Artwork by Eryn Goodman
'the night will bend'

Maternal-Fetal Transmission of Lyme Disease: Research Gaps and Opportunities

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Maternal-Fetal Transmission of Lyme Disease: Research Gaps and Opportunities

Overview of maternal-fetal transmission of Bb and adverse outcomes in humans

What is the best diagnostic approach to detect Bb infection in a pregnant mother and neonate?

What is the best treatment approach for gestational Lyme and congenital Lyme?

Case study

Research Opportunities

Lyme disease (Borrelia burgdorferi) can infect the fetus and result in congenital infection

Table 1-4 Suggested Acronym for Microorganisms Responsible for Infection of the Fetus: TORCHES CLAP

TO	*Toxoplasma gondii*
R	Rubella virus
C	Cytomegalovirus
H	Herpes simplex virus
E	Enteroviruses
S	Syphilis (*Treponema pallidum*)
C	Chickenpox (varicella-zoster virus)
L	Lyme disease (*Borrelia burgdorferi*)
A	AIDS (HIV)
P	Parvovirus B19

AIDS, Acquired immunodeficiency syndrome; *HIV*, human immunodeficiency virus.

'A new acronym is needed to include other, well-described causes of in utero infection: syphilis, enteroviruses, varicella zoster virus, HIV, **Lyme disease (Borrelia burgdorferi)** and parvovirus.'

Authors suggest expanding the well recognized acronym TORCH to TORCHES CLAP (**L=Lyme Disease**)'

Table 1-5 Effects of Transplacental Fetal Infection on the Fetus and Newborn Infant

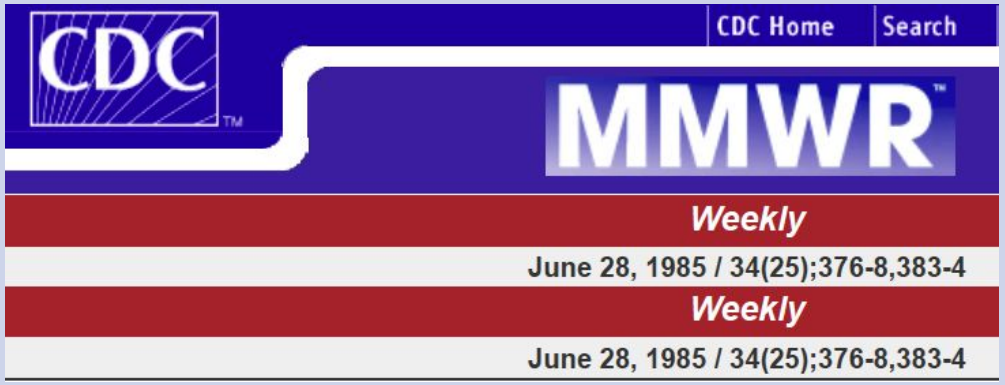
	DISEASE				
Organism	**Prematurity**	**Intrauterine Growth Restriction/Low Birth Weight**	**Developmental Anomalies**	**Congenital Disease**	**Persistent Postnatal Infection**
Viruses	CMV HSV Rubeola Smallpox HBV HIV*	CMV Rubella VZV* HIV*	CMV Rubella VZV Coxsackievirus B* HIV*	CMV Rubella VZV HSV Mumps* Rubeola Vaccinia Smallpox Coxsackievirus B Poliovirus HBV HIV LCV Parvovirus	CMV Rubella VZV HSV HBV HIV
Bacteria	*Treponema pallidum* *Mycobacterium tuberculosis* *Listeria monocytogenes* *Campylobacter fetus* *Salmonella typhi*			*T. pallidum* *M. tuberculosis* *L. monocytogenes* *C. fetus* *S. typhi* *Borrelia burgdorferi*	*T. pallidum* *M. tuberculosis*
Protozoa	*Toxoplasma gondii* *Plasmodium** *Trypanosoma cruzi*	*T. gondii* *Plasmodium* *T. cruzi*		*T. gondii* *Plasmodium* *T. cruzi*	*T. gondii* *Plasmodium*

CMV, Cytomegalovirus; *HBV*, hepatitis B virus; *HIV*, human immunodeficiency virus; *HSV*, herpes simplex virus; *LCV*, lymphocytic choriomeningitis virus; *VZV*, varicella-zoster virus.
*Association of effect with infection has been suggested and is under consideration.

Maldonado Y, Nizet V, Klein J et al. Current Concepts of Infections of the Fetus and Newborn Infant (Chapter 1). Found in Remington and Klein's Infectious Diseases of the Fetus and Newborn Infant, 8th ed., 2015.

Epidemiological Report

Statement on Transplacental (Maternal-Fetal) Transmission of Borrelia burgdorferi

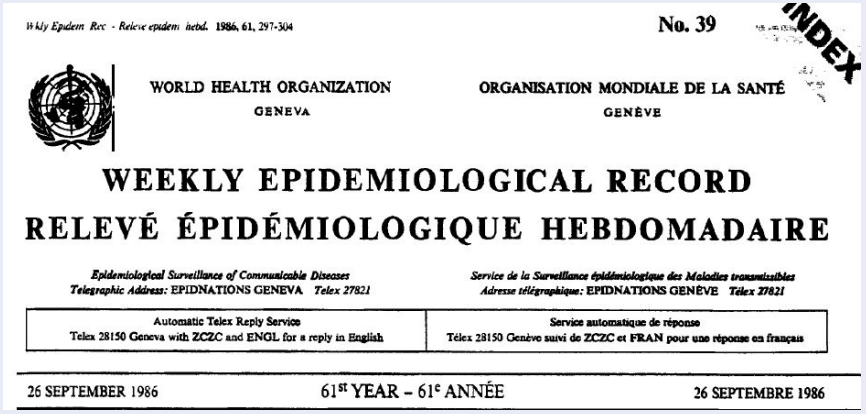


CDC Morbidity and Mortality Weekly Report, June 28, 1985

"Transplacental transmission of B. Burgdorferi has been documented in a pregnant woman with Lyme disease who did not receive antimicrobial therapy. She delivered an infant with a congenital heart defect."

"Since transplacental transmission of B. burgdorferi has been documented, it will be important to determine whether maternal infection with B. burgdorferi is associated with an increased risk of adverse pregnancy outcome."

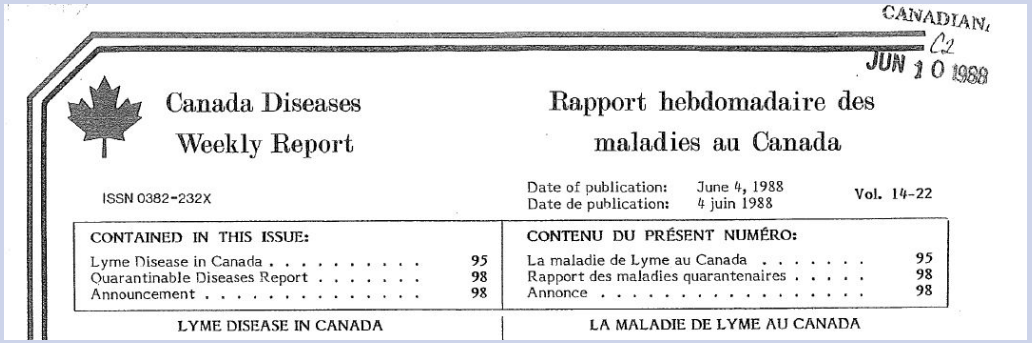
In MMWR. 'Lyme disease and cases occurring during pregnancy' Vol 34, No 25, June 28, 1985), pp. 376-378. Published by Centers for Disease Control and Prevention (CDC).



World Health Organization Weekly Epidemiological Record, Sept 26, 1986

'The possible association between Lyme disease during pregnancy and adverse outcome has recently received attention. Transplacental transmission of B. burgdorferi has been documented in a pregnant woman with Lyme disease who did not receive antimicrobial therapy. She delivered an infant with a congenital heart defect. '

World Health Organization, Geneva. Weekly Epidemiological Record. No. 39. 26 Sept 1986. P 297-304.



Canada Diseases Weekly Report, June 4, 1988

'Transplacental transmission of Borrelia burgdorferi has been documented and may be associated with and increased risk of adverse pregnancy outcomes.'

Health and Welfare Canada. Lyme Disease in Canada. Canada Dis Wkly Report, June 4, 1988.

ANNALS of THE NEW YORK ACADEMY OF SCIENCES

LYME DISEASE IN MATERNAL INFECTIONS

It is clear that *B. burgdorferi* can be transmitted in the blood of infected pregnant women across the placenta into the fetus. This has now been documented with resultant congenital infections[28] and fetal demise.[29] Spirochetes can be recovered or seen in the infant's tissues including the brain, spleen and kidney. The chorionic villi of the placenta show an increase in Hofbauer cells as in luetic placentitis. Inflammatory changes of fetal or neonatal changes are not as pronounced as in the adult, but cardiac abnormalities, including intracardiac septal defects, have been seen.[28,29] It is not known why inflammatory cells are so sparse from maternal transmission, but it is possible that an immature immune system plays a role.

