

In another study, 60 placentas from asymptomatic women with increased levels of antiborrelial antibodies and who lived in an area endemic for borreliosis (Figueroa et al. 1996) were examined with silver staining. Three placentas (5%) were positive for spirochetes, and the PCR results were positive for *Borrelia* in two of the three placentas. The women had negative serologic results for borreliosis and syphilis, with normal pregnancy outcomes.

These observed birth defects and adverse pregnancy outcomes could not be clearly linked with fetal infections. Instead, a maternal inflammatory reaction to the infection was considered to be responsible. Further, Lyme disease during pregnancy is immediately treated with antibiotics, which decreases the frequency of a possible fetal symptom by two-thirds, according to most studies. However, a teratogenic effect cannot be excluded, although evidence for this has not yet been demonstrated. Altogether, the risk of an intrauterine transmission from the mother to the fetus has been thought to be unlikely (Stiernstedt 1990), especially when a high-dose antibiotic is administered early. Still, a connatal infection despite oral antibiotic treatment of the mother has been reported (Weber et al. 1988).

Epidemiological studies

Several studies have looked at the connection between seropositivity during pregnancy and fetal malformation and adverse pregnancy outcome. A slightly elevated seropositivity (6%) was detected for spontaneous early abortions in 49 women in an Italian *Borrelia*-endemic area, in comparison to control groups (Carlomagno et al. 1988). In another study, 421 serum specimens obtained from cord blood did not show an association between the presence of immunoglobulin G (IgG) antibodies to *B. burgdorferi* and congenital malformations (Williams et al. 1995).

In 1416 pregnant women, of which 12 (0.85%) were seropositive, no increased risk of malformation could be demonstrated (Nadal et al. 1989). Another clinical and serological study was performed where 2000 women were examined at the first prenatal visit and again at delivery (Strobino et al. 1993). Eleven women (0.7%) were seropositive and 79 (4%) had reported Lyme disease in the past. No association between exposure of the mother to *B. burgdorferi* either before conception or during pregnancy could be made with adverse pregnancy outcome or congenital malformations (Williams et al. 1995).

Yet another study, which compared 5000 infants in an endemic area to a control group, showed no significant difference in the incidence of congenital malformation

(Williams et al. 1995). There was a statistically significant higher incidence of congenital heart malformation in the endemic areas, although within this population there was no correlation between heart malformation and clinical or serological *Borrelia* infection. In a retrospective case–control study of 796 patients with heart disease documented at birth and 704 control cases, a correlation was found between heart failure at birth and anamnestic tick bites or borreliosis cases during pregnancy. However, there was no association between congenital heart defects and either a tick bite or Lyme disease (Strobino et al. 1999).

Lyme Disease During the Postpartum Period

Since there have been no reported cases of transmission of *Borrelia* via breast milk, the risk of this cannot be assessed. While it is noteworthy that it was possible to obtain *Borrelia* DNA via PCR from two lactating mothers (Schmidt et al. 1995), it is unclear whether this indicated that intact bacteria or fragments of the bacterial genome were present. Due to the lack of data on this topic, a contraindication to lactation has been established. A recommendation for this may be especially prudent, as *Treponema* transmission through such a pathway is entirely possible. However, it must be noted that the transmission of *Treponema* through mucous membranes such as occurs in genital and oral sex has not been seen in *Borrelia* infection in humans or in animal experiments (Woodrum and Oliver 1999). An additional problem is the use of antibiotic therapy during lactation, as these drugs can pass into the breast milk and lead to diarrhea or candidosis in children. The patient should be advised of these risks, and made aware of the results from relevant studies. Overall, even though the risk of transmission through breast milk is minimal, it cannot be excluded, and lactating mothers should be made aware of all possible risks.

