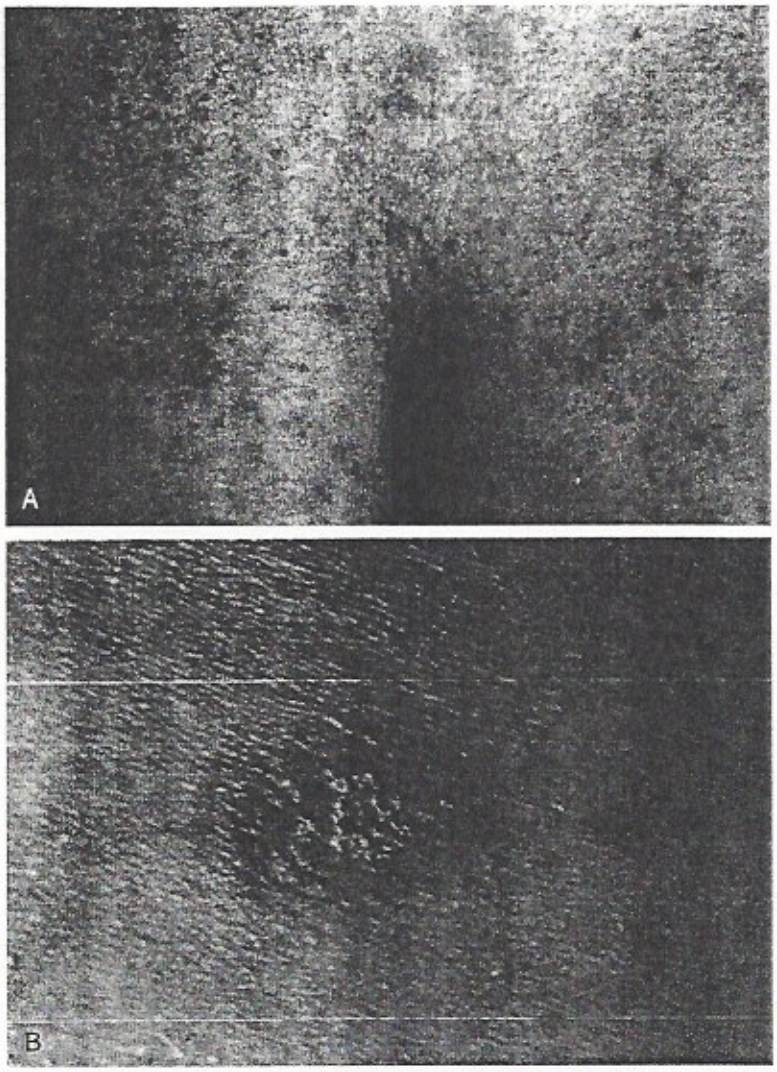

FIGURE 11–7 The rash of early disseminated Lyme disease. Dense erythematous maculopapular rash on the chest *(A)* and an erythematous oval expanding erythema migrans lesion on the buttock *(B)* in a first-trimester pregnant woman (patient 23 in Table 11–8).

indicates a need for antibiotic therapy; PCR negativity in chronic Lyme arthritis is consistent with an immunopathologic process likely to be antibiotic-unresponsive.[312]

It was initially thought that Lyme arthritis was found only in North American patients with Lyme borreliosis; however, once it was recognized, it was subsequently also found in European[39, 502, 511, 546, 649, 650, 652] and Asian patients.[374, 438]

NEUROBORRELIOSIS

Before the routine use of antibiotic therapy for early Lyme disease, about 4% of patients with Lyme borreliosis presented with neurologic symptoms without any preceding skin lesions.[464] Because routine antibiotic therapy of early Lyme borreliosis has become standard, especially when associated with the pathognomonic EM lesion, fewer patients with neuroborreliosis present with a history of EM; 10 to 64% of patients with neuroborreliosis report a history of EM, and 10 to 65% a history of tick bite.[268, 289, 290, 310, 404, 435] Approximately 5 to 17% of untreated patients develop neurologic abnormalities, usually 2 to 4 weeks to several months after the initial infection.[268, 325] Two thirds of patients with early disseminated Lyme borreliosis even without symptoms of central nervous system involvement had evidence of spread of the spirochete to the central nervous system by PCR assay for *B. burgdorferi* DNA.[282] Chronic peripheral nervous system manifestations develop over a median of 16 months, and chronic central nervous system manifestations over a median of 26 months after initial infection.[655]

It was initially thought that neuroborreliosis was primarily a European* manifestation of Lyme borreliosis, but it is now recognized to occur in North America and Asia as well.[288, 291, 292, 437] The reported incidence of neuroborreliosis is higher in Europe than in North America, and there is a suggestion that it is higher in the northern European countries, particularly Scandinavia, than in the southern, central, and eastern European countries.[11, 12, 501, 532] Involvement of the peripheral nervous system is more frequent than that of the central

*See references 90, 162, 268, 290, 404, 435, 502, 511, 516, 546, and 550.

nervous system[265]; the incidence of central nervous system infection may be higher in North America than Europe, and the incidence of peripheral neuropathy may be higher in Europe,[268, 532] although severe and even fatal central nervous system neuroborreliosis has been reported from Europe.[311]

Patients with Lyme borreliosis may develop either central or peripheral nervous system involvement at any stage of the infection.[265, 286–292, 435, 655–657] The early neurologic syndromes (meningitis, cranial neuropathy, and radiculoneuropathy) usually develop a median of 1 month after EM, the chronic peripheral nervous system syndromes (polyradiculopathies) develop over a median of 16 months, and the central nervous system syndromes (encephalopathy and leukoencephalitis) a median of 26 months after EM.[291] The diversity of clinical manifestations is great and includes central nervous system infection (including acute or chronic lymphocytic meningitis, acute or chronic mild encephalopathy, and acute multifocal or chronic progressive multifocal encephalomyelitis),[267, 286, 292, 311, 516, 655, 657] cranial neuropathy (including Bell's palsy),[90, 659, 660] peripheral neuropathy,[291, 656, 662] and painful meningopolyneuritis with peripheral extremity paresis (Bannwarth's syndrome),[516, 572] neuropsychiatric disorders,[663–665] transverse myelitis,[668, 669] acute focal meningoencephalitis, Guillain-Barré syndrome,[265, 289, 530] acute cerebellar ataxia,[261, 311, 530] and chorea.[90] Peripheral nervous system manifestations are grouped under the designation of mononeuropathy multiplex, with perivascular inflammation and axonal loss.[265]