'It is clear that B. burgdorferi can be transmitted in the blood of infected pregnant women across the placenta into the fetus. This has now been documented with resultant congenital infections and fetal demise. Spirochetes can be recovered or seen in the infant's tissues including the brain, spleen and kidney..'

Duray P, Steere A. Clinical Pathologic Correlations of Lyme Disease by Stage. Annals of the New York Academy of Sciences, 1988;539:65-79.

Opportunity:

- **R**e-initiate CDC and State Health Department(s) Lyme and Pregnancy Registry for epidemiological surveillance and data collection
- Formation of a biobank/ biorepository with clinical samples from mother/baby pairs

Pregnancy Registry

'Cases of Lyme disease during Pregnancy should be reported to state health departments and the CDC before delivery so the types and approximate frequency of any adverse outcome can be determined, and appropriate diagnostic tests obtained.'

Lyme Disease occurring During Pregnancy. Clinical Pediatrics. Vol 25, No 4. 1986.

'The Centers for Disease Control and Prevention (CDC) maintains a registry of pregnant with Lyme disease to advance the understanding of the effects of Lyme disease on the developing fetus.'

CDC: Lyme Disease 01/01/1991

HEALTH INFO

Lyme Disease

THE FACTS THE CHALLENGE

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
National Institutes of Health

National Institute of Allergy and Infectious Diseases

National Institute of Arthritis and Musculoskeletal and Skin Diseases

NIH Publication No. 05-7045
May 2005
www.niaid.nih.gov

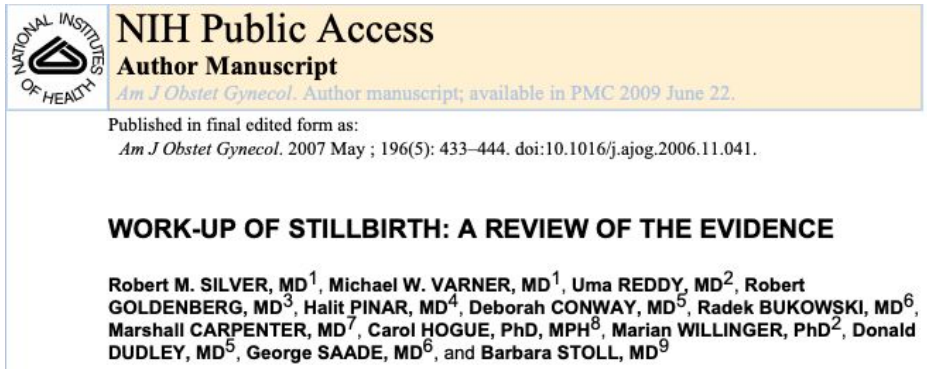
Lyme Disease Prevention

If you are pregnant, you should be especially careful to avoid ticks in Lyme disease areas because infection can be transferred to your unborn child. Although rare, such a prenatal infection may make you more likely to miscarry or deliver a stillborn baby.

‘Infection can be transferred to your unborn child. Although rare, such a prenatal infection may make you more likely to miscarry or deliver a stillborn baby.’

Lyme disease and stillbirth

‘Toxoplasma gondii, leptospirosis, Listeria monocytogenes and the organisms which cause leptospirosis, Q fever and **Lyme disease have all been implicated as etiologic for stillbirth**.’



Silver RM, Varner MW, Reddy U, et al. Work-up of stillbirth: a review of the evidence. *Am J Obstet Gynecol*. 2007;196(5):433-444.

‘Lyme disease, a systemic illness caused by the tick-borne Borrelia burgdorferi, was associated with stillbirth in 1987. Small series of stillbirths **associated with maternal Lyme disease have been reported**, with most fetal deaths occurring in the mid-trimester.

Goldenberg RL, McClure EM, Saleem S, Reddy UM. Infection-related stillbirths. Lancet. 2010 Apr 24;375(9724):1482-90.

Opportunity:

Develop prenatal intake questionnaires to identify women who may have a history of Lyme disease (based on clinical symptoms or tick bite).

UK Royal College of Obstetricians and Gynecologists,

October 2010.

Transplacental infections associated with IUFD include cytomegalovirus[30] (Evidence level 2+), syphilis[31–34] (Evidence level 1+) and parvovirus B19[34,35] (Evidence level 2++) as well as listeria[36,37] (Evidence level 2+), rubella[38] (Evidence level 3), toxoplasmosis[33,34] (Evidence level 2+), herpes simplex[30] (Evidence level 2+), coxsackievirus, leptospira, Q fever, and Lyme disease.[39] *Malaria parasitaemia* has also been associated with stillbirth (OR 2.3, 95% CI 1.3–4.1)[40] (Evidence level 2++).

Summary of cases reporting maternal-fetal transmission of Borrelia burgdorferi /spirochetes/borrelia to offspring and/or placenta

19 cases identification through via in autopsy of fetal tissue, neonate tissue

- 8 neonatal deaths
- 4 cases of stillbirth
- 7 cases of miscarriage

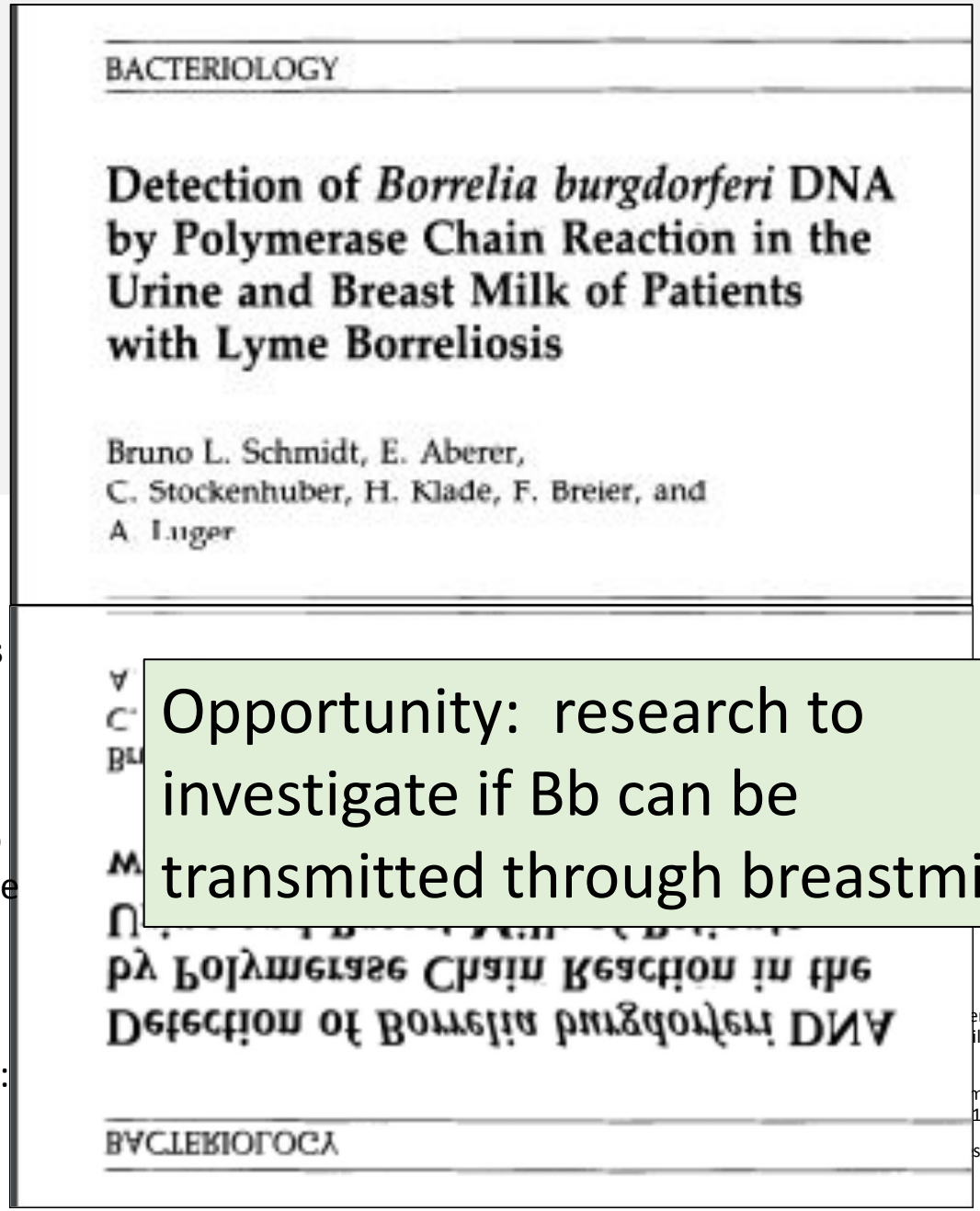
14 cases of live-birth, neonatal infection and adverse outcomes

2 cases of live-birth, Bb identified by PCR in cord blood of infants whose mothers were treated

17 cases Bb identified by PCR in placentas of treated (15) and untreated (2) women

1 case Bb identified by immunohistochemical techniques in placenta of treated woman

Bb identified by PCR in human breast milk, in cow milk and cultured from cow colostrum



BACTERIOLOGY

Detection of *Borrelia burgdorferi* DNA by Polymerase Chain Reaction in the Urine and Breast Milk of Patients with Lyme Borreliosis

Bruno L. Schmidt, E. Aberer,
C. Stockenhuber, H. Klade, F. Breier, and
A. Luger

Opportunity: research to investigate if Bb can be transmitted through breastmilk

'The **lack of adequate information on transmission of *B. burgdorferi* via breast milk cannot be taken as proof that it is not occurring**. If one extrapolates from data on syphilis and the *Treponema pallidum* spirochete, **it would be prudent to discuss the lack of information on the transmission of *B. burgdorferi* via breast milk** with the mother or parents and to consider withholding breast milk at least until therapy for Lyme disease has begun or been completed.'