Diagnosis

The diagnosis can be difficult since antibody production can be delayed (2–3 weeks postinfection). Moreover, a negative antibody titer cannot exclude an acute infection. Direct detection of bacteria through microscopy or culture is possible in only few laboratories and is unsuitable for routine diagnostic procedure. Evidence of bacterial DNA can be detected by using PCR, although this does not guarantee a primary infection. IgM antibodies can persist for months, and therefore their presence does not conclusively point to a fresh infection (Table 3).

A *Borrelia* infection should be determined serologically (Table 3), and erythema migrans should be treated even in the case of negative antibody titers. IgG antibodies are generally reliable indicators of stage III infection. Further serological examinations should be performed after 3 weeks postinitial illness, to 6 weeks post-tick bite (Wilske et al. 2000). It can be

Table 3. Diagnostic Evaluation[a]

				Conclusions	
	Material	*Sensitivity*	*Specificity*	*Negative*	*Positive*
IgM/IgG antibodies	Serum	Stage I: 20%–50% Stage II: ~70% Stage III: 90%–100%	High	Borreliosis implausible	Previous borreliosis Active borreliosis
	Cerebrospinal fluid	~80% (<6 weeks after symptoms) Almost 100% (>6 weeks after symptoms)	High	Neuroborreliosis implausible	Neuroborreliosis Previous treated borreliosis
Isolated IgM antibody (just IgM antibody positive)	Serum	—	Potential false positive results	—	Acute infection Potential false positive result
	Cerebrospinal fluid	—	—	—	—
Microbiological culture	Serum	Low	Very high	Low validity	Borreliosis
	Cerebrospinal fluid	Stage II: 10%–30%	Very high	Neuroborreliosis implausible	Neuroborreliosis
	Biopsy	50%–70%	Very high	Borreliosis implausible	Borreliosis
PCR	Serum	Low Stage I: 10% Stage II: 40%	High	Low validity	Borreliosis
	Cerebrospinal fluid	Stage II: 10%–30%	High	Neuroborreliosis implausible	Neuroborreliosis
	Synovia	50%–70%	High (<99%)	Borreliosis implausible	Borreliosis
	Biopsy	50%–70%	High	Borreliosis implausible	Borreliosis

[a]Wilske et al. (2000), Wilske (2002), and Mylonas and Friese (2009).
IgG, immunoglobulin G; IgM, immunoglobulin M; PCR, polymerase chain reaction.

Table 4. Therapy of a *Borrelia* Infection During Pregnancy and Postpartum Period[a]

Stage	*Medication*	*Dosage*	*Duration (days)*
Stage I	Amoxicillin	3×750–1000 mg p.o.	21
	Cefuroximaxetil	2×500 mg p.o.	21
	Roxithromycin	1×300 mg p.o.	21
	Clarithromycin	2×250 mg p.o.	21
Stage II	Ceftriaxon	2–4 g i.v.	14–21
	Cefotaxim	2×3 g i.v.	14–21
	Penicillin G	4×5 Million IU i.v.	14–21
Stage III	Ceftriaxon	2–4 g i.v.	14–21
	Cefotaxim	2×3 g i.v.	14–21
	Penicillin G	4×5 Million IU i.v.	14–21

Roxithromycin and clarithromycin have not been completely evaluated for the use during pregnancy and postpartum period.
[a]Friese et al. (2003), Mylonas and Friese (2004, 2009), Mylonas et al. (2005), and Shapiro and Gerber (2006).
i.v., intravenous; p.o., per os.

difficult in some cases to reach a diagnosis from laboratory findings, and often the laboratory data must be combined with clinical findings to reach a diagnosis.

In the case of neuroborreliosis, it is typical to find lymphocytic pleocytosis and intrathecal antibody synthesis, which is established by parallel analysis of serum/plasma pairing. The enzyme-linked immunosorbent assay results must also be confirmed by immunoblot (Western blot) (Wilske et al. 2000, Wilske 2002), and it is possible to determine in detail to which antigens of the bacterium the antibodies were binding.