Acute lymphocytic meningitis may occur as a manifestation of early disseminated Lyme borreliosis, with or without radiculitis or cranial neuritis[290–292, 657, 658]; it occurs in up to 15% of patients with other manifestations of Lyme borreliosis.[657] Spinal fluid of patients with acute neuroborreliosis shows a lymphocytic pleocytosis of approximately 100 to 250 cells per mm^3; slightly elevated protein, normal glucose, and sometimes oligoclonal bands; and intrathecal production of *B. burgdorferi*–specific antibody.[260, 265, 268, 287, 290–292] In some patients with neuroborreliosis, particularly those with very early infection, spinal fluid *B. burgdorferi* antigen-detection methods such as PCR[282, 309] or antigen capture ELISA[283] may be positive before the development of specific intrathecal antibody, and even without evidence of inflammation.[283]

One of the more common neurologic manifestations of early Lyme disease in both North American and European patients is cranial neuropathy, especially unilateral (Fig. 11–8) or bilateral Bell's palsy, which develops in about 10% of patients with Lyme borreliosis, and in 50 to 75% of patients with early neuroborreliosis, within 4 weeks of EM.[659, 660] Because Bell's palsy may also be the initial presentation, without preceding tick bite or EM, the possibility of Lyme borreliosis should be considered as a potential etiology for idiopathic Bell's palsies in Lyme-endemic areas.[661] Sixth nerve palsy is reported in 1 to 2% of pediatric neuroborreliosis patients in North America[289] and Europe.[435] In a large study of North American pediatric Lyme facial palsy patients, the incidence of CSF pleocytosis, increased CSF protein, intrathecal specific antibody, and neuroborreliosis was 55, 45, 82, and 92%, respectively.[289, 661] In patients with isolated cranial neuropathy, CSF evaluation for pleocytosis, *B. burgdorferi* antibody, and PCR, is helpful in determining the presence of CNS spread, as this has therapeutic implications.[291, 654, 657, 661]

FIGURE 11–8 Bell's palsy. Persistence of residual left facial weakness 2½ years after the onset of last-trimester gestational Bell's palsy in a young woman who was later diagnosed as having Lyme disease (clinical case described in asymptomatic infant with gestational Lyme exposure).

Bannwarth's syndrome,[502, 572] also known as Garin-Boujadoux-Bannwarth syndrome, tickborne meningopolyneuritis, meningoradiculoneuritis, or lymphocytic meningoradiculitis, occurs in 10 to 15% of patients with North American Lyme borreliosis,[265] is the most common manifestation of European neuroborreliosis, and occurs in 75% of patients with European neuroborreliosis[288, 290]; it occurs infrequently in pediatric neuroborreliosis,[289, 435] with a reported incidence of 4% in a large European study[435] and 1% in a large North American study.[289] Symptoms and signs consist of intense radicular pain with paresthesias or hyperesthesias, progressing to asymmetrical polyneuritis, with sensory loss, weakness, or hyporeflexia, often with cranial nerve palsy (particularly unilateral or bilateral facial palsy), and sometimes with transverse myelitis and lymphocytic meningitis that develops within a few days to weeks after the initial EM or tick bite and lasts approximately 3 to 5 months if untreated. Manifestations of progressive peripheral nervous system involvement (mononeuritis multiplex) are cranial neuropathy, radiculoneuropathy, brachial or lumbosacral plexopathy, distal axonopathy, acute disseminated neuropathy (Guillain-Barré–like), and motor neuropathy.[265] Most patients with Lyme radiculoneuritis are *B. burgdorferi*–seropositive and have CSF pleocytosis and specific CSF *B. burgdorferi* antibody, some have CSF culture or PCR positivity, and some (European patients) have CSF oligoclonal bands.[290–292]

Manifestations of late parenchymal central nervous system and spinal cord neuroborreliosis include progressive encephalomyelitis,[265, 292, 657] with cranial and peripheral neuropathies, myelitis, meningitis, and multifocal encephalitis[265, 286, 311]; spastic paraparesis or quadriparesis,

bladder dysfunction, ataxia, cranial nerve deficits, and dementia[98, 311]; seizures[311, 325]; and chronic encephalopathy and leukoencephalitis.[655] The incidence of Lyme encephalomyelitis is estimated to be 0.1% of cases of untreated Lyme borreliosis[265, 292, 657]; most patients have intrathecal *B. burgdorferi* antibody, some (European patients) have oligoclonal bands, and some have CSF PCR positivity.[290, 657] Late neuroborreliosis manifestations may also include distal limb paresthesias, carpal tunnel syndrome, painful radiculopathy, Bell's palsy, and disseminated multifocal patchy axonal neuropathy similar to mononeuritis multiplex.[289] Spinal fluids of patients with chronic neuroborreliosis show slight lymphocytic pleocytosis of approximately 150 to 200 cells per mm^3, slightly elevated protein, and usually *B. burgdorferi*–specific intrathecal antibody production.[290, 655, 656] Spinal fluid and lesion brain biopsy[311] may also be positive for *B burgdorferi*–specific antigen by PCR.[287, 309, 311]

Neuropsychiatric disorders have been reported.[664, 665, 682–684] Encephalopathy, or neurocognitive dysfunction, particularly subjective perception of memory deficits, may occur during or after Lyme borreliosis, with and even without evidence of invasive inflammatory neurologic infection; it was initially thought to occur only in North American patients, but is now recognized in European patients as well.[265, 681]

Magnetic resonance imaging (MRI) of the brain may be useful in evaluation of central nervous system neuroborreliosis,[311, 610, 671, 672, 685] including meningitis, encephalitis, acute or indolent multifocal encephalitis, chronic neuroborreliosis with encephalopathy and leukoencephalitis, and even facial palsy, as well as other manifestations of Lyme borreliosis that may also involve the central nervous system,[679] including neuro-ophthalmic manifestations; it has demonstrated focal nodular areas or large patchy areas of hyperintense T_2 signal in deep or periventricular white matter, sometimes with ringlike enhancement with gadolinium contrast suggestive of demyelination, perivascular inflammation, or even pontine, frontal, or parietal mass lesions, and occasionally lesions in cortical or subcortical gray matter. MRI imaging has also demonstrated T_2 hyperintense areas with gadolinium contrast enhancement of the nerve roots and cauda equina in Bannwarth's syndrome.[680]

Functional brain imaging, by single photon emission computed tomography (SPECT) or positron emission tomography (PET), may be useful in determination of whether there are objective abnormalities in patients with subjective neuropsychiatric complaints in late Lyme encephalopathy; in some of these patients, including some with normal brain MRI imaging,[666, 667] it has demonstrated multifocal areas of diminished perfusion in the cortex and subcortical white matter, including the frontal white matter, basal ganglia, and medial cortex.

