Perinatal transmission of Lyme disease: A Path Forward

by Sue Faber RN, BScN, March 4, 2023

Shining a Light on Perinatal Transmission of Lyme Disease

Dear Reader, March 4, 2023

I'm sharing this new compilation and analysis of research with you on the topic of Perinatal Transmission of Lyme disease. This includes detailed descriptions from the primary literature identifying cases of congenital and/or placental infection with *Borrelia burgdorferi* in humans as well as findings from animal studies, epidemiologic studies and much more. I've also included direct quotes in gold/yellow boxes at the beginning of each section, from subject matter experts related to maternal-fetal transmission of Lyme disease and/or adverse outcomes from peer-reviewed, published articles. This is a work in progress and will be regularly updated as new research findings come available.

I also want to your attention a report which was written for the Clinical Presentation and Pathogenesis Subcommittee for the 2022 US Tickborne Disease Working Group. I was honored to receive an invitation to participate as a member of this subcommittee, and our report includes an extensive section (Priority 4) on Lyme disease and Pregnancy including research gaps and opportunities. The report can be found here.

In 2022, myself and several co-chairs/organizers who participated in the Banbury meeting on Perinatal Transmission of Lyme disease, participated in a panel discussion for the Cohen Foundation LymeMIND conference in a panel titled: The Value Partnerships: A multi-disciplinary Approach to Addressing Perinatal Transmission of Lyme disease. I invite you to watch this session which is available here includes a powerful video with stories of families impacted by congenital Lyme disease along with several experts sharing on the subject matter.

I am so thankful for all my incredible colleagues who helped me find important papers and information along the way, especially Maggie S, Joanna C, and Michael M, this was certainly a team effort! I am forever grateful to our extraordinary pediatrician, Dr. Charles Ray Jones who specialized in pediatric Lyme disease, and sadly passed away in 2022. His expert care of tens of thousands of children from around the world exemplified clinical excellence, courage, resilience, and kindness. He taught me that courage is contagious, healing is possible, and learning is life-long. I thank God for giving me the strength and endurance to keep going in an area rife with so much unnecessary controversy and marginalization – however, this IS changing!

For families that have been impacted by this alternate mode of transmission, I see you, I hear you and I care so deeply, because I too walk in your shoes. Keep going and don't give up. Each day is a new beginning. These beautiful lyrics and song by JJ Heller 'Hold On' sum up the words I would share with you, if I were to meet you over a cup of tea.

'Hold on, Hold on, I know you've been fighting so long
Stay strong, stay strong, It's the darkest before the dawn, Hold on'

I believe that collaborative, multi-sectoral research will open new doors for better diagnostics, treatment, healthcare professional education and resources, policy tools and ultimately support and medical care for families and children impacted by perinatal transmission of Lyme disease. There is a path forward, a light has been turned on and these issues are being now being seen, heard, amplified, and actioned– and I'm excited about the momentum now and in the future.

Warmly and *with hope*,

Sue Faber RN, BScN. Co-Founder and President LymeHope
www.lymehope.ca

LymeHope
Beacon of Hope. Anchored in Integrity.

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

'..now we had found a spirochete capable of spreading transplacentally to the organs of the fetus, causing congenital heart disease and possible death of the infant.'

Burgdorfer, W. The Enlarging Spectrum of Tick-Borne Spirochetosis: R.R. Parker Memorial Address. Reviews of Infectious Diseases, Vol 8(6) Nov/Dec, 1986.

'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.'

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.

'The causative spirochetal agent is not directly transmitted from one person to another, except, in apparently rare instances, by crossing the placenta to infect the fetus.'

Dennis, D. Epidemiology. Chapter 4. In: Coyle PK. (ed) Lyme disease. Mosby Year Book, 1992.

"A factor complicating Lyme disease is that B. burgdorferi has the capacity to cross the placental membrane between a pregnant female and her unborn child."

Johnson, WA. Report on Lyme Disease Prepared for US Army Corps of Engineers Field Personnel. USAE Waterways Experimental Station, Environmental Laboratory. MS 39180-6199, 1993.

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

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., 2016.