Lawrence, Robert M.. "Transmission of Infectious Diseases Through Breast Milk and Breastfeeding." *Breastfeeding* (2011): 406–473. doi:10.1016/B978-1-4377-0788-5.10013-6

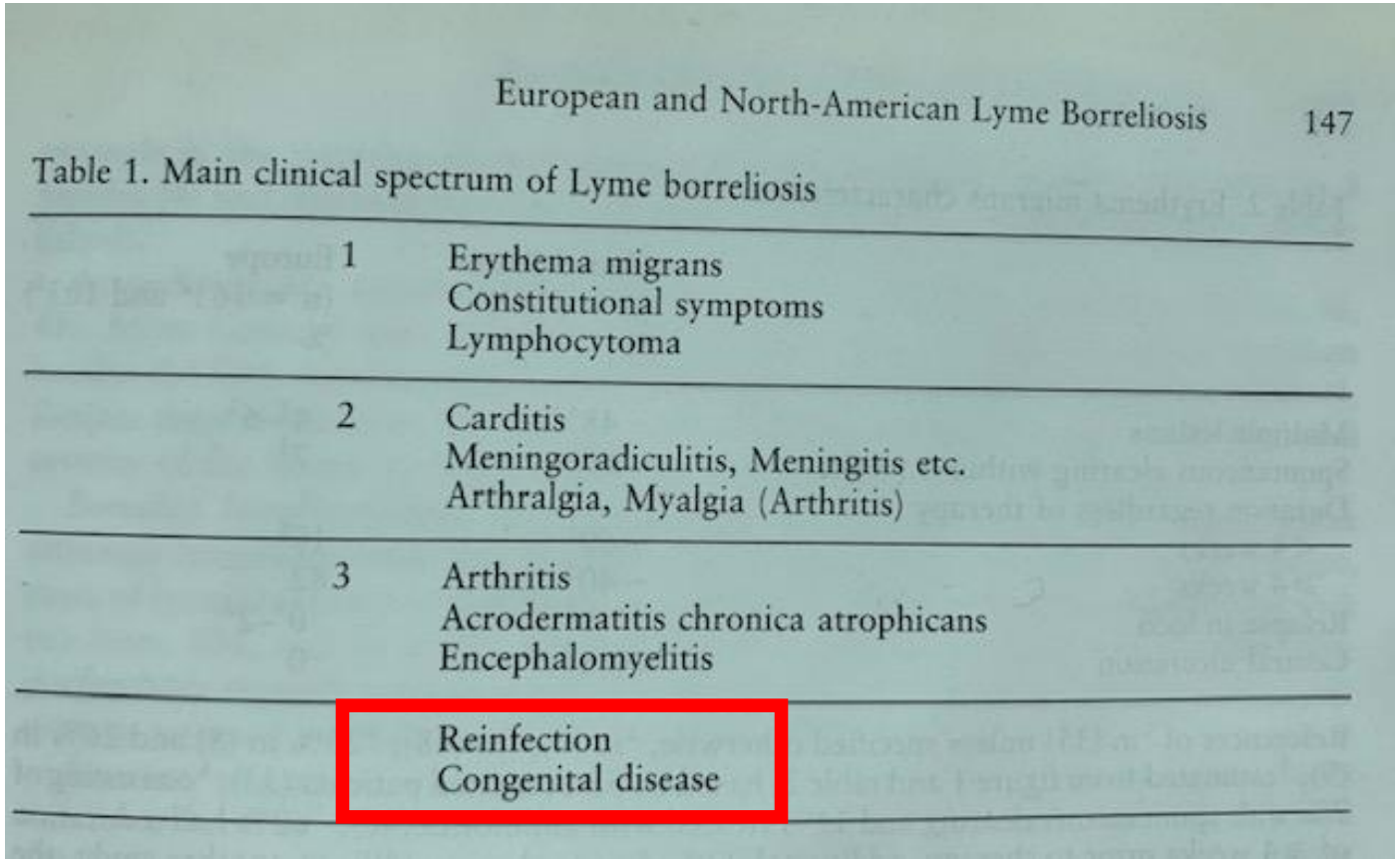
er A. Detection of Borrelia burgdorferi
ilk of patients with Lyme borreliosis.

me disease in two cows by the
146(17):497-9.

s and cows. Annals of the New York

Clinical Spectrum of Lyme borreliosis must include congenital disease

Weber, K. Clinical Features of Lyme Borreliosis. Clinical differences between European and North-American Lyme borreliosis – a Review. Stanek (Ed.). Lyme borreliosis II, Zbl Bakt. Suppl. 18, 1989.



European and North-American Lyme Borreliosis 147

Table 1. Main clinical spectrum of Lyme borreliosis

1	Erythema migrans Constitutional symptoms Lymphocytoma
2	Carditis Meningoradiculitis, Meningitis etc. Arthralgia, Myalgia (Arthritis)
3	Arthritis Acrodermatitis chronica atrophicans Encephalomyelitis
	Reinfection Congenital disease

'European and North-American Lyme borreliosis have in common the development of a disease in three stages and the occurrence of reinfection and congenital disease.'

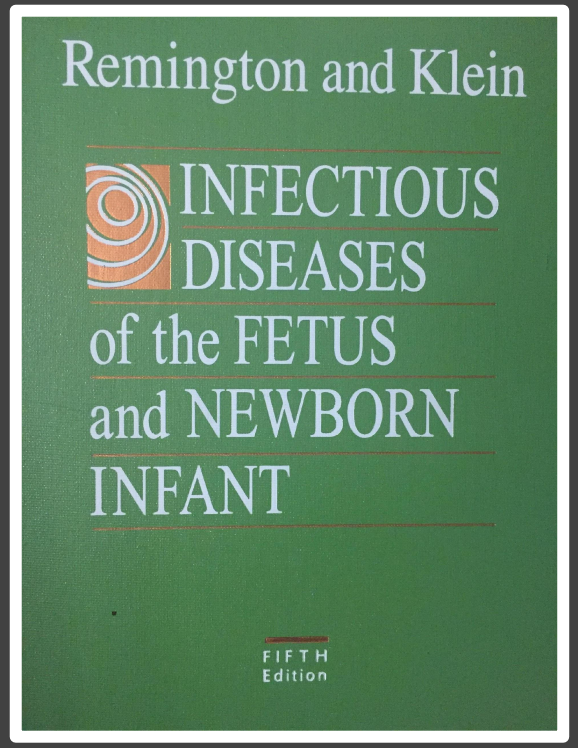
'Reinfection and congenital disease are other features of LB with similarities to syphilis.'

Frequency of occurrence of various types of fetal or neonatal adverse outcomes after Gestational Lyme (Table 11-3)

Cardiac - 23%	Neurologic 15%	Orthopedic 12%
Dermatologic 9%	Ophthalmic 4.5%	Genitourinary 11%
Miscellaneous anomalies 12%	Miscellaneous abnormalities	Fetal/Neonatal demise 39%

66 cases from 263 reported cases of gestational Lyme found to represent an adverse event at least associated with an episode of gestational Lyme including:

- Miscarriage
- Stillbirth
- Perinatal death
- Congenital anomalies
- Systemic illness
- Early onset fulminant sepsis
- Later onset chronic progressive symptoms



Gardner T. Infectious Diseases of the Fetus and Newborn Infant. In: Remington JS, Klein JO, editors. Lyme Disease, Chapter 11. 5th ed. Philadelphia, PA: The W.B. Saunders Co.;2001. pp. 519-641.

Signs and Symptoms of Congenital Lyme Borreliosis

Gardner, T. Lyme disease in pregnancy. Program and abstracts of the 14th International Scientific Conference on Lyme Disease and other Tick-Borne Disorders; April 21-23, 2001, Hartford, Connecticut.