CARDITIS

About 2 to 8% of patients with North American Lyme borreliosis present with carditis initially and 4 to 10% develop it if untreated, usually within 2 to 4 weeks but up to 3 months after the initial infection.[325, 643, 686–688] Although Lyme carditis was initially thought to occur only in North American patients, it has now been reported, with a lower rate of 0.3 to 4%, from Europe as well,[10, 435, 502, 516, 546, 689] and has also been occasionally reported in Asia.[374, 438]

The most common findings are conduction disturbances,[689–986] including mild transient fluctuating first- and second-degree atrioventricular block, Wenckebach periodicity, intraventricular conduction disturbances, and bundle branch block, but complete heart block may also occur and may manifest as syncopal episodes, seizure-like episodes, dizziness, chest pain, and fatigue,[686, 687, 689, 890] although other manifestations also have been reported.[607, 691–693] Electrocardiograms commonly show atrioventricular block or other conduction defects, ST changes, T wave flattening or inversion, intraventricular conduction defects, or occasional premature ventricular contractions. Because carditis is usually a complication of early Lyme borreliosis, specific *B. burgdorferi* antibody is not always detectable at the time of presentation, but it develops later.

The prognosis of acute Lyme carditis is usually good, and it usually resolves spontaneously within 3 days to 6 weeks.[687]

ACRODERMATITIS CHRONICA ATROPHICANS

ACA is a late chronic cutaneous manifestation of Lyme borreliosis that occurs in 2 to 16% of European patients with Lyme borreliosis,[39, 251, 352, 404, 502, 525, 532, 546, 641] 6 months to 10 years after initial infection.[600] Although this is rare in North America, is more common in the elderly, and is rare in childhood, it has been reported in both a child and two young women in the United States,[695] and occasionally in European children.[435, 530] Progression of erythema migrans skin lesions to ACA skin lesions in the same patient over time has been demonstrated.[696] There is an initial inflammatory phase that manifests as insidious onset of bluish red discoloration and doughy induration of the skin on the distal extremities at the site of a previous EM lesion, followed by the atrophic phase, which produces atrophic skin changes in the previously affected areas of skin.[501, 599, 600, 612] Patients may have periarticular bursitis, Achilles tendinitis and epicondylitis, juxta-articular fibrotic nodules, peripheral neuropathies, and joint deformities, including subluxation and degenerative arthritis.[600, 612, 670, 697] Most patients with ACA are seropositive by IgG^* antibody assay and by the lymphocyte proliferative assay.[219] Antibiotic therapy has resulted in improvement of the inflammatory component but not the permanent atrophic component of ACA.

OTHER ORGAN INVOLVEMENT IN DISSEMINATED INFECTION

During the dissemination phase of the infection, there have also been reports of hepatitis,[243, 698] necrotizing splenitis,[604] eosinophilic lymphadenitis,[606] localized or generalized myositis,[616, 617] eosinophilic fasciitis,[603] panniculitis resembling erythema nodosum,[598] tenosynovitis with ligament involvement,[304] multifocal osteomyclitis

(in distal tibial and femoral metaphyses),[699] and rarely hematologic abnormalities.[711, 712]

Ophthalmologic manifestations of Lyme borreliosis may occur alone or in combination with other manifestations of Lyme borreliosis.[320, 702] These include cranial nerve palsies affecting extraocular movements[643]; conjunctivitis, nodular episcleritis, and keratitis[284, 325]; and orbital myositis,[703] optic neuritis,[704] retinitis, and panophthalmitis. The incidence of otologic complications, other than facial nerve palsy, is less than 12%; these include vestibular neuronitis, moderate hearing loss, tinnitus, otalgia, and temporomandibular joint pain.[284, 707]

Post-Lyme Syndromes

The post-Lyme syndrome (PLS), which includes persistence of fatigue and arthralgia for longer than 6 months after adequate antibiotic therapy of confirmed Lyme disease, has been reported to be associated with objective neuropsychiatric and neurocognitive abnormalities,[682, 683, 713, 714] and with delayed initial antibiotic therapy.[683, 714]

Fibromyalgia has been reported in 8 to 10% of patients with Lyme borreliosis, but it persisted after resolution of the symptoms of Lyme disease and was not considered to be related to active Lyme disease.[279, 715]

REINFECTION WITH *BORRELIA BURGDORFERI*

Reinfection rates as high as 5 to 21%, based on clinical histories, have been reported in some highly endemic areas in both North America and Europe.[522, 683, 714, 716] Reinfection with different strains of *B. burgdorferi* has been confirmed serologically and by culture[717, 718] in both North America and Europe; these patients developed seropositivity after the initial episode, but some became seronegative before the second episode and others remained seropositive between episodes. Serologic evaluation by IgG as well as IgM *B. burgdorferi* assays is recommended in patients suspected of having reinfection, as some have only an IgG response.[233]

CO-INFECTION WITH *BABESIA* OR *EHRLICHIA*

Babesiosis, caused by the protozoan *Babesia microti* in the United States, and *Babesia divergens* and *Babesia bovis* in Europe, is another tickborne infection of increasing prevalence and significance, which is co-vectored by the ticks that transmit Lyme borreliosis and human granulocytic ehrlichiosis and shares the same geographic distribution. There are two reports of infants with probable transplacental acquisition of babesiosis.[630]

HGE shares tick vectors and some geographic distribution with Lyme borreliosis. Co-infections with Lyme disease and ehrlichiosis are being increasingly reported, including one case in pregnancy,[632] and there is one report of probable transplacental transmission of HGE.[631]

Clinically symptomatic as well as asymptomatic past or recent co-infection with Lyme borreliosis and babesiosis[481–483] or ehrlichiosis[484] has been reported,[397, 400, 401, 481, 485–488, 498] although some seropositivity to more than one agent may be due to cross-reactivity. There is recent concern because of accumulating evidence for increased severity of Lyme disease in patients with concurrent babesiosis,[481] and it is uncertain if this occurs also with ehrlichiosis and Lyme borreliosis.