Identification of Bb in fetal, infant, child tissue (22 cases)

- 1 death of child
- 8 neonatal deaths
- 5 cases of stillbirth
- 8 cases of miscarriage

Live Birth: (18 cases)

15 cases of live-birth, neonatal infection and adverse outcomes
2 cases of live-birth, Bb identified by PCR in cordblood of infants whose mothers were treated
1 case live-birth (twins), one twin had IgG and IgM antibodies (mother was treated)

Placenta: (28 cases)

17 cases Bb identified by PCR in placentas of treated pregnant women
2 cases Bb identified by PCR in placentas of (treatment not stated) pregnancies
4 cases Bb identified in placenta by histology/staining/IFA in untreated pregnancies
4 cases Bb identified in placenta by histology/staining/MaB in treated pregnancies
1 case Bb identifed in placenta by silver stain in pregnancy (maternal treatment not indicated)

Breastmilk:(2 cases)

2 cases whereby Bb has been identified in breastmilk by PCR of women with EM rash

Bb identified/isolated in human fetal/infant/child tissues/placenta/cordblood/breastmilk

'Once Borrelia burgdorferi disseminates, it has the potential of becoming a progressive, chronic, infectious disease involving multiple organ systems.'
Luft, B. J., & Dattwyler, R. J. (1989). Treatment of Lyme borreliosis. *Rheumatic diseases clinics of North America*, *15*(4), 747–755.

'It is possible that B. burgdorferi s.l. has a high ability to penetrate mammalian placentae due to its ability of active movement, antigenic and morphological variation, and many other features and causes diagnostic difficulties and problems.'

Jasik KP, Okła H, Słodki J, Rozwadowska B, Słodki A, Rupik W. Congenital Tick Borne Diseases: Is This An Alternative Route of Transmission of Tick-Borne Pathogens In Mammals? Vector Borne Zoonotic Dis. 2015 Nov;15(11):637-44.

"Despite these limitations, B. burgdorferi can cross the placenta, presumably during a period of spirochetemia. The frequency and clinical significance of transplacental transmission are unclear however."

Shapiro E, Gerber M. Borrelia Infections: Lyme Disease and Relapsing Fever. Chapter 17. Found in Remington and Klein's Infectious Diseases of the Fetus and Newborn Infant, 7th ed., 2011.

Findings	Reference.
Fetal tissue (PCR)	Horowitz et al, 2003
Cord blood (PCR)	Vanousova et al, 2007
Breast milk (PCR)	Schmidt et al, 1995
Placenta (PCR/SS/EM)	MacDonald et al, 1987; Burrascano, 1993; Spector et al, 1993; Patmas,1994; Figueroa et al, 1996; Horowitz, 2003; Hercagova 2008; Hulinksa et al 2009; Vanousova et al, 2007; Hulinksa et al, 2011.
Skin (PCR)	Trevison et al, 1997
Cerebral spinal fluid (CSF) (Bb specific antibody)	Horst, 1992; Dattwyler et al, 1989.
Cord/Infant Blood (IgG, IgM) antibodies)	Hulinska et al, 2009; Spector et al 1993
Cord Bood (cellular response – LPA))	Gardner, 2001
Spleen (SS)	Neubert 1987, Schlesinger et al, 1985
Renal tubules (SS)	Schlesinger et al, 1985
Kidneys (Cul)	Neubert 1987, Macdonald 1989, Spector et al, 1993
Adrenal Gland (DK)	MacDonald et al, 1987
Bone marrow (SS)	Schlesinger et al, 1985
Myocardium/heart (IHC)	MacDonald et al, 1987, Macdonald, 1989, Spector et al, 1993
Lungs (DK)	Maraspin et al, 1999
Liver (Cul) (MA) (DK)	Neubert, 1987; MacDonald et al, 1987; Weber et al, 1988; Maraspin et al, 1999
Brain(Cul)(MA)(IFA)(IHC)(DK)	MacDonald et al, 1987, Lavoie et al, 1987; Weber et al, 1988; Maraspin et al, 1999
Eye (SS)(EM)	Spector et al, 1993

SS = silver stain; DK = darkfield microscopy; Cul = culture; IHC = immunohistochemistry;
MA = monoclonal antibodies H5332; IFA = indirect immunofloursence; EM – electron microscopy;
PCR = polymerase chain reaction

Findings highlighted in gold are confirmation of Bb in tissues by PCR.

Findings in green include cases of Bb cultured and in two cases confirmed with monoclonal antibodies MaB H5332.

Findings in orange indicate Bb antibodies or cellular response identified in symptomatic infant cerebral spinal fluid and in infant cord-blood.

Identification of Spirochetes in Fetal/Child Autopsy Tissues

"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 is produces in children and adult patients, which could explain some of the adverse outcomes reported."

Gardner, T. Lyme disease, Chapter 11. In: Remington JK, J. editor. Infectious Diseases of the Fetus and Newborn, 5th ed: Saunders; 2001. pp. 519-641.