Table. Signs and Symptoms of Congenital Lyme Borreliosis

Stage	Mild Early	Severe Early	Late
Onset	Usually first 2 weeks of life	Usually first week of life	Usually > 2 wks and < 2 yrs of age
Maternal gestational Lyme borreliosis	Usually first or second trimester	Usually first or second trimester	Usually second or third trimester
Signs and symptoms	• Mild suspected sepsis or meningoencephalitis • Hyperbilirubinemia • Adenopathy • Rash • Intrauterine growth retardation • Miscellanous anomalies (eg, genitourinary [GU], skeletal, cardiac)	• Severe suspected sepsis or meningoencephalitis • Respiratory distress • Perinatal death • Intrauterine growth retardation • Fever • Rash • Adenopathy, hepatosplenomegaly • Hyperbilirubinemia • Miscellaneous anomalies (eg, GU, skeletal, cardiac)	• Subacute illness • Developmental delay/meningoencephalitis • Growth retardation/failure to thrive • Prematurity • Fever • Adenopathy • Rash • Hepatosplenomegaly • Miscellaneous anomalies (eg, GU, skeletal, cardiac)
Prematurity?	< 4 weeks	< 5 weeks	--

Multi-system Symptoms in Children born with Lyme infection

‘The insidious nature of gestational LD can present a complicated diagnosis due to:

- delay of presentation
- multi-systemic, often transient nature of symptoms that can vary in degree of severity and change with progression of the disease
- unreliability of standard diagnostic tests.’

72% - fatigue lack of stamina
69% - joint pain
59% - Low grade fevers
56% - hyperactivity, lack of concentration
55% - jointed sensitivity
54% - irritability and mood swings
50% - headaches
43% - photophobia (sensitive to light)
42% - pale and sickly – dark eye circles
39% - poor memory
36% - hyperacuity (sensitive to noise)
30% - vertigo
32% - diarrhea and constipation
29% - Abdominal pain
27% - Gastroesophageal reflux disease (GERD)
23% - night sweats
23% - nausea
23% - cardiac manifestations – palpitations, PVC, Mitral VP, heart murmur
23% - generalized muscle pain or spasms

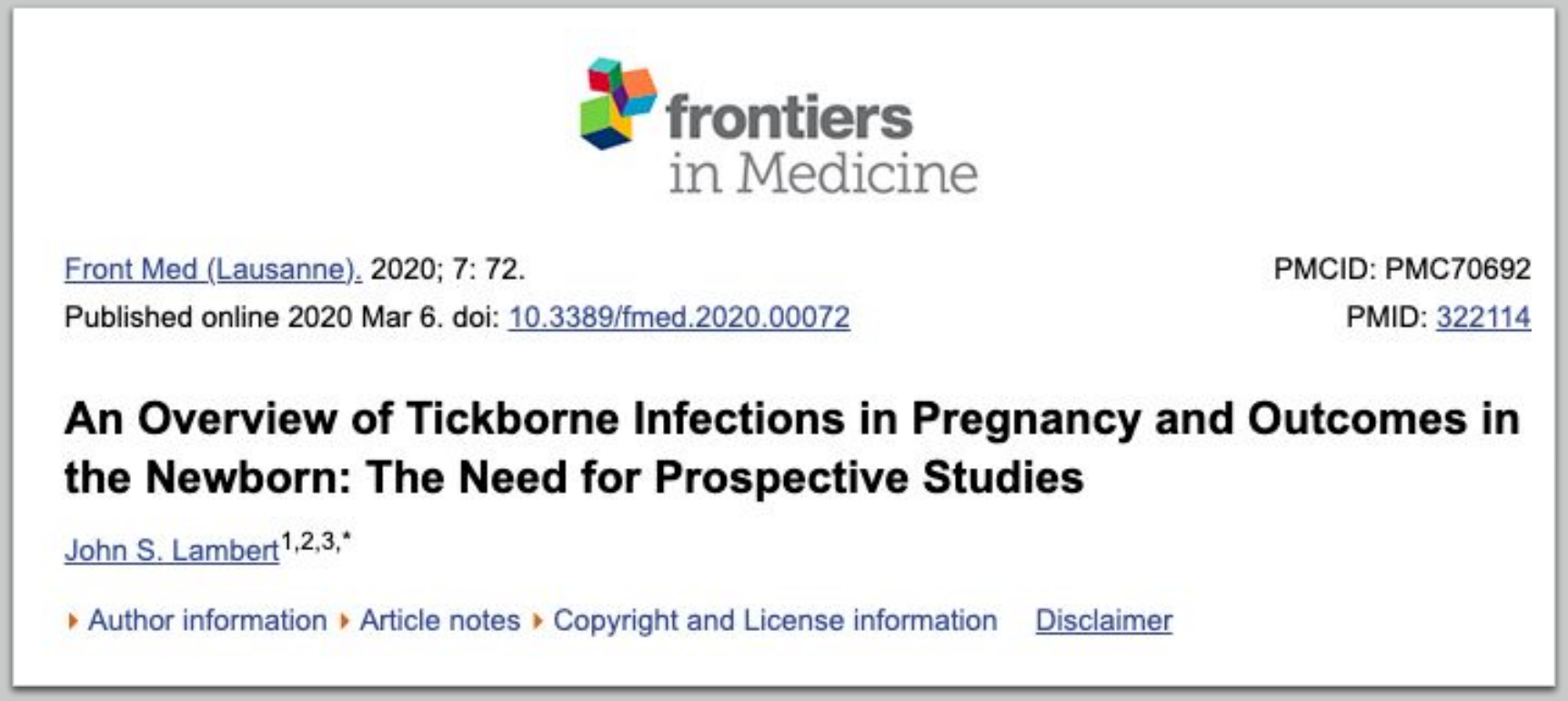
23% - anger and rage
21% - anxiety
21% - speech delay
19% - reading and writing delay
18% - developmental delays
14% - tic disorders
13% - auditory/visual processing problems
13% - aggression or violence
13% - depression
12% - word selection problems
14% - tic disorders
11% - Obsessive Compulsive Disorder
11% - seizure disorder
9% - involuntary movements
9% - motion sickness
9% - autism
8% - dyslexia
7% - suicidal thoughts
7% - hypotonia at birth (floppy, poor muscle tone)

Jones, Charles Ray, Smith, Harold, Gibb, Edina, and Johnson, Lorraine JD, MBA, “Gestational Lyme Disease Case Studies of 102 Live Births,” Lyme Times, 2005.

Gardner T. Infectious Diseases of the Fetus and Newborn Infant. In: Remington JS, Klein JO, editors. Lyme Disease, Chapter 11. 5th ed. Philadelphia, PA: The W.B. Saunders Co.;2001. pp. 519-641.

Large scale prospective studies of sufficient numbers of patients with gestational Lyme borreliosis

- Follow-up to determine pregnancy outcome of each enrolled patient;
- B burgdorferi specific evaluation of any fetal or neonatal demise;
- Long-term follow-up of each infant born to determine the occurrence of possible early and late sequalae are needed.'



"The literature on "Congenital Lyme" is at present incomplete due to lack of intensive investigations, and lack of longitudinal follow up of exposed infants, as has been done for another spirochete, syphilis. There is no doubt that congenital infection occurs with Borrelia; whether a congenital syndrome occurs as a result of this *in utero* infection remains to be further investigated."

Is the identification of a congenital syndrome a prerequisite to acknowledging congenital infection?

Congenital *T. cruzi* infection **has no specific clinical signs**. Infected newborns often are **asymptomatic or have subtle manifestations**.

The 10%–40% of newborns who are symptomatic might have low birth weight, low Apgar scores, hepatosplenomegaly, respiratory distress, anasarca, cardiac failure, or meningoencephalitis (*4*).

Severe congenital Chagas disease carries a high risk for neonatal death. However, even severe disease **might not be recognized because of the lack of defining clinical features and because the diagnosis is not considered.**

MMWR: Congenital Transmission of Chagas Disease — Virginia, 2010

July 6, 2012 / 61(26);477-479

Timeline of North American Research/Publications on Lyme Disease and Pregnancy/ Congenital Lyme 1985-2020

1985
First case of congenital transmission of described Schlesinger et al, 1985

1986
1: Case series – Fetal borreliosis MacDonald, 1986
2: 19 cases of Lyme disease in Pregnancy Markowitz et al, 1986

1987
1: Stillbirth following maternal Lyme disease. MacDonald et al, 1987
2: Culture positive, Seronegative Transplacental Lyme Borreliosis Infant Mortality. (abstract) Lavoie et al, 1987
3: Prospective Study of Pregnancy Outcomes in Women with Lyme disease (abstract). Ciesielski et al, 1987

1988
Lyme Disease During Pregnancy, a Cord blood Serosurvey. Williams et al, 1988

1989
1: Gestational Lyme Borreliosis, Implications for the Fetus. MacDonald, 1989
2: Neonatal Lyme: in Immunologic Aspects of Lyme Dattwyler et al, 1989
3: Lyme Seropositivity and Pregnancy Outcome in the absence of symptoms of Lyme disease. (abstract) Dlesk et al, 1989

1992
1: Prevalence of Sero positivity to the Lyme disease Spirochete during Pregnancy in an Epidemic Area: a Preliminary Report. Bracero et al, 1992)
2: Lyme Disease and Adverse Birth outcomes in New York State: An Ecologic Study (abstract) Druschel et al, 1992

1993
Lyme disease and Pregnancy outcome: A prospective study of two thousand prenatal patients. Strobino et al, 1993

1994
Childhood Neurologic Disorders and Lyme Disease During Pregnancy. Gerber et al, 1994.

1995
Maternal Lyme disease and congenital malformations: a cord blood serosurvey in endemic and control areas. Williams et al, 1995.