Insufficient data are available so far to determine the frequency of transplacental transmission of babesiosis or ehrlichiosis, or the optimal antibiotic therapy of either gestational or neonatal infection.

The possibility that co-infection with *B. burgdorferi* and tickborne encephalitis (TBE) may increase the severity of TBE has been raised.

Clinical Manifestations of Congenital Lyme Borreliosis

CONGENITAL AND GESTATIONAL LYME BORRELIOSIS

A review of the congenital and gestational Lyme borreliosis literature yielded 259 reported cases for which the outcome of the individual episode of gestational Lyme borreliosis was noted,* and addition of four of the author's cases brought the total to 263 cases. A total of 66 cases of the 263 were found that the author considers to represent an adverse event at least associated with an episode of gestational Lyme borreliosis,[25, 26, 28–48] including miscarriage, stillbirth, perinatal death, congenital anomalies, systemic illness, early-onset fulminant sepsis, and later-onset chronic progressive infection (Tables 11–8, 11–13, and 11–14). These 66 cases have been divided into logical groups (Table 11–15) based on an understanding of the pathophysiology and clinical course of Lyme borreliosis in older patients, and on inescapable similarities of Lyme borreliosis to syphilis. Many of the calculations of rates of adverse outcomes became apparent only when all of the available case information was compared, as each individual report of one or several cases represented too few cases from which to draw conclusions; in the larger, population-based studies or serologic surveys, individual outcomes of gestational Lyme disease were not provided for all patients, which made difficult the recognition of a small number of individual adverse outcomes associated with gestational Lyme disease. The reader is directed to additional information about these cases of congenital Lyme borreliosis, which are discussed in the individual sections of Pathology and Pathogenesis, Diagnosis and Differential Diagnosis, Therapy, Prevention, and Prognosis, in this chapter.

In some of these reports, the gestational trimester of onset of Lyme borreliosis, the clinical manifestation of Lyme borreliosis, the gestational antibiotic therapy, the *B. burgdorferi* serologic status of the mother, and details about the specific type of fetal or neonatal abnormality that may have occurred, including specific malformations, birth weight, prematurity, serologic status of the infant, trimester of miscarriage, antibiotic therapy of the infant, and placental and autopsy pathologic information, are indicated; in others, this information is missing.

Several reports that involved serologic screening of

*See references 25–39, 42–48, 531, 536, 537, 622, 632, and 719–723.

TABLE 11–13
Frequency of Specific Adverse Outcomes[a] of 66 Pregnancies Complicated by Gestational Lyme Borreliosis (GLB) and Adverse Clinical Outcome

FETAL/NEONATAL ABNORMALITY	NO. WITH FINDING[b]	% WITH FINDING	REFERENCE
Cardiac	15/66	22.7%	
Myocardial dysfunction	5/66	7.6%	25, 31–33, 621
VSD	6/66	9.1%	33–35, 37, 48
PDA	3/66	4.5%	25, 33, 42, 621
Coarctation aorta	2/66	3.0%	25, 33, 34
ASD	2/66	3.0%	33, 34, 48
Other[d]	4/66	6.1%	25, 32, 33, 37, 46, 621
Neurologic	10/66	15.2%	
Developmental delay/mental abnormalities	5/66	7.6%	31, 36, 42, 44, 621
Hydrocephalus/macrocephaly	5/66	7.6%	31, 33, 37, 41
Hypotonia/lethargy	3/66	4.5%	32, 37, 621
Meningoencephalitis[e]	4/66	6.1%	31, 621
CNS lesions on scan[f]	2/66	3.0%	31, 621
Cortical blindness	1/66	1.5%	36
Hemiparesis	1/66	1.5%	621
Meningomyelocele	1/66	1.5%	33
Orthopedic	8/66	12.1%	
Syndactyly/clubfoot/metatarsus adductus	4/66	6.1%	29, 33, 36, 45
Arthritis/contractures	2/66	3.0%	31, 621
Long bone metaphyseal bands	2/66	3.0%	621
Pectus excavatum	1/66	1.5%	621
Vertebral defects	3/66	4.5%	33, 41, 45
Radial dysplasia	1/66	1.5%	45
Dermatologic	6/66	9.1%	
Rash	6/66	9.1%	31, 36, 43, 621
Ophthalmic	3/66	4.5%	
Blepharitis/exophthalmos	1/66	1.5%	31
Punctate retinal lesions	1/66	1.5%	621
Eso- /exotropia	1/66	1.5%	621
Genitourinary	7/66	10.6%	
Cryptorchidism	2/66	3.0%	42, 46
Hypospadias	1/66	1.5%	46
Inguinal hernia, bilateral	1/66	1.5%	621
Hydrocele	1/66	1.5%	46
Renal dysplasia	1/62	1.5%	45
Ureteral stenosis with hydronephrosis, bilateral	1/66	1.5%	48
Miscellaneous anomalies	8/66	12.1%	
Pilonidal dimple	2/66	3.0%	621
Sacral hemangioma with gluteal atrophy	1/66	1.5%	44
Facial/ear dysmorphia	1/66	1.5%	621
Simian crease, unilateral	1/66	1.5%	621
Absence of hemidiaphragm	1/66	1.5%	33
Omphalocele	1/66	1.5%	33
Laryngomalacia	1/66	1.5%	46
Tracheoesophageal fistula	1/66	1.5%	45
Imperforate anus	1/66	1.5%	45
Hypoplastic dental enamel/dental anomalies	3/66	4.5%	42