Spirochetes identified in Fetal/Infant Brain

1986	33 week stillborn infant. Mother had positive serology (IFA) neg. syphilis. No recall tickbite/symptoms.	Spirochetes identified by darkfield microscopy in infant lung, liver and **brain tissue specimens**.	Maraspin et al; (1999)
1987	Mother had EM rash in first trimester Not treated. Seropositive for Bb at 2/3 labs.	Spirochetes were identified by immunofluorsence in the fetal myocardium, adrenal gland, and **subarachnid space of the midbrain**, and silver stains disclosed rare spirochetes in the myocardium, placenta, liver and **brain**."	MacDonald et al, 1987.
1987	Mother had no history of tickbite or EM rash. Mother had been experiencing arthralgias And fatigue since experiencing horse fly And mosquito bites while camping in Maine in 1971. Was seronegative by ELISA at Yale No cardioilpin antibodies found.	Infant healthy at birth (delivered by C section) died at 8 days Admitted with profound lethargy leading to unresponsiveness, marked peripheral cyanosis, systemic hypertension, metabolic acidosis, Myocardial dysfunction and abdominal aortic thrombosis. **Bb cultured from infant frontal cerebral cortex.** Silver stain confirmed infection in brain and heart.	Lavoie et al., 1987
1988	Infant born initially healthy, died 23 hours later. Mother had tickbite, EM, seropositive.	Bb spirochetes identified in **neonate brain** and liver. Bb identified in paraffin sections of **infant brain** w monoclonal antibody H5332.	Weber et al, 1988
1989	Two cases of neonatal death 4 month male died at 4 months 4 month femake died at 4 months from SIDS.	In both cases spirochetes morphologically consistent with Bb were identified by silver stain in **neonate brain**.	MacDonald, 1989
1989	(Case 7: Fetal Lyme Borreliosis with miscarriage 17 weeks gestation) 2 weeks prior mother had experienced vaginal bleeding and cramping. Post partum Bb serology negative.	Autopsy revealed hydrocephalus and spirochetes identified in **fetal brain by indirect immunofluorescence**.	Macdonald, 1989
1989	(Case 8: Fetal Lyme Borreliosis with Miscarriage at 16 weeks gestation) 2 weeks prior, mother experienced vaginal bleeding, abdominal cramps and low grade fever. Post partum Bb serology negative	Autopsy revealed **spirochetes in fetal brain** with **immunohistochemistry using monoclonal antibodies**, no malformations noted. No inflammation noted in viscera.	MacDonald, 1989

Spirochetes identified in Fetal/Child Heart

Untreated mother had EM in first trimester. Infant had multiple cardiac defects	Autopsy identified widespread cardiac abnormalities Borrelia compatible w Bb identified in spleen, renal tubules/kidney and bone marrow by silver stain. **Bb later identified in Myocardium later by IHC by MacDonald.** Placenta not available for study.	Schlesinger et al. 1985 MacDonald, 1989
Mother had EM rash in first trimester Not treated. Seropositive for Bb at 2/3 labs.	Spirochetes were identified by immunofluorsence in the **fetal myocardium**, adrenal gland, and subarachnid space of the midbrain, and silver stains disclosed rare spirochetes in the **myocardium**, placenta, liver and brain."	MacDonald et al, 1987.

Mother had no history of tickbite or EM rash. Mother had been experiencing arthralgias And fatigue since experiencing horse fly And mosquito bites while camping in Maine in 1971. Was seronegative by ELISA at Yale No cardioilpin antibodies found.	Bb cultured from infant frontal cerebral cortex. **Silver stain** confirmed infection in brain and **heart.**	Lavoie et al., 1987
Mother had been treated for serologically pro Lyme disease over a period of one year before pregnancy.	At 7 years of age the child died because of cerebral complications of congenital Lyme borreliosis. **Autopsy findings** • **Spirochetes also detected** in **heart** and kidneys at autopsy.	Spector et al, 1993

Spirochetes in Fetal / Infant Liver			
1986	Mother had tickbite and EM. Was treated for Bb with antibiotics Serologic tests for Bb positive. Retreated with PCN BID for 14 days and sympton improved. . At follow-up after delivery, mother's serologic tests or Bb were negative.	Infant born at 32 weeks, died hours later. Autopsy of infant revealed hydrocephalus, fluidothorax, ascites but no malformations. **Darkfield microscopy revealed spirochetes** in fetal lung, **liver**. No attempt to culture spirochetes from fetal autopsy tissues.	Maraspin et al., 1999
1986	No recall tickbite/symptoms. Mother had positive serology (IFA) neg. syphilis. Stillbirth at 33 weeks	33 week stillborn infant. **Spirochetes identified by darkfield microscopy** in infant lung, **liver** and brain tissue specimens.	Maraspin et al; (1999)
1987	Miscarriage in early pregnancy due to Lyme disease	'In a still unpublished case of a miscarriage due to Lyme disease in early pregnancy, Borrelia burgdorferi was isolated from the **liver**, spleen and kidneys of the fetus (Russel C. Johnson, personal communication).' (translated from German)	Neubert, 1987.
1985	Mother had EM rash in first trimester Not treated. Seropositive for Bb at 2/3 labs.	Spirochetes were identified by immunofluorsence in the fetal myocardium, adrenal gland, and subarachnid space of the midbrain, and silver stains disclosed rare spirochetes in the myocardium, placenta, **liver** and brain."	MacDonald et al, 1987.
1988	Infant born initially healthy, died 23 hours later. Mother had tickbite, EM, seropositive.	Bb spirochetes identified in **neonate brain** and liver. Bb identified in paraffin sections of **infant brain** w monoclonal antibody H5332.	Weber et al, 1988
1989	(Case 4: Fetal Lyme borreliosis with miscarriage at 15 weeks gestation) Uneventf first trimester of pregnancy. Postpartum Bb serology was negative.	Autopsy revealed spirochetes in **fetal liver** and in placenta. No inflammation in fetal viscera. Bb was identified in tissue by indirect immunofluorescence .	MacDonald, 1989