1996
Confirmation of Borrelia burgdorferi in Polymerase chain reaction in Placentas of Women with Reactive Serology for Lyme Antibodies. Figueroa et al, 1996.

1999
Maternal Lyme disease and congenital heart disease: A case control study in an endemic area. Strobino et al, 1999

2001
Description of Congenital Lyme Borreliosis. In: Chapter 11, Lyme disease. Gardner, 2001

2003
Lyme disease and Pregnancy: Implications of Chronic Infection, PCR Testing and Prenatal Treatment. (abstract). Horowitz et al, 2003

2005
Gestational Lyme Disease Case Studies of 102 Live Births. Jones et al, 2005

2020
Health outcomes of people with Lyme disease during pregnancy. McMaster Midwifery Research Institute, Darling et al, 2020 - in progress

The McMaster Midwifery Research Centre is conducting research on the transmission of Lyme disease from pregnant people to their babies.

RESEARCH PARTICIPANTS WANTED

Have you had **Lyme disease** or suspect you may have had Lyme disease during a pregnancy(ies)?

We want to hear from you in an **online survey:**

Visit **https://is.gd/lymeinpregnancystudy** for more information

McMaster University | Midwifery Research Centre

This study has been reviewed by the Hamilton Integrated Research Ethics Board under Project #11222

McMaster University | Midwifery Research Centre

Health outcomes of people with Lyme disease during pregnancy

https://obsgynresearch.mcmaster.ca/surveys/index.php?s=MN9CCXDTW9

More information can also be found at www.lymehope.ca under the research tab

What is best diagnostic approach to detect Bb infection in a pregnant mother and neonate?

“Like syphilis, Lyme disease has been called a “great imitator” and **is often difficult to diagnose clinically, particularly when erythema migrans is absent**.”

Dennis DT. Lyme disease. Tracking an epidemic. JAMA. 1991 Sep 4;266(9):1269-70.

Attenuation of Symptoms in Pregnancy

1

‘We show that during pregnancy in a murine model, the severity of pathogenic inflammatory responses associated with Lyme arthritis is significantly attenuated.’

Moro MH, Bjornsson J, Marietta EV, Hofmeister EK, Germer JJ, Bruinsma E, David CS, Persing DH. Gestational attenuation of Lyme arthritis is mediated by progesterone and IL-4. J Immunol. 2001 Jun 15;166(12):7404-9.

2

‘Contrary to what we expected, levels of spirochetemia were significantly lower and symptoms were markedly less severe in pregnant than in non pregnant mice.’

‘Although the mother is partially protected, gestational RF clearly has detrimental consequences for the fetus as demonstrated by intrauterine growth restriction, increased risk of fetal abnormalities and transplacental transmission.’

Larsson C, Andersson M, Guo BP, Nordstrand A, Hagerstrand I, Carlsson S, Bergstrom S. Complications of pregnancy and transplacental transmission of relapsing-fever borreliosis. J Infect Dis. 2006 Nov 15;194(10):1367-74.

3

’the proportion of constitutional symptoms accompanying EM was lower in pregnant women indicating that the course of EM during pregnancy is milder than in the age-matched non-pregnant women.’

Maraspin, V.; Lusa, L.; Blejec, T.; Ružić-Sabljić, E.; Pohar Perme, M.; Strle, F. Course and Outcome of Erythema Migrans in Pregnant Women. *J. Clin. Med.* **2020**, *9*, 2364.

Opportunity:
Development of novel diagnostics for Lyme must be inclusive of the pregnant population and neonates exposed in-utero

Comprehensive review of 14 cases of adverse fetal and neonatal outcomes of gestational borreliosis.

2/10 SIDS cases showed spirochetes morphologically compatible with Bb in infant brain.

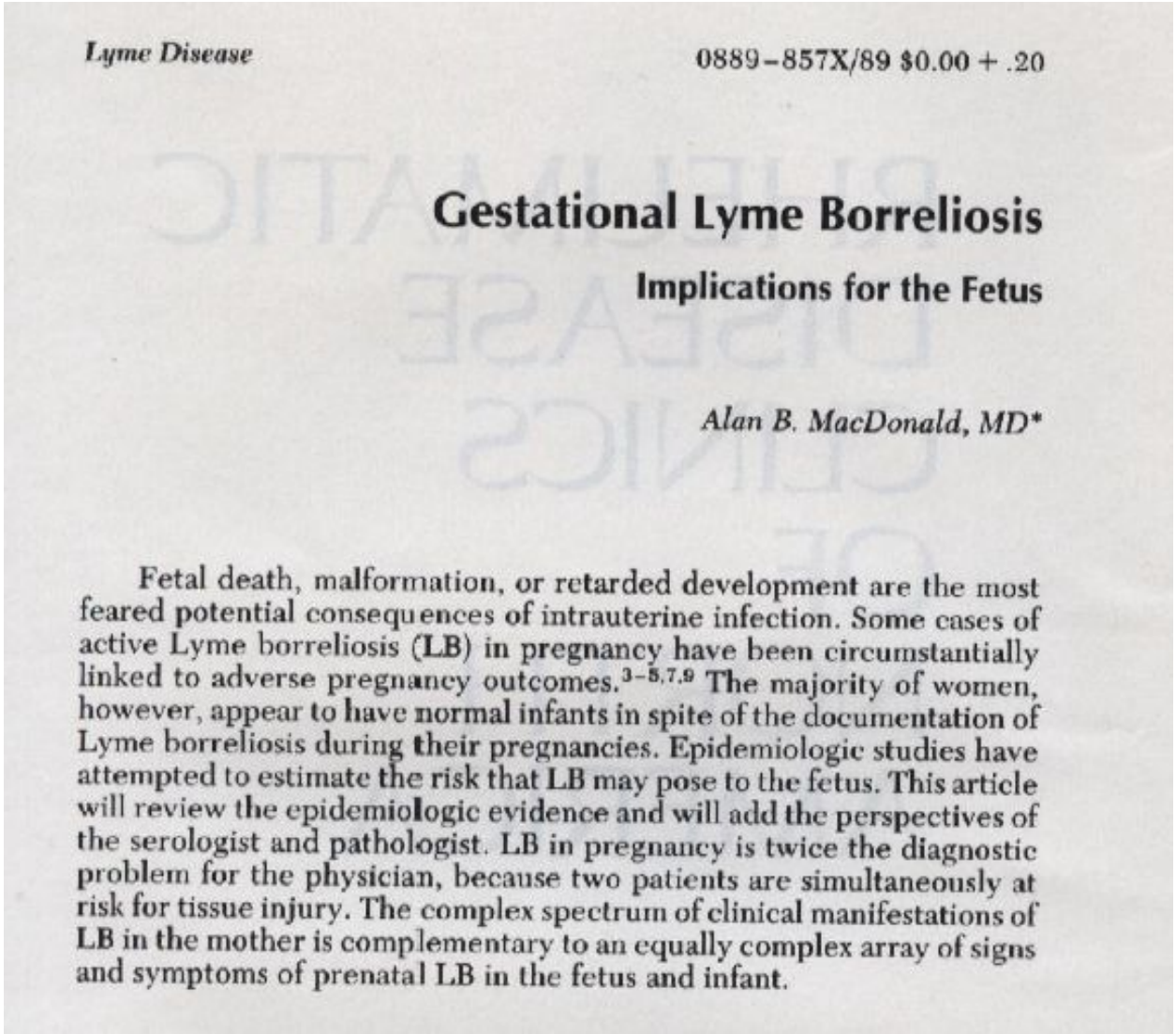
Gestational Lyme borreliosis may be associated with fetal death in-utero, fetal death at term or infant death after birth

Utility of Serology:

'The tendency toward seronegativity in pregnancy makes maternal serology a less satisfactory discriminator of maternal infection and useless as a practical tool to predict the actual state of the fetus.'

Comparisons with prenatal syphilis:

'It is my expectation that the spectrum of gestational Lyme borreliosis will expand into many of the clinical domains of prenatal syphilis.'



Lyme Disease 0889-857X/89 $0.00 + .20

Gestational Lyme Borreliosis

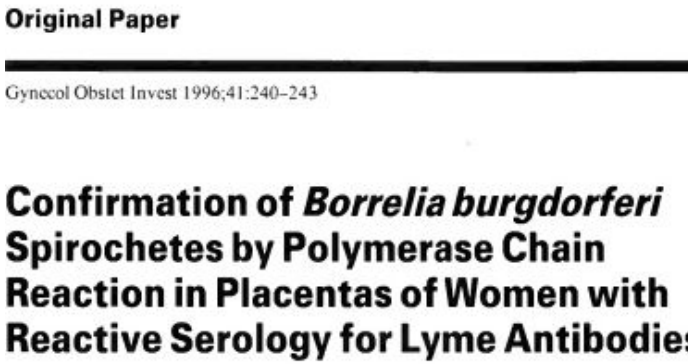
Implications for the Fetus

*Alan B. MacDonald, MD**

Fetal death, malformation, or retarded development are the most feared potential consequences of intrauterine infection. Some cases of active Lyme borreliosis (LB) in pregnancy have been circumstantially linked to adverse pregnancy outcomes.[3-5,7,9] The majority of women, however, appear to have normal infants in spite of the documentation of Lyme borreliosis during their pregnancies. Epidemiologic studies have attempted to estimate the risk that LB may pose to the fetus. This article will review the epidemiologic evidence and will add the perspectives of the serologist and pathologist. LB in pregnancy is twice the diagnostic problem for the physician, because two patients are simultaneously at risk for tissue injury. The complex spectrum of clinical manifestations of LB in the mother is complementary to an equally complex array of signs and symptoms of prenatal LB in the fetus and infant.