Table continued on opposite page

large populations of obstetric patients, but provided no information about the occurrence, treatment, or specific outcomes of any clinically symptomatic cases of gestational Lyme borreliosis, could not be used in evaluation of outcomes of gestational Lyme borreliosis; however, they provided data on seroprevalence in the obstetric patient population.[530, 724] In Germany, the seroprevalence of *B. burgdorferi*–specific IgM and IgG antibody was 0.8 and 7%, respectively, in 2600 patients in obstetric clinics, and pregnancy outcomes were considered the same in seropositive and seronegative groups of patients.[530] A large *B. burgdorferi* antibody serosurvey of 1039 preg-

TABLE 11–13
Frequency of Specific Adverse Outcomes[a] of 66 Pregnancies Complicated by Gestational Lyme Borreliosis (GLB) and Adverse Clinical Outcome *Continued*

FETAL/NEONATAL ABNORMALITY	NO. WITH FINDING[b]	% WITH FINDING	REFERENCE
Miscellaneous abnormalities			
Neonatal sepsis/DIC/respiratory distress	11/66	16.7%	25, 26, 33, 38, 39, 47, 48, 621
Hyperbilirubinemia	8/66	12.1%	36, 37, 41, 621
Growth retardation[g]	8/66	12.1%	31, 33–35, 37, 41, 47, 621
Hepatomegaly/splenomegaly	3/66	4.5%	31, 621
Adenopathy	4/66	6.1%	31, 43, 621
Recurrent fever	2/66	3.0%	43, 44
Recurrent infections	2/66	3.0%	31, 621
Dysphagia/GE reflux/aspiration	2/66	3.0%	31, 45
Meconium ileus	1/66	1.5%	621
Fetal/Neonatal demise	26/66	39.4%	
GLB prior to conception or first prenatal visit	10/66	15.2%	27, 32, 33
GLB in first trimester	5/66	7.6%	25, 29, 33–36, 38, 39, 42
GLB in second trimester	8/66	12.1%	33, 34
GLB in third trimester	0/66	0.0%	
GLB in unspecified trimester	2/66	3.0%	30, 33, 41, 46

[a]Underestimate of incidence of findings, as autopsies not done on all fetal deaths.
[b]Number with finding/total number.
[c]Author's patients.
[d]Endocardial fibroelastosis, aortic stenosis, left superior vena cava, multiple congenital heart defects, aortic thrombosis, or arrhythmia.
[e]Chronic meningitis, or CSF pleocytosis/elevated protein.
[f]Cortical atrophy on CT or white matter lesions on MRI.
[g]Intrauterine or postnatal.
ASD = atrial septal defect; CNS = central nervous system; DIC = disseminated intravascular coagulation; GE = gastroesophageal; GLB = gestational Lyme borreliosis; PDA = patent ductus arteriosus; VSD = ventricular septal defect.

nant women in the Perm area of Russia from 1992 to 1994 found a 5.5% seropositivity rate (57 of 1039) and noted that their data indicated that Lyme borreliosis is a serious risk factor for miscarriage and perinatal death, but provided no information on individual outcomes of gestational Lyme borreliosis.[724] Some reports note the occurrence of adverse effects of gestational Lyme borreliosis such as stillbirth and congenital defects but provide no details.[725]

In 1989, Nadal and associates[37] reported a large serosurvey of 1416 mothers and their infants at the time of delivery, from 1986 to 1987, in a Lyme-endemic area of Switzerland, and found a *B. burgdorferi*–specific seropositivity rate of 0.85% (12 of 1416) in maternal sera. Of the seropositive mothers, one had a history of first-trimester tick bite and Lyme borreliosis and her infant had a congenital ventricular septal defect (VSD); five mothers had histories of pre-gestational Lyme borreliosis, one had a history of pre-gestational tick bite, and five were asymptomatic; 6 of their infants had minor problems that resolved.

Bracero and colleagues,[47] in a serosurvey of pregnant women at the first prenatal visit in an endemic area of New York from 1988 to 1989, found a seropositivity rate of 1.1% (7 of 638), and noted non–statistically significant but interesting differences in the pregnancy outcomes of seropositive and seronegative women: The frequencies of low birth weight, birth size small for gestational age, and Apgar less than 7 were 28.6, 14.3, and 14.3% for seropositive women, and 16.4, 2.6, and 5.2% for seronegative women.

In 1993, Strobino and co-workers[45] reported a prospective *B. burgdorferi* serosurvey of 2000 pregnant women from areas of high and low Lyme endemicity in New York, from 1988 to 1990, at the first prenatal visit and at delivery; pregnancy outcomes were available for 96%. Eleven patients were seropositive at the first visit (rate 0.7%); only one patient seroconverted by delivery, and this patient had an untreated second-trimester flu-like illness and delivered a normal infant; the seropositive mothers delivered live-born infants, one with gastroesophageal reflux, one with metatarsus adductus, and one with multiple major anomalies. Fifteen developed Lyme disease during the pregnancy, but the specific outcomes of these pregnancies were not provided. They concluded that gestational Lyme disease or *B. burgdorferi* exposure was not associated with an overall increase in fetal death, prematurity, or congenital malformations, but noted that the incidence of cardiac defects was two times higher in infants born to mothers in high versus low endemicity areas, and that there was an association of minor malformations with a history of maternal tick bite less than 3 years before conception. The frequencies of total, major, and minor malformations in the infants born to these mothers were 24, 7, and 17% for those with a history of previous Lyme disease at any time; 19, 3 to 7, and 15 to 16% for those with a history of tick bite within 3 years; 16, 5, and 10% for those with no history of previous Lyme disease; and 15, 5, and 10% for those with no history of tick bite. They qualified their conclusions by noting that the miscarriage rate in this study was 8%, which is lower than the usual rate of

TABLE 11–14
Outcomes of 263 Pregnancies Complicated by Lyme Borreliosis (LB)[a]