Spirochetes in Fetal /Child Kidneys			
1987	Miscarriage in early pregnancy due to Lyme disease	'In a still unpublished case of a miscarriage due to Lyme disease in early pregnancy, Borrelia burgdorferi was isolated from the liver, spleen and **kidneys** of the fetus (Russel C. Johnson, personal communication).' (translated from German)	Neubert, 1987.
1989	(Case 9: Fetal Lyme Borreliosis with Miscarriage at 12 weeks gestation). Mother had history of two past pregnancy losses 8 and 26 weeks gestation but neither fetus had been examined histologically.	Culture of fetal viscera in BSK revealed **spirochetes in fetal kidney**. No spirochetes were identfied in fetal viscera using immunohistochemistry.	MacDonal 1989
1993	Mother had been treated for serologically proven Lyme disease over a period of one year before pregnancy.	At 7 years of age the child died because of cerebral complications of congenital Lyme borreliosis. **Autopsy findings** • **Spirochetes also detected** in heart and **kidney**s at autopsy.	Spector et al, 1993

Spirochetes in Infant Renal Tubules			
1985	Untreated mother had EM in first trimester. Infant had multiple cardiac defects	Autopsy identified widespread cardiac abnormalities Borrelia compatible w Bb identified in spleen, **renal tubules** and bone marrow by silver stain. Bb later identified in Myocardium later by IHC by MacDonald. Placenta not available for study.	Schlesinger et al. 1985

Spirochetes in Infant Bone Marrow			
1985	Untreated mother had EM in first trimester. Infant had multiple cardiac defects	Autopsy identified widespread cardiac abnormalities Borrelia compatible w Bb identified in spleen, renal tubules and **bone marrow** by silver stain. Bb later identified in Myocardium later by IHC by MacDonald. Placenta not available for study.	Schlesinger et al. 1985

Spirochetes in Child Eyes (thought to have been infected congenitally)			
1993	Mother had been treated for serologically proven Lyme disease over a period of one year before pregnancy.	**Baby/Child:** Child was diagnosed with Lyme disease in neonatal period proven by serology (ELISA 1:512) and PCR identification of Bb in placental tissues At 7 years of age the child died because of cerebral complications of congenital Lyme borreliosis. **Autopsy findings** • **Retinal pigment epithelium (RPE) focally atrophic and hypertrophic w/ "salt and pepper" appearance to fundus and focal RPE migration into retina** • **Optic nerve atrophic** • **Non-granulomatous choroiditis with rare spirochetes by Warthin-Starry stain in the choroid at the posterior pole. Transmission electron microscopy confirmed their presence in vascular endothelium of the choroid** • Spirochetes also detected in heart and kidneys at autopsy. The Histologic findings suggest that **pigmentary changes in the fundus in congenital Lyme disease are similar to those described in congenital syphilis**. Spirochetes were most likely transmitted from the mother to fetus transplacentally.	Spector et al, 1993

Spirochetes in Fetal/Infant Lungs			
1986	33 week stillborn infant. Mother had positive serology (IFA) neg. syphilis. No recall tickbite/symptoms.	**Spirochetes identified by darkfield microscopy** in infant **lung**, liver and brain tissue specimens.	Maraspin et al; (1999)
1986	Mother had tickbite and EM. Was treated for Bb with antibiotics Serologic tests for Bb positive. Retreated with PCN BID for 14 days and symptoms improved. . At follow-up after delivery, mother's serolog tests or Bb were negative.	Infant born at 32 weeks, died hours later. Autopsy of infant revealed hydrocephalus, fluidothorax, ascites but no malformations. **Darkfield microscopy revealed spirochetes** in **fetal lung,** liver. No attempt to culture spirochetes from fetal autopsy tissues.	Maraspin et al., 1999

Spirochetes in Fetal Adrenal Gland			
1985	Mother had EM rash in first trimester Not treated. Seropositive for Bb at 2/3 labs.	Spirochetes were identified by immunofluorsence in the fetal myocardium, **adrenal gland,** and subarachnid space of the midbrain, and silver stains disclosed rare spirochetes in the myocardium, placenta, liver and brain."	MacDonald et al, 1987.