MacDonald A. Gestational Lyme Borreliosis. Implications for the fetus. Rheum Dis Clin North Am. 1989 Nov;15(4):657-77

Bb positive placentas in asymptomatic, seronegative women



Original Paper

Gynecol Obstet Invest 1996;41:240–243

Confirmation of *Borrelia burgdorferi* Spirochetes by Polymerase Chain Reaction in Placentas of Women with Reactive Serology for Lyme Antibodie

‘No relationship between the presence of placental spirochetes and the results of Lyme serology or the pregnancy outcome.’

Figueroa R, Bracero LA, Aguero-Rosenfeld M, Beneck D, Coleman J, Schwartz I. Confirmation of Borrelia burgdorferi spirochetes by polymerase chain reaction in placentas of women with reactive serology for Lyme antibodies. Gynecol Obstet Invest. 1996;41(4):240-3.

- 3 placentas with spirochetes
- (2/3 pos for Bb by PCR):
- Women were either borderline or seronegative by two tier criteria, asymptomatic, no known history of a tick bite.
- 2/3 women would be considered seronegative by two tier testing criteria (equivocal ELISA and negative WB)
- 1 woman had both an equivocal ELISA and WB
- Authors stated ‘presence of Bb spirochetes in placenta implies fetal transmission’
- Cord blood serology IgG and IgM was done in all 3 infants and negative. A normal perinatal outcome was observed in all cases – no mention follow-up
- Authors recommended long-term follow-up of infants born to mothers with placenta spirochetes is needed to determine what effect, if any, placental spirochetes may have on health and development of these individuals

Diagnosing Congenital Lyme Infections: what is the best testing approach?

Neonatal Lyme Disease

In humans, *B. burgdorferi* is capable of infecting the fetus [35]. Sequelae (including abortion and fetal abnormalities) have been associated with infection [36, 37]. The time, incidence, and morbidity of in utero infection are not known. However, both humoral and cellular *B. burgdorferi*–specific responses can be detected in cord blood of previously infected neonates (authors' unpublished observations). In addition, *Borrelia*-specific antibodies have been found in the CSF of an infant with evidence of neonatal neurologic dysfunction whose mother had been infected in the second trimester. The mother, who was asymptomatic, had been treated with oral antibiotics and did not have diagnostic levels of antibodies to *B. burgdorferi* at the time of parturition (authors' unpublished observations). Effective therapy to eradicate borreliae on both the maternal and the fetal side of the placenta is essential, as persistent infection may be difficult to diagnose after the initial course of antibiotics.

Dattwyler, R. J.; Volkman, D. J.; Luft, B. J. (1989). *Immunologic Aspects of Lyme Borreliosis. Clinical Infectious Diseases, 11(Supplement 6), S1494–S1498.*

'The time, incidence, and morbidity of in utero infection are not known. However, both humoral and cellular B. burgdorferi-specific responses can be detected in cord blood of previously infected neonates (authors' unpublished observation).'

'In addition, Borrelia specific antibodies have been found in the CSF of an infant with evidence of neonatal neurologic dysfunction.'

'The mother, who as asymptomatic, had been treated with oral antibiotics and did not have diagnostic levels of antibodies to Bb at time of parturition.'

Is cord blood IgM an adequate stand-alone endpoint to determine congenital infection?

Several US studies on Lyme and Pregnancy used cord blood IgM as the only diagnostic marker to identify if an infant was infected. No case of positive Bb IgM was reported.

Ciesielski et al, 1987; Williams et al, 1988; Strobino et al, 1993; Williams et al, 1995

Infection	Regarding Sensitivity of serology	Ref:
Toxoplasmosis	'the **absence of congenital disease markers (IgM and IgA) in newborns, even after confirming the absence with several techniques, does not constitute an exclusion criterion for toxoplasmosis**.' (1) '**Neonatal Toxoplasma IgM and/ or IgA tests could fail to identify approximately 20% to 50% of CT cases**.'(2)	(1) Rodrigues, Imx et al. Congenital toxoplasmosis: evaluation of serological methods for the detection of anti-Toxoplasma gondii IgM and IgA antibodies. *Mem. Inst. Oswaldo Cruz* [online]. 2009, vol.104, n.3 [cited 2021-03-17], pp.434-440 (2) Maldonado YA, Read JS, AAP Committee on Infectious Diseases. Diagnosis, treatment, and prevention of congenital toxoplasmosis in the United States. *Pediatrics*. 2017;139(2):e20163860.
Cytomegalovirus	**'IgM antibody in neonates is of limited diagnostic value with a sensitivity ranging from 20-75%.'** (3)	(3) Revello MG, Gerna G. Diagnosis and management of human cytomegalovirus infection in the mother, fetus, and newborn infant. *Clin Microbiol Rev*. 2002;15(4):680-715.
Syphilis	**The absence of a fourfold or greater titer for a neonate does not exclude congenital syphilis.** **No commercially available immunoglobulin (IgM) test can be recommended**	CDC 2015 Guidelines for Syphilis: https://www.cdc.gov/std/tg2015/congenital.htm

Diagnostic testing for evaluation of Congenital Lyme Borreliosis

- Direct and indirect testing methodologies including paired maternal/baby serology, culture, PCR and cellular response testing such as lymphocyte proliferation assay.
- Multi-disciplinary assessment and follow-up with cardiology and neurology if clinical suspicion of congenital heart disease or neurologic involvement
- Full histopathologic testing, culture and PCR of any placenta, miscarriage, stillbirth or perinatal death from a pregnancy complicated by gestational Lyme

Gardner T. Infectious Diseases of the Fetus and Newborn Infant. In: Remington JS, Klein JO, editors. Lyme Disease, Chapter 11. 5th ed. Philadelphia, PA: The W.B. Saunders Co.;2001. pp. 519-641. (page 596)

Needed: Interim Guidelines for the Evaluation of Infants Born to Mothers Infected with Lyme disease in Pregnancy

Standardized assessment tool to guide clinical evaluation, treatment and follow-up of infants born to mothers with Lyme during pregnancy

- Laboratory testing
- Clinical Assessment Tools
- Treatment recommendations
- Recommendations for histological examination/ testing of placenta, umbilical cord tissue

What is the best treatment approach for Lyme in Pregnancy and for babies exposed in-utero?

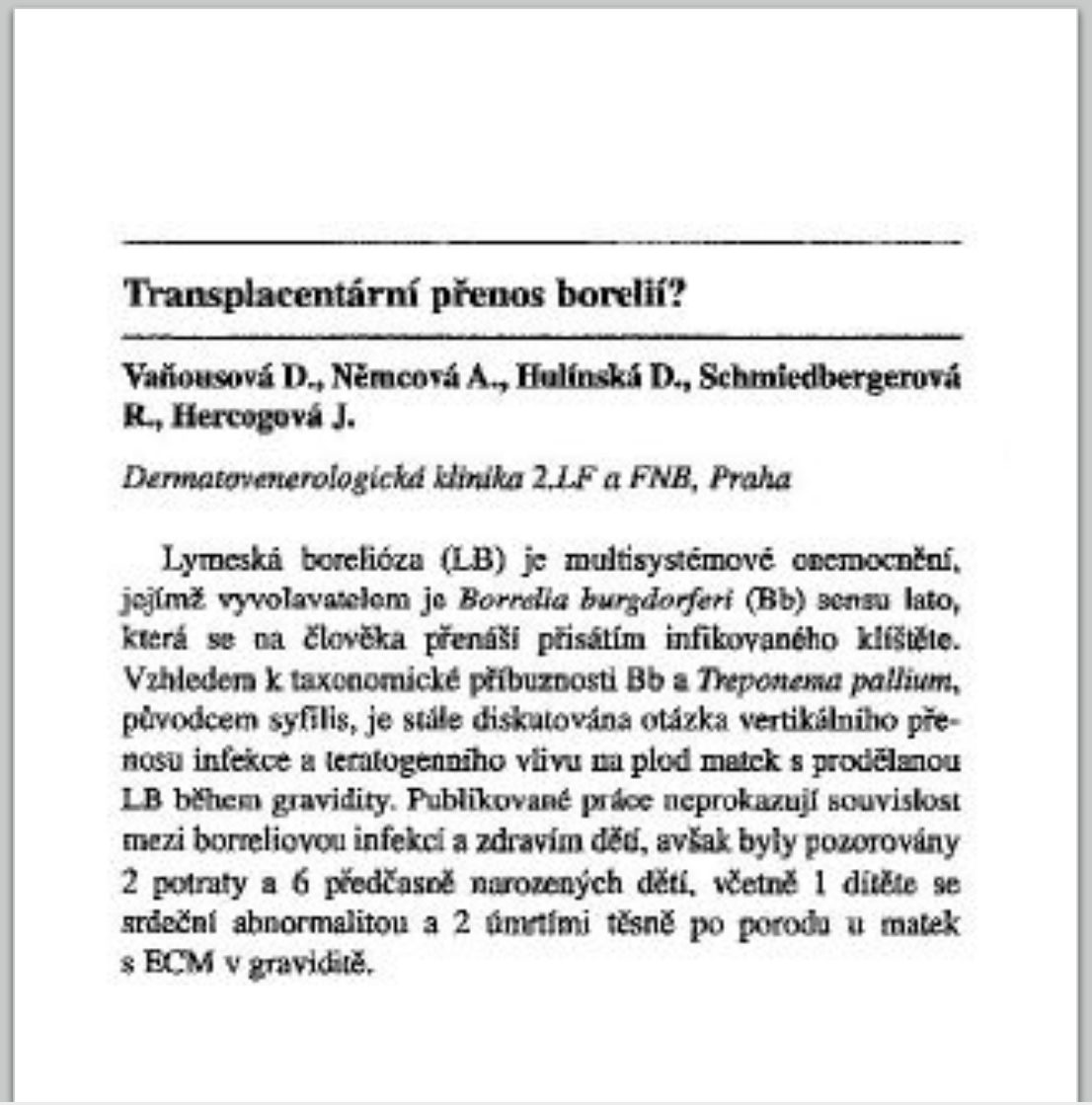
Treated versus Untreated Gestational Lyme disease