TRIMESTER OF LB[b]	ANTIBIOTIC THERAPY OF LB[c]	NO. PATIENTS	NO. FETAL DEATHS[d]	NO. NEONATAL DEATHS[e]	NO. LIVEBORN, ILL, OR ABNORMAL[f]	NO. LIVEBORN, NORMAL	NO. TOTAL ADVERSE OUTCOMES[g, h]	NO. TOTAL NORMAL OUTCOMES[h]
≤1[i]	yes	57[j]	4	1	5	47	10 (17.5%)	47 (82.5%)
	no	11	4	2	2	3	8 (72.7%)	3 (27.3%)
	unknown	6	3	2	1	0	6 (100.0%)	0 (0.0%)
	Total	74	11	5	8	50	**24 (32.4%)**	**50 (67.6%)**
2	yes	56	0	0	9	47	9 (16.1%)	47 (83.9%)
	no	6	4	0	0	2	4 (66.7%)	2 (33.3%)
	unknown	6	4	0	0	2	4 (66.7%)	2 (33.3%)
	Total	68	8	0	9	51	**17 (25.0%)**	**51 (75.0%)**
3	yes	32	0	0	3	29	3 (9.4%)	29 (90.6%)
	no	6	0	0	3	3	3 (50.0%)	3 (50.0%)
	unknown	0	0	0	0	0	0 (0.0%)	0 (0.0%)
	Total	38	0	0	6	32	**6 (15.8%)**	**32 (84.2%)**
Unknown	yes	12	0	0	1	11	1 (8.3%)	11 (91.7%)
	no	7	1	0	4	2	5 (71.4%)	2 (28.6%)
	unknown	64[k]	0	1	12	51[k]	13 (20.3%)	51 (79.7%)
	Total	83	1	1	17	64	**18 (21.7%)**	**64 (77.1%)**
Total	yes	157	4	1	18	134	**23 (14.6%)**	**134 (85.4%)**
	no	30	9	2	9	10	**20 (66.7%)**	**10 (33.3%)**
	unknown	76	7	3	13	53	**23 (30.3%)**	**53 (69.7%)**
	Total	263	20	6	40	197	**66 (25.1%)**	**197 (74.9%)**

[a]Data from cases reported in references 25–39, 41–48, 531, 536, 537, 621, 622, 632, 719–723.
[b]LB either by clinical history or positive *Borrelia burgdorferi* assay.
[c]Antibiotic therapy given for the episode of LB.
[d]Miscarriages or stillbirths.
[e]Four neonatal deaths occurred before 2 days of age, and one at 8 days.
[f]Includes nonfatal congenital anomalies, growth retardation, developmental delay, and neonatal illness (see Table 11–8).
[g]Includes miscarriages, stillbirths, neonatal deaths, illness, or abnormality.
[h]Percentage of total in treatment category is included despite small numbers in some categories.
[i]Trimester ≤1 indicates LB in first trimester, or prior to conception or first prenatal care visit.
[j]2 of 23 patients in one group in this category were not treated with antibiotics but, as specific outcomes were not separated out from their group, these were placed in the treated group and considered as Live Born, Normal, for use in this table to avoid overestimation of adverse outcome risk.
[k]Unspecified outcome for two pregnancies was considered as Live Born, Normal, for use in this table.

TABLE 11–15
Clinical Manifestations of Congenital Lyme Borreliosis (CLB)[a]

Fetal Death[b]
30% (9/30) risk after untreated GLB[c]
2.5% (4/157) risk after treated GLB
8% (20/263) risk after any GLB (9/20+)[d]
Most (75%, 15/20) occur at ≤20 weeks of gestation (range, 8–40 weeks) and may present with
  High frequency of
    Cardiac anomaly/abnormality (40%, 4/9, of fetal deaths after untreated GLB; 0%, 0/4, of fetal deaths after treated GLB)
Most occur after first- or second-trimester GLB (95%, 19/20), with variable interval between GLB and fetal demise.

Early Congenital, Severe
20% (6/30) risk after untreated GLB
4% (6/157) risk after treated GLB
6% (16/263) risk after any GLB (7/16+)[e]
Present in first week of life with acute suspected sepsis
  High frequency of
    Mortality (36%, 6/16)
    Cardiac anomaly or abnormality (56%, 9/16, overall; 85%, 5/6, in fatal cases)
    Respiratory distress (50%, 8/16)
    Prematurity (50.0%, 8/16, most ≤5 wks premature)
  May also have
    Intrauterine growth retardation
    Skeletal anomaly/abnormality/metaphyseal bands
    Neurologic abnormality/meningoencephalitis
    Fever
    Hepatosplenomegaly
    Hyperbilirubinemia
    Adenopathy
    Rash
    Lethargy/meningoencephalitis
    Miscellaneous anomalies
Most occur after first- or second-trimester GLB (63%, 10/16, overall; 100%, 10/10, when trimester of GLB is known).

Early Congenital, Mild
10% (3/30) risk after untreated GLB
4% (6/157) risk after treated GLB
8% (22/263) risk after any GLB
Present in first 2 weeks of life with mild illness
  Moderate frequency of
    Hyperbilirubinemia (32%, 7/22)
  May also have
    Genitourinary anomaly/abnormality
    Skeletal anomaly
    Cardiac abnormality/anomaly
    Rash
    Neurologic abnormality/meningoencephalitis/hypotonia
    Prematurity (all ≤4 weeks premature)
    Suspected sepsis
    Intrauterine growth retardation
    Adenopathy
    Miscellaneous anomalies
Most occur after first- or second-trimester GLB (41%, 9/22, overall; 90%, 9/10, when trimester of GLB is known).

Late Congenital
7% (2/30) risk after untreated GLB
4% (7/157) risk after treated GLB
4% (10/263) risk after any GLB (1/10+)[f]
Risk is a minimum estimate as long-term follow-up unavailable for most patients. 70% (7/10) of cases of late CLB occurred after treated GLB.
Present after 2 weeks of life, usually within first 2 years, with subacute illness
  High frequency of
    Developmental delay/meningoencephalitis (50%, 5/10)
  Moderate frequency of
    Genitourinary anomaly/abnormality (30%, 3/10)
  May also have
    Skeletal abnormality/metaphyseal bands
    Rash
    Prematurity
    Adenopathy
    Hepatosplenomegaly
    Fever
    Growth retardation/failure to thrive
    Miscellaneous anomalies
Potential progression to chronic neurologic, cardiac, skeletal, cutaneous, ocular involvement should be considered.
Most occur after second- or third-trimester GLB (60%, 6/10, overall; 86%, 6/7, when trimester of GLB is known).