In defined *Borrelia* infection in early pregnancy, amniocentesis can be performed to examine fetal conditions. Further examination of the mother's blood and the umbilical cord blood is possible, and the newborn should be examined until the sixth month for any noticeable signs and symptoms.

Treatment

Several medications are available for clinically manifested borreliosis, and infections should be treated thoroughly and in excess doses (Table 4). Even a self-limiting erythema presents a indicator for therapy. If there are general symptoms besides erythema migrans in State I, such as flu-like symptoms, headaches, limb aches, arthralgia, night sweat, or fever, at least a temporary bacteremia should be suspected. In such cases, parenteral treatment should be started. There is no indication for pregnancy termination (Strobino et al. 1999, Friese et al. 2003, Mylonas et al. 2005, Mylonas and Friese 2009).

Skin manifestations respond well to tetracycline (doxycycline). If the diagnosis is still unclear, treatment with 2×100 mg doxycycline/day over 3 weeks is possible (Steere 2001). Interestingly, a one-time administration of 200 mg doxycycline is successful against *Borrelia* infection within 72 h after a tick bite (Nadelman et al. 2001). However, doxycycline treatment is contraindicated during pregnancy and lactation.

Since an intrauterine death is possible following acute borreliosis, prophylactic treatment should be given in pregnant individuals. To assess the likelihood of transmission, the removed tick can be assayed by PCR for an infection with *Borrelia*. Depending on the results and the duration of time that the tick was present on the host (a transmission from <24 h contact is rare), prophylactic treatment with amoxicillin (7–10 days) can be performed.

If no response to treatment is seen within 3 months, the causal link between serological findings, symptoms, and diagnosis must be questioned. The role of macrolides is not yet defined, although treatment during pregnancy is possible. Neuroborreliosis is preferably treated with ceftriaxon (Table 4) due to its pharmacological properties; since the high protein-binding ability and consequent long half-life gives it a better chance to cross the blood–brain barrier, a higher concentration of antibiotics is delivered to the affected area. In chronic cases, the therapeutic duration should be extended from 14 to 21 days.

Vaccination

An effective vaccine is not yet available, although several vaccines are currently in development. Surface antigens (OspA) have been used for immunization in the past. In 1998, the first vaccine against *Borrelia* infections was introduced in the United States, and was targeted to OspA. This vaccination was found to be safe and effective in phase III clinical trials (Sigal et al. 1998, Steere et al. 1998). However, this substance was pulled from the market after 4 years, most likely due to limited acceptance of this vaccine and its possible side effects. Moreover, the low risk of Lyme disease in most parts of the United States, the necessity for frequent booster injections and the higher costs compared with antibiotic treatment of early infection (Meltzer et al. 1999, Shadick et al. 2001) have contributed to the withdrawal of this vaccine. However, the major issue was the theoretical, but never proven, assertion that vaccination could trigger autoimmune arthritis (Hanson and Edelman 2003, Anonymous 2006).

The prevention of Lyme borreliosis depends nowadays on public and physician education and appropriate antibiotic therapy (Hayes and Piesman 2003). However, further research toward the development of second-generation vaccines is still ongoing.

Conclusions

In general, an acute infection is considered to entail a higher risk during pregnancy for fetal transmission than does a chronic infection, as the mother already has IgG antibodies against the pathogen. The results of clinical, serological, and epidemiological studies have not confirmed a causal association

between *B. burgdorferi* infection and adverse outcomes. However, the therapeutic approach in pregnant women with Lyme disease should be antibiotic treatment according to the clinical manifestation and the timing of the tick bite.

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Disclosure Statement

The authors declare that they have no competing interests.

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Address correspondence to:
Ioannis Mylonas
Division of Infectious Diseases in Gynaecology and Obstetrics
1st Department of Obstetrics and Gynaecology
Ludwig-Maximilians-University Munich
Maistrasse 11
Munich 80337
Germany

E-mail: ioannis.mylonas@med.uni-muenchen.de