Reference	Findings
Gardner, T. Lyme Disease. Chapter 11. Infect Dis Fetus and Newborn Infant. 5th edition Saunders, 2001.	**Treated:** 14.6% of the pregnancies with adverse outcomes **Untreated:** 66.7% of the pregnancies with adverse outcomes. Proper, prompt diagnosis and antibiotic therapy are vital for healthy neonates born with congenital Lyme disease.
Lakos A, Solymosi N. Maternal Lyme borreliosis and pregnancy outcomes. Inf J Infect Dis 2010;14:e494-e498.	**Treated:** parentally (IV antibiotics) 8/66 (12.1%) with adverse outcomes. **Treated:** oral antibiotics 6/19 (31.6%) with adverse outcomes. **Untreated:** 6/10 (60%) adverse outcomes. In comparison to patients treated with antibiotics, **untreated women had a significantly higher risk of adverse pregnancy outcome** (odds ratio (OR) 7.61, p = 0.004).
Waddell LA, Greig J, Lindsay R, Hinckley AF, Ogden NH. A systematic review on the impact of gestational Lyme disease in humans on the fetus and newborn. PLoS ONE 13 (11): e0207067.	**Treated:** 11% of pregnancies have adverse outcomes **Untreated:** 50% of pregnancies with adverse outcomes. 'A meta-analysis of nine studies showed significantly fewer adverse birth outcomes in women reported to have been treated for gestational LD (11%, 95%CI 7–16) compared to those who were not treated during pregnancy (50%, 95%CI 30–70) providing indirect evidence of an association between gestational LD and adverse birth outcomes.'

Presence of borrelia in cord blood and placenta despite antibiotic treatment.

- Bb was detected in umbilical cord blood in one child by PCR positive genome and suspected plasmid Bb
- in another case a positive genome and the suspected plasmid were captured in the placenta together with the electron microscopic detection of the spirochete in the placenta,
- in the third case the suspected genome and plasmid in the umbilical cord blood and a positive genome with the suspected plasmid in the placenta.
- Based on these findings, it can be assumed that borreliosis have the ability to permeate transplacentally.

*translated from Czech.



Transplacentární přenos borelií?

Vaňousová D., Němcová A., Hulínská D., Schmiedbergerová R., Hercogová J.

Dermatovenerologická klinika 2.LF a FNB, Praha

Lymeská borelióza (LB) je multisystémové onemocnění, jejímž vyvolavatelem je *Borrelia burgdorferi* (Bb) sensu lato, která se na člověka přenáší přisátím infikovaného klíštěte. Vzhledem k taxonomické příbuznosti Bb a *Treponema pallium*, původcem syfilis, je stále diskutována otázka vertikálního přenosu infekce a teratogenního vlivu na plod matek s prodělanou LB během gravidity. Publikované práce neprokazují souvislost mezi borreliovou infekcí a zdravím dětí, avšak byly pozorovány 2 potraty a 6 předčasně narozených dětí, včetně 1 dítěte se srdeční abnormalitou a 2 úmrtími těsně po porodu u matek s ECM v graviditě.

Vanousova D, Nemcova A, Hulinska D, Schmiedbergerova R., Hercogova J. Transplacentární přenos borelií? Čes-slov Derm, 2007, roč. 82, č. 4, s. 218

Presence of Borrelia in placenta despite antibiotic treatment in First Trimester.

‘In 2008-2010, we detected the presence of Borrelia by direct methods (PCR assays and electron microscopy) in the placenta of patients who had been treated with penicillin for erythema migrans in trimester 1.’

ZPRÁVY EPIDEMIOLOGIE A MIKROBIOLOGIE (SZÚ, PRAHA) 2011; 20(1)

Diseminovaná borrelióza a její průkaz v laboratoři

Disseminated Lyme borreliosis and its laboratory diagnosis

Dagmar Hulínská, Jiří Votýpka, Jan Hořejší

Souhrn • Summary

Perzistující borrelióza přináší diagnostické i léčebné problémy, na které chceme v tomto příspěvku up
Na základě našich vyšetření jsme prokázali pomocí přímých metod (PCR a elektronové mikroskopie) v
2008–2010 výskyt borrelií v placentě pacientek, které měly v prvním trimestru erythema migrans a byly
penicilinem, dále v srdci u pacientů s myokarditidou a náhle vzniklou dilatační endomyokarditidou, v
a v synoviální tekutině pacientů s déle trvajícími kloubními problémy.
Všichni pacienti byli posláni k našemu laboratornímu vyšetření lékaři, kteří se klinikou lymeské borrelió
zabývali. Pacienti měli symptomy, které lékaři uznali za možné pro LB. U některých pacientů s přímým
zem byly pozitivní Western bloty ve třídě IgG proti borreliím až po opakované léčbě. V srdci, v placentě
noviu byly borrelie prokázané též elektronmikroskopicky. Někteří pacienti byli opakovaně léčeni vz
k opakovaně pozitivní PCR nebo séropozitivitě při opakovaných klinických symptomech v průběhu 3–

*Persistent Lyme borreliosis is a diagnostic and therapeutic challenge to which we would like to draw at
In 2008-2010, we detected the presence of Borrelia by direct methods (PCR assays and electron microsc
the placenta of patients who had been treated with penicillin for erythema migrans in trimester 1, in the
patients with myocarditis and fulminant endomyocarditis, and in the synovial fluid of patients with pe
joint complaints.
All these patients were referred to our laboratory by clinicians experienced in Lyme borreliosis(LB) bec
the symptoms potentially suggestive of LB. Some patients only showed IgG Western blot positivity after n
treatment. In the heart, placenta and synovial fluid, borreliae were also detected by electron microscop
patients were treated repeatedly after presenting with re-emerging clinical symptoms and retesting PCR
or seropositive over 3-4 years.*

Zprávy EM (SZÚ, Praha) 2011; 20(1): 24–26.

Hulinksa, D., Votypka J., Horejsi J. Disseminated Lyme borreliosis and its laboratory diagnosis. Zpravy Epidemiologie A Mikrobiologie (SZU Praha) 2011:20(1)

‘The **aim of treatment of early Lyme disease during pregnancy is not only to treat the infection and prevent long-term sequelae but to eliminate the infection as quickly as possible so as to prevent congenital transmission to the fetus**.

Recently, Weber et al. [56] reported **the congenital transmission of B. burgdorferi to an infant whose mother had been treated with 1 million units of oral penicillin** for 7 days.

Given the significant failure rate described by Steere et al. [2] in patients treated with 250 mg of oral penicillin (more than 50% of whom developed "minor" and "major" disease), **it would seem reasonable to administer more vigorous treatment to pregnant patients with acute EM.**

No study has established the optimal treatment in this instance; however, either oral amoxicillin plus probenecid or parenteral ceftriaxone has been used. **Further studies must establish the duration of therapy necessary to eradicate this infection and thus to prevent congenital transmission**.’