[a]Data from Tables 11–8, 11–13, and 11–14, summaries of 66 adverse outcomes of gestational Lyme borreliosis.
[b]Miscarriages (including one induced abortion with congenital anomalies) or stillbirths. This represents a minimum estimate, as many of the published reports included patients enrolled only at the first prenatal visit or at delivery, and therefore did not include early miscarriage data.
[c]GLB-gestational Lyme borreliosis; treated/untreated refers to gestational antibiotic therapy.
[d]9 positive for borreliae in tissue samples.
[e]7 positive for borreliae in tissue samples.
[f]1 positive for borreliae in tissue samples.

10 to 15%; however, they indicated that enrollment at the first prenatal visit would have missed miscarriages that occurred before that visit. They also noted that if *B. burgdorferi* were to have very specific fetal teratogenic effects, if the period of fetal susceptibility to such effects were narrow, and if successful antibiotic therapy were to decrease the risk of such teratogenesis, a much larger study would be needed to determine a teratogenic effect.

In 1995, Williams and associates,[46] from the same group, reported a large cord blood serosurvey of 2500 infants in a Lyme-endemic and 2500 in a nonendemic area from 1986 to 1988 in New York; clinical information regarding congenital malformations was available for 95% of endemic and 97% of nonendemic area infants. Maternal *B. burgdorferi* exposure was 5 to 10 times higher in mothers from endemic than from nonendemic areas, and infants from endemic areas had a (significantly higher) 13% incidence of congenital cardiac defects and murmurs compared with a 5% incidence in those from nonendemic areas; there was no increase in the incidence of other malformations. Of cardiac malformations, VSD was the most common in both endemic and nonendemic infants; other defects in the endemic infants included tetralogy of Fallot, atrial septal defect, patent

ductus arteriosus, pulmonic stenosis, cyanotic congenital heart disease, multiple cardiac defects, hypoplastic right heart, and dextrocardia. Among endemic area infants, major malformations occurred in 17, 9, and 5% of infants born after gestational Lyme disease, pre-gestational Lyme disease, and gestational tick bite, compared with 3% born after neither maternal Lyme disease nor tick bite. Six infants, all from the endemic area, had histories of antibiotic-treated gestational Lyme disease, and one had had hypospadias. The authors note that late developmental sequelae would not be detected by this study owing to absence of long-term follow-up, and that a larger study would be needed to address the question of cardiac teratogenicity.

Two retrospective studies assessed the possible association of late neurologic or cardiac sequelae in infants with histories of gestational Lyme disease exposure.[727, 728] Gerber and Zalneraitis[727] surveyed 162 of 176 listed pediatric neurologists in Lyme-endemic areas of the northeastern and upper midwestern United States, as well as a random subset of adult neurologists in Connecticut, from 1989 to 1990, for possible cases of congenital Lyme disease in their practices. Only three children with a diagnosis of congenital Lyme disease were found, but the clinical histories were not considered by the study authors to meet criteria for gestational Lyme disease, and they concluded that one of the following is true: (1) congenital Lyme disease with neurologic sequelae is very rare; (2) it may involve sequelae not recognized as related; (3) the association of sequelae with congenital Lyme disease may be underrecognized because the association between the child's neurologic disorder and maternal Lyme disease was not made; or (4) neurologic sequelae could be too subtle to result in pediatric neurology consultation. Additionally, they note that the incidence of gestational Lyme disease is low in these areas because pregnant women commonly avoid tick exposure, because women with recent Lyme disease commonly delay pregnancy until after full recovery, because antibiotic prophylaxis of gestational tick bites by obstetricians in these areas is routine, and because prompt antibiotic therapy of gestational Lyme disease occurs. They note that a larger study would be needed to determine any association between subtle neurologic sequelae and congenital Lyme disease.

Strobino and colleagues[728] conducted a retrospective case-control study of 796 children who were followed by pediatric cardiologists for congenital cardiac anomalies (and 705 controls evaluated by those cardiologists for possible cardiac disease and found to have none), from 1985 to 1995, in a Lyme-endemic area in New York; they found no association of the occurrence of congenital cardiac anomalies with histories of maternal gestational or pre-gestational Lyme disease or tick bite, based on maternal retrospective questionnaires. Only four patients in each group had histories of maternal Lyme disease within 3 months before or during the pregnancies with these patients. Because the enrollment population included only children with congenital cardiac anomalies who survived to be referred to pediatric cardiologists, no conclusions could be made regarding any association of gestational or pre-gestational Lyme disease with cardiac anomalies that might have resulted in miscarriage, stillbirth, or early infant death.

Sigal suggests that because organogenesis is complete by the end of the second trimester, the risk of congenital anomaly should be very low in the late second and third trimesters.[729] It is generally agreed that the incidence of adverse outcomes of gestational Lyme borreliosis is low,[435, 530, 729–732] probably because of prompt antibiotic therapy for early gestational Lyme borreliosis, particularly when it presents with its easily recognized and most common manifestation, erythema migrans. Shapiro suggests that the existence of congenital Lyme borreliosis has not been ruled out, but it must be very rare.[733]

REVIEW OF 66 CASES OF ADVERSE OUTCOMES OF GESTATIONAL LYME BORRELIOSIS

Table 11–8 lists 66 individual cases of adverse outcomes of gestational Lyme borreliosis. Only five groups—Schlesinger and co-workers,[25] MacDonald,[33–35] Lavoie and associates,[32] Weber and colleagues,[38, 39] and Hercogova and co-workers[41]—have had any success in demonstrating spirochetes in either fetal autopsy or placental tissues, and only Trevisan and associates have confirmed spirochetes in a tissue biopsy.[43] Only one infant was found to be seropositive for *B. burgdorferi* antibody (patient 24), and this was transient; therefore, this does not appear to be a sensitive method of diagnosis, and reliance on seropositivity leads to misdiagnosis of the majority of congenitally infected infants. The poor protection provided by short courses of oral antibiotic therapy against the development of serious adverse complications of gestational Lyme borreliosis is evident from this table; this is discussed in detail in the section on Therapy.