Spirochetes identified in Fetal/Infant Spleen			
	Untreated mother had EM in first trimester. Infant had multiple cardiac defects	Autopsy identified widespread cardiac abnormalities Borrelia compatible w Bb identified in **spleen,** renal tubules and bone marrow by silver stain. Bb later identified in Myocardium later by IHC by MacDonald. Placenta not available for study.	Schlesinger et al. 1985

1987	Miscarriage in early pregnancy due to Lyme disease	'In a still unpublished case of a miscarriage due to Lyme disease in early pregnancy, Borrelia burgdorferi was isolated from the liver, **spleen** and kidneys of the fetus (Russel C. Johnson, personal communication).' (translated from German)	Neubert, 1987.

Spirochetes in Placenta – with immunohistochemistry, stains, monoclonal antibodes

See pages 21-22 of this document for more details.

Identification of Bb by PCR in Fetal/Placental Tissues

PCR – Fetal Tissue

2003	Mother was diagnosed with Lyme disea prior to Pregnancy. Sero + IgG WB. Antibiotic treatment prior to pregnancy. Miscarriage 18wks	Miscarriage 18wks ; **PCR Bb positive placenta and fetal tissues** at MDL labs	Horowitz, 2003

PCR – Cord blood

2007	13 pregnant patients with EM during pregnancy, treated in pregnancy. Maternal blood, umbilical cord blood and placenta were examined during childbirth. Borrelia was detected in umbilical cord blood and placenta by direct and indirect methods in 3 case	Case 1: **suspected plasmid Bb by PCR in cordblood**; Case 2: positive genome and suspected plasmid in placenta along w electron microscope detection in placenta, Child 3: **suspected genome and plasmid in umbilical cord blood** and positive genome w suspected plasmid in placenta.	Vanousova e al, 2007

PCR – Placenta

See page 21-23 of document for full details of histological and PCR findings of Bb in Placenta

PCR – Breastmilk

See page 34 and 39-40 (animals studies regarding oral transmission of Bb)

Identification of Bb antibody in Cerebral Spinal Fluid (CSF) of Symptomatic Infants

Bb specific antibody identified in CSF			
1989	Mother infected in second trimester. Treated for Lyme. Seronegative. 'The mother, who was asymptomatic, had been treated with oral antibiotics did not have diagnostic levels of antibodies to Bb at time of parturition.'	Baby was born with neurologic dysfunction. Spinal tap on neonate **reveals serological evidence of antibodies specific to borrelia in CSF.**	Dattwyler et al, 1989
1992	No maternal tick bite, no EM Asymptomatic, Maternal serology revealed significantly increased IgM titer and slightly increased IgG. Untreated pregnancy	3 day old newborn diagnosed with sepsis and treated with antibiotics. No other details given. **Increased IgM and IgG Bb antibodies in infant blood and CSF**. Negative for syphilis and mononucleosis.	Horst, 1993

Identification of Bb antibody in infant and cord blood

1 case of Bb IgG and IgM Antibodies identified in infant born to treated mother

2009	A pregnant woman (no.12) was treated for Lyme disease and had positive IgM and IgG to Ap and Bbsl in the blood after bearing twins.	One twin had positive IgG and IgM antibodies against Bb. No other information given.	Hulinska et al, 2009

1 case of positive Bb ELISA in infant born to treated mother

1993	Mother had been treated for serologically proven Lyme disease over a period of one year before pregnancy.	**Baby/Child:** Child was diagnosed with Lyme disease in neonatal period **proven by serology (ELISA 1:512) and PCR identification of Bb in placental tissues**	Spector et al, 1993

Identification of cellular response to Bb in infant cord blood

See 67-69 for details

Live birth, congenital infection and subsequent death age 7

Transplacental passage of B. burgdorferi can occur and has been associated with congenital heart disease, developmental delay, cortical blindness, spontaneous abortion, and stillbirth.'

Eichenfield AH, Athreya BH. Lyme disease: of ticks and titers. J Pediatr. 1989 Feb;114(2):328-33. doi: 10.1016/s0022-3476(89)80808-x. PMID: 2644410.

"Transplacental transmission of B burgdorferi in humans has been documented in association with adverse fetal outcomes"

"Studies in both human and animal models have established that B. burgdorferi can cross the placenta, presumably occurring during a period of spirochetemia."

"Because gestational Lyme disease has been clearly linked to fetal loss in animal studies, the potential for a causal effect in human gestational LD exists."

Elliot D, Eppes S, Klein, J. Teratogen Update: Lyme Disease. Teratology 64:276-281, 2001.

"During gestation B. Burgdorferi may spread transplacentally to the fetus, causing adverse outcome of the pregnancy, including various congenital abnormalities, premature birth and even fetal death."

"When spirochetemia occurs during pregnancy, the placenta may be involved and the fetus infected. Transplacental transmission of B. Burgdorferi has been well documented and may result in various forms of fetal involvement."

Maraspin, V., Cimperman, J., Lotric-Furlan, S., Pleterski-Rigler, D., & Strle, F. (1996). Treatment of erythema migrans in pregnancy. Clinical infectious diseases: an official publication of the Infectious Diseases Society of America, 22(5), 788-793.

1993	Mother had been treated for serologically proven Lyme disease over a period of one year before pregnancy.	**Baby/Child:** Child was diagnosed with Lyme disease in neonatal period proven by serology (ELISA 1:512) and PCR identification of Bb in placental tissues At 7 years of age the child died because of cerebral complications of congenital Lyme borreliosis. **Autopsy findings** • Retinal pigment epithelium (RPE) focally atrophic and hypertrophic w/ "salt and pepper" appearance to fundus and focal RPE migration into retina • Optic nerve atrophic • Non-granulomatous choroiditis with rare spirochetes by Warthin-Starry stain in the choroid at the posterior pole. Transmission electron microscopy confirmed their presence in vascular endothelium of the choroid • Spirochetes also detected in heart and kidneys at autopsy. The Histologic findings suggest that **pigmentary changes in the fundus in congenital Lyme disease are similar to those described in congenital syphilis**. Spirochetes were most likely transmitted from the mother to fetus transplacentally.	Spector et al, 1993

Citation:

Spector, R, Rummelt, V, Folbert R (1993). The pathology of ocular congenital Lyme borreliosis [abstract] In: Association for Research in Vision and Ophthalmology annual meeting; May 2-7, 1993, Sarasota, Florida. Rockville, MD: Invest Ophthalmol Vis Sci; 1993. Abstract 1466-27.

Live birth, congenital infection and subsequent neonatal death

'Well-documented cases of fetal infection have been reported describing stillbirth and infant demise shortly after birth due to disseminated B burgdorferi infection acquired in utero. In these cases, obvious disseminated infection occurred during pregnancy and was either untreated or inadequately treated according to treatment guidelines.'

Rahn DW. Lyme disease: clinical manifestations, diagnosis and treatment. Semin Arthritis Rheum. 1991. Feb; 20(4):201-18.

"There is currently very limited information about Lyme disease infection during pregnancy. Presently there is no conclusive evidence that Lyme disease produces an increase in spontaneous abortions, stillbirth, or fetal abnormalities. However, there have been several reports of the Lyme bacteria being found in stillborns, and in infants born with severe abnormalities. Therefore, pregnant women should be promptly treated if suspected of having been infected.

CDC Prevention Guidelines Database (Archive). Vector-Borne Diseases (Lyme disease, Japanese Encephalitis, Yellow Fever.). Publication date 08/01/1991.

'In cases of intrauteral fetal infections among patients with Lyme disease, symptoms are not homogeneous. Thus, confirming that B. burgdorferi s.l. is transmitted transplacentally may play important role in the spreading of these pathogens."

Jasik KP, Okła H, Słodki J, Rozwadowska B, Słodki A, Rupik W. Congenital Tick Borne Diseases: Is This An Alternative Route of Transmission of Tick-Borne Pathogens In Mammals? Vector Borne Zoonotic Dis. 2015 Nov;15(11):637-44.

1 case Bb cultured
4 cases Borrelia/spirochetal fragments identified by IHC/IFA/H5332
1 case spirochetes identified by darkfield microscopy (mother seropos for Bb)
2 cases (SIDS) spirochetes morphologically compatible w Bb by silver stain.

1985	28 yr. woman EM rash – first trimester camping in Wisconsin No antibiotic therapy Lyme serology IFA positive postpartum i	Infant born at 35 weeks, died after 39 hours. **Autopsy identified widespread cardiac abnormalities** **Borrelia compatible w Bb identified in spleen,** **renal tubules/kidney and bone marrow by silver stain**. Bb later identified in Myocardium later by IHC by MacDonald. Placenta not available for study.	Schlesinger et al. 1985 MacDonald, 1989
1986	Mother had tickbite and EM. Was treated for Bb with phenoxymethyl penicillin 1 million IU TID for 10 days and skin lesion disappeard. End of second trimester developed vertigo. Lumbar puncture Identified elevated concentration of proteins and leukocytes. Serologic tests for Bb positive. Retreated with PCN BID for 14 days and symptoms improved. At 32 weeks gestation delivered a female infant. seropositive. At follow-up after delivery, mother's serologic tests for Bb were negative	Infant born at 32 weeks, died hours later. Autopsy of infant revealed hydrocephalus, fluidothorax, ascites but no malformations. **Darkfield microscopy revealed spirochetes** in fetal lung, liver. No attempt to culture spirochetes from fetal autopsy tissues.	Maraspin et al., 1999
1987	Mother had no history of tickbite or EM rash. Mother had been experiencing arthralgias And fatigue since experiencing horse fly And mosquito bites while camping in Maine in 1971. Was seronegative by ELISA at Yale No cardioilpin antibodies found.	Infant healthy at birth (delivered by C section, died at 8 days) Admitted with profound lethargy leading to unresponsiveness, marked Peripheral cyanosis, systemic hypertension, metabolic acidosis, Myocardial dysfunction and abdominal aortic thrombosis. Bb **cultured** from infant frontal cerebral cortex. Silver stain **confirmed infection in brain and heart**.	Lavoie et al., 1987
1988	Mother had tickbite, EM, Initial testing for IgM and IgG antibody titers against Bb were negative Reexamination of the sera when other tests were available years later yielded a significant rise in antibody in the IgM ELISA indirect Hemagglutination test. IgG ELISA negative. Was treated with oral penicillin three times daily for a week.	Infant born initially healthy, developed respiratory distress died 23 hours later. Death probably due to espiratory failure due to consequence of perinatal brain damage. Autopsy - R side scalp was a swollen and hemorrhagic area but no skull fract Brain showed no bleeding or rupture other than a small infratentorial hemorrhage. In the tentorium and falx cerebri, a few small hemorrhages we discovered. No significant inflammation found in any organ including heart, liver, brain and kidney. Immunohistologic examination of cerebral tissue and matrix of brain for leukocyte antigen was negative. A small perivenous hemorrhage with	Weber et al, 1988

		minor aggregates of leukocytes was detected in pons. Lungs showed extreme congestion, microscopic edema and a small amount amniotic fluid without inflammatory signs. Cardivascular system showed no malformations. **Bb spirochetes identified in neonate brain and liver.** Bb identified in paraffin sections of infant brain using monoclonal antibody H5332. Placenta not available for study	
1989	**Case 5: Fetal Lyme Borreliosis in Term Deliv and Postnatal Death after 4 hours.** 25 yr mother presented in labor in 39 weeks pregnancy. Anepartum course remarkable for brief episode of vaginal bleeding in second month of pregnancy.	Live birth 39 weeks died shortly thereafter. Multiple anomalies at delivery including hydrocephalus, omphalocoele, clubfoot, spina bifida and meningomyelocele. Respiratory distress developed and 4 hours later infant died. Autopsy discloed a large ventriculoseptal defect as an additional malformation. Spirochetes i**dentified by immunohistochemistry in fetal tissue.**	Macdonald, 1989
1989	**Case 6: Fetal Borreliosis, Term Pregnancy, with Postnatal Death at 30 minutes.** 33 yr woman admitted week 40 of pregnancy.	Uterine growth retardation detected by serial obstetrical ultrasound examinations. 1950g female infant born at 40 weeks showed profound bradycardia with progressive decline in cardiac output despite maximun suport in neonatal nursery. Autopsy revealed a large ventriculoseptal defect and showed an Absence of the left hemidiaphragm with herniation of Abdominal viscera into the left hemithorax. **Spirochetal fragments identified in fetal autopsy tissue by indirect immunofloursence**.	Macdonald, 1989
1989	Two cases of neonatal death 4 month male died at 4 months 4 month femake died at 4 months from SIDS.	In both cases spirochetes **morphologically consistent with Bb were identified by silver stain in neonate brain.**	MacDonald, 1989

Live birth and neonatal death
(mothers treated in first trimster for Lyme infection, silver stain negative. Culture and PCR of fetal tissues not performed.)

1999	**Case 1:** 26 yr woman developed EM 2 weeks after tick bite – four weeks prior to second pregnancy. EM was recorded at 6 weeks gestation, EM disappeared after antibiotic treatment. At 25 weeks delivered a boy who died within minutes.	Autopsy baby showed no malformations. Histology of tissues revealed chorioamniotis and vasculitis of umbilical vessels. Silver stain did not reveal spirochetes, placenta was normal. Culture and PCR of Bb from fetal tissues not performed.	Maraspin et al, 1999
1999	**Case 2: 25 yr woman** noted EM associated with mild itching in 10th week pregnancy after insect bite, disappeared 16 days after antibiotic treatment. At 25 weeks she gave birth to a girl who died immedately at birth.	Autopsy baby showed no malformations. Histology tissues showed no marked abnormality. Silver stain did not reveal spirochetes. Placenta was normal. Culture and PCR detection from fetal tissues not performed.	Maraspin et al,1999

Citations:

1. Schlesinger PA, Duray PH, Burke BA, Steere AC and Stillman MT. Maternal-Fetal transmission of the Lyme disease spirochete, Borrelia Burgdorferi. Ann Intern Med. 1985;103(1):67-8
2. Maraspin V, Cimperman J, Lotric-Furlan, S et al. Erythema migrans in pregnancy. Wein Klin Wochenschr (1999) 111/22-23:933-940.
3. Lavoie PE, Lattner BP, Duray PH, Barbour AG, Johnson RC. Culture positive seronegative transplacental Lyme Borreliosis infant mortality (1987) Arthritis Rheum, 30(4), 3(suppl):S50
4. Weber K, Bratzke H, Neubert UWE et al. Borrelia Burgdorferi in a newborn despite oral penicillin for Lyme borreliosis during pregnancy. Pediatric Infectious Disease Journal Vol 7, No 4, 286-289, 1988
5. MacDonald A. Gestational Lyme Borreliosis. Implications for the fetus. Rheum Dis Clin North Am. 1989 Nov;15(4):657-77.

Stillbirth/Intrauterine Fetal Death (IUFD)

"Pregnant women should seek treatment for Lyme disease as soon as possible as Lyme disease can cause stillbirth if left untreated.'

Pennsylvania Public Health. Accessed May 2022: https://www.health.pa.gov/topics/disease/Vectorborne%20Diseases/Pages/Lyme.aspx#

Transplacental infections associated with IUFD include cytomegalovirus30 (Evidence level 2+), syphilis31–34 (Evidence level 1+) and parvovirus B1934,35 (Evidence level 2++) as well as listeria36,37 (Evidence level 2+), rubella38 (Evidence level 3), toxoplasmosis33,34 (Evidence level 2+), herpes simplex30 (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++).

Royal College of Obstetricians and Gynaecologists. Green-top Guideline No. 55: Late Intrauterine Fetal Death and Stillbirth (2010, reaffirmed 2014/2017)). Retrieved June, 2022 from https://www.rcog.org.uk/en/guidelines-research-services/guidelines/gtg55/.

'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.

'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.

"In recent years, Lyme disease, a systemic illness caused by tick-borne spirochete Borrelia burgdorferi also has been shown to cause stillbirth. The first cases of perinatal transmission were described in the mid 1980's, and the first case of stillbirth associated with Lyme disease was described in 1987." "In other reports, after first trimester infection and subsequent fetal deaths, spirochetes have been found in fetal liver, spleen, kidney, hepatic vein lumen and brain tissue. Subsequently, small series of stillbirths after maternal Lyme disease have been described with most deaths occurring in the mid trimester."

Goldenberg, R.L., & Thompson, C. (2003). The infectious origins of stillbirth. American Journal of Obstetrics and Gynecology, 189(3), 861-873.

'"Spirochetes cross the placenta and have been found in fetuses; however, the frequency of fetal infection is unknown. Hence the obstetric dilemma is when to treat women who are suspected of having early-onset Lyme disease but are sero-negative. It may be preferable to treat pregnant patients on the basis of the described clinical picture prior to the development of late maternal disease."

ACOG Committee Opinion: Committee on Obstetrics: Maternal and Fetal Medicine. Lyme disease during pregnancy. Int J. Gynecol Obstet 1992, 39; 59-60

5 cases Bb identified in fetal/placental tissues

- 1 case Bb identified by culture and monoclonal antibody H5332
- 1 case spirochetes identified by darkfield microscopy of mother seropositive for Bb
- 2 case Bb identified by indirect immunofluorescence
- 1 case Bb identified in placenta by PCR

1986	Pregnant mother delivered a stillborn infant at 34 weeks. Prenatal record negative for infections. No recall of tickbite and no symptoms suggestive of Lyme borreliosis no medication taken during gestation. Positive Bb IgG serology (IFA) negative syphilis testing Subsequently treated with doxycycline for three weeks after delivery six months later serology Bb negative.	33 week stillborn infant. Upon autopsy of fetus: cutaneous macerations, fluidothorax, ascites, hepatoplenomegaly. Histological examination of tissues revealed only mild predominantly perivascular lymphocytic infiltration. Clinically, congenital syphilis was suspected however maternal syphilis tests were negative and Bb IgG antibody tests (IFA) were positive. Spirochetes identified by darkfield microscopy in lung, liver and brain tissue specimens.	Maraspin et al; (1999)
1986/1987 /1989	**Case 1: Fetal Lyme Borreliosis with Ventriculoseptal Defect** Mother had EM rash in first trimester Not treated. Seropositive for Bb at 2/3 labs.	40 week term stillborn infant