REVIEWS OF INFECTIOUS DISEASES • VOL. 11, SUPPLEMENT 6 • SEPTEMBER-OCTOBER 1989

A Perspective on the Treatment of Lyme Borreliosis

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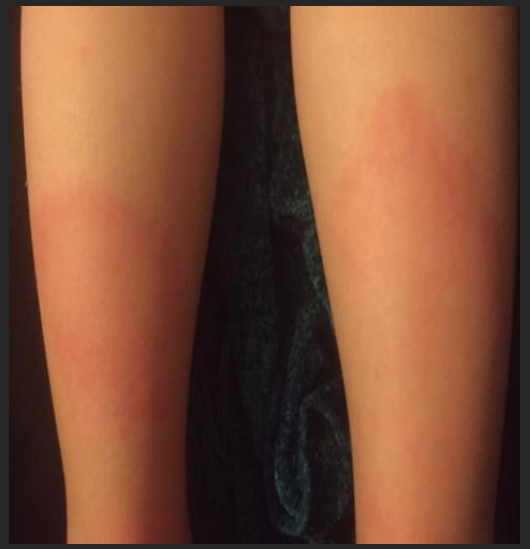
Lyme borreliosis has become the most common tick-borne infection in the United States. Although both β-lactam and tetracycline antibiotics have been shown to be effective in the treatment of this spirochetosis, the development of optimal therapeutic modalities has been hampered by the lack of reliable microbiologic or immunologic criteria for the diagnosis or cure of this infection. In vitro sensitivity studies have been performed by several laboratories, but there has been no standardization of the methodology for measuring either inhibitory or bactericidal levels. Clinical studies have documented the efficacy of antibiotics, but therapy has failed in as many as 50% of cases of chronic infection. Although new antibiotic regimens appear promising, the optimal treatment of this infectious disease remains to be determined. In this report we review the clinical and experimental rationale for the antibiotic regimens that we currently use and the need for a more standardized approach to treatment trials.

Luft, B. J.; Gorevic, P. D.; Halperin, J. J.; Volkman, D. J.; Dattwyler, R. J. (1989). *A Perspective on the Treatment of Lyme Borreliosis. Clinical Infectious Diseases, 11(Supplement 6), S1518–S1525.*

‘The prevention, diagnosis, and treatment of Lyme disease is a formidable new challenge in medicine today. In no specialty is there greater concern for the adverse effects of this disease as in obstetrics, **where the full consequences of prenatal exposure are as yet unknown**.’

Williams CL, Strobino BA (1990) Lyme disease transmission during pregnancy. Contemporary Ob/Gyn, 35, 48-64.

Case Review



CDC/NYS-RESULT	NEGATIVE
18 kDa	-
**23-25 kDa	-
28 kDa	-
30 kDa	-
**31 kDa	+++
**34 kDa	++
**39 kDa	+
**41 kDa	+++
45 kDa	-
58 kDa	+
66 kDa	-
**83-93 kDa	-

Analysis	Result	Unit
Borrelia EliSpot		
Borrelia b. Full Antigen	1	SI
Borrelia b. OSP-Mix	2	SI
Borrelia burgdorferi LFA-1 !	**4**	**SI**
0-1 = negative		
2-3 = weak positive		
> 3 = positive		

Test	Result
Lyme IgG/IgM EIA	Non-Reactive
Borrelia burgdorferi (Lyme disease) Interpretation	No serological evidence of infection.

Fitting the pieces together

- **Patient-Centered inclusive research partnerships** which welcome and value patient/family priorities.

- **Developing interim guidelines** for assessing/testing/treating infants born to mothers with Lyme disease and as more data emerges, developing a case definition for congenital Lyme.

- **Multi-center long-term prospective follow-up studies** of mother-baby pairs to determine maternal cofactors (acute vs chronic infection) related to maternal-infant transmission and short and long-term maternal and infant outcomes.

- **Novel diagnostic methods** to detect Borrelia-infected mothers and infants including comparative antibody studies, identifying immunodominant antigens in WB, potential biomarkers, T-cell testing, nucleic acid testing, culture, PCR, whole genome sequencing in serum, cord-blood, amniotic fluid, urine, CSF.

- **Study of the sensitivity and specificity of current laboratory tests** in pregnant women and neonates for diagnosing Lyme infection

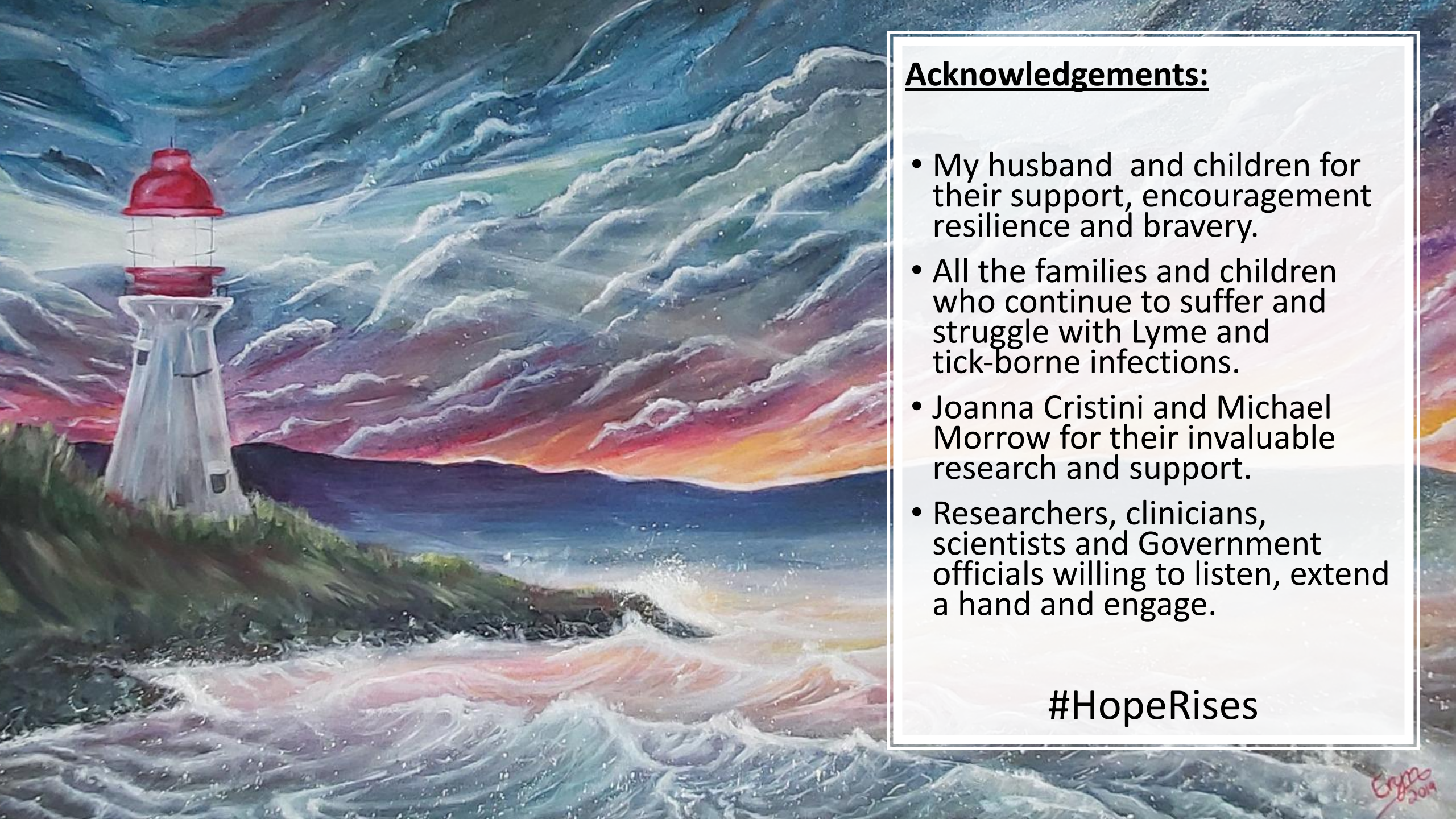
- **Lyme and Pregnancy Registries**: National/State/Provincial

- **Biorepositories:** Samples of pregnant people with acute Lyme, late-stage Lyme, subclinical Lyme and post-treatment Lyme Disease including serum, amniotic fluid, placenta, products of conception. Samples of offspring exposed to Lyme in-utero including cordblood, serum, urine.

- **Screening:** Effective approaches for Borrelia burgdorferi screening in pregnant women

Research Opportunities

- **Detailed Histopathologic evaluation** of any placenta, miscarriage, stillbirth or perinatal death from a pregnancy complicated by Lyme borreliosis.
- **Maternal and neonate immune response** to Bb infection in pregnancy
- **Breast-milk studies** from lactating mothers with Lyme borreliosis (acute or chronic) and risk assessment/study regarding potential transmissibility of Bb through breastmilk.
- **Treatment:** Identification of optimal treatment options for gestational Lyme, including dosages, duration and modes (oral vs IV) to prevent vertical transmission of Bb. Optimal treatment for babies exposed to Bb in-utero.
- **Animal models:** Use of appropriate animal models including non-human primate studies aimed at determining pathophysiology of disease, possible biomarkers of congenital infection, investigation of effects of chronic vs acute infection in pregnancy.
- **Family studies** with retrospective, qualitative questionnaires and data analysis. Direct testing of family members using culture, PCR and genomic sequencing
- **Prevention:** Identifying strategies to prevent maternal-fetal transmission of Lyme



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- All the families and children who continue to suffer and struggle with Lyme and tick-borne infections.
- Joanna Cristini and Michael Morrow for their invaluable research and support.
- Researchers, clinicians, scientists and Government officials willing to listen, extend a hand and engage.

#HopeRises

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