Of the 20 fetal deaths among the 66 patients with adverse outcomes after gestational Lyme borreliosis, 95% (19 of 20) of the fetal deaths occurred after first- or second-trimester infection, 75% (15 of 20) of these fetal deaths occurred before 20 weeks of gestational age, and the incidence of cardiac anomaly or abnormality in fetal deaths after untreated and treated gestational Lyme borreliosis was 40% (4 of 9) and 0% (0 of 4), respectively. Information from fetal autopsies was available only for fetuses over 25 weeks' gestation, and all three stillborn infants and the 25-week miscarried fetus had significant cardiac anomalies.

Of the 16 infants with an early severe presentation among the 66 patients with adverse outcomes after gestational Lyme borreliosis, 100% (10 of 10) in whom the trimester of gestational Lyme disease was known occurred after first- or second-trimester infection; the incidence of cardiac anomaly or abnormality was 56% (9 of 16) overall and 85% (5 of 6) in fatal cases.

Currently, it is uncertain whether or not *B. burgdorferi* is teratogenic, although there is an indication that there may be, as noted earlier, an increased risk of congenital cardiac malformations after first- and early second-trimester gestational Lyme borreliosis, which is decreased by antibiotic therapy for the gestational episode. It is also possible that *B. burgdorferi* gestational infection with

transplacental dissemination could cause fetal pathology simply by causing Lyme borreliosis with the same manifestations (cutaneous, musculoskeletal, neurologic, neuropsychiatric, neurocognitive, and urologic) that it produces in children and adult patients, which could explain some of the adverse events noted in Table 11–8.

It is likely that prompt and adequate antibiotic therapy of gestational Lyme borreliosis may attenuate its potential adverse fetal effects, and may shift the clinical manifestations away from the more severe presentations such as miscarriages, stillbirths, perinatal deaths, and cardiac anomalies. This could result in higher infant survival rates, with an increased incidence of presentation with late sequelae, which would be expected to exhibit features similar to those of late Lyme borreliosis as described in the section Clinical Manifestations. It is also likely that neonates or infants with undiagnosed congenitally acquired *B. burgdorferi* infection who have received antibiotic therapy for bacterial culture–negative presumed sepsis may not be seropositive for *B. burgdorferi* antibody because of attenuation or prevention of seroconversion by early antibiotic therapy. If the antibiotic therapy has been inadequate to eliminate *B. burgdorferi* infection, these infants may present the dilemma of seronegative late Lyme borreliosis.

It is anticipated that more infants and fetuses with complications related to gestational Lyme borreliosis will be diagnosed in the future as the diagnosis is more frequently considered; it eventually will be possible to better describe the various clinical manifestations of congenital Lyme borreliosis. Large-scale prospective studies of sufficient numbers of patients with gestational Lyme borreliosis, with follow-up to determine the pregnancy outcome of each enrolled patient; *B. burgdorferi*–specific evaluation of any fetal or neonatal demise; and long-term follow-up of each infant born to determine the occurrence of possible early and late sequelae are needed.

FREQUENCY OF SPECIFIC ADVERSE OUTCOMES OF GESTATIONAL LYME BORRELIOSIS

Table 11–13 shows the frequency of occurrence of various types of fetal or neonatal adverse outcomes after gestational Lyme borreliosis.

The 23% incidence of cardiac malformation is strikingly high and includes significant abnormalities such as ventricular septal defect, coarctation of the aorta, and myocardial dysfunction, as well as less severe abnormalities such as patent ductus arteriosus and atrial septal defect; it is reminiscent of the ability of the spirochete to cause carditis, including cardiomyopathy and pancarditis, in older patients.

The 15% incidence of neurologic abnormalities is also high, and includes meningoencephalitis, hydrocephalus, and developmental delay; this would also be consistent with the neurotropic nature of the infection in older patients. One infant (patient 24) had focal parenchymal brain lesions with increased T_2 signal demonstrated by MRI scan that were similar to those reported in the literature in adult patients with chronic meningoencephalomyelitis.

The incidence of orthopedic abnormalities was 12%, but there were some unique features of this involvement, including 4 patients of the 66 with syndactyly or clubfoot, 2 with significant joint contractures, and 2 with a new finding of transverse metaphyseal bands.

The incidence of genitourinary abnormalities was 11%; these included cryptorchidism, inguinal hernia, hydrocele, hypospadias, renal dysplasia, and ureteral stenosis with hydronephrosis.

The incidence of maculopapular erythematous rash was 9%, which would be consistent with disseminated spirochetosis, and many of these rashes increased or developed during the first few days of antibiotic therapy and resembled Jarisch-Herxheimer reactions. The one infant (case 25) with chronic distal extremity rash that resolved after prolonged antibiotic therapy raises the possibility that this was similar to the rash of secondary syphilis or disseminated Lyme borreliosis in older patients.

Among the miscellaneous abnormalities reported were three patients (4.5%) with dental anomalies, including two with hypoplastic enamel and one with structural anomalies.

Hepatosplenomegaly and inguinal adenopathy were also seen in several patients and probably represent disseminated spirochetal infection, as these findings resolved with antibiotic therapy.

Congenital Lyme borreliosis presenting as manifestations that are not specific for *B. burgdorferi*, such as the 17% incidence of presentation as fulminant early sepsis, the 12% presentation with hyperbilirubinemia, and the 12% presentation with growth retardation, may be missed unless careful maternal gestational and pre-gestational histories are obtained.

Thirty percent (20 of 66) of the total number of adverse outcomes were miscarriages (including one aborted fetus with congenital anomalies), 9% (6 of 66) were neonatal deaths, and 39% (26 of 66) were either fetal or neonatal deaths.

FREQUENCY OF ADVERSE OUTCOMES OF 263 CASES OF GESTATIONAL LYME BORRELIOSIS

Table 11–14 shows the fetal and neonatal mortality rates, and the total fetal and neonatal adverse outcome rates divided by trimester and according to whether or not gestational antibiotic therapy was given. Those considered treated or untreated were patients in whom antibiotic therapy was specifically reported as having been specifically given or not given to the individual patient, and those considered as having unknown treatment were those in whom statements about treatment could not be correlated with the individual patient.

Effect of Trimester of Infection

Lyme borreliosis in the first trimester carried an overall 32% (24 of 74 patients) risk of adverse outcome. In the second trimester, the risk was 25% (17 of 68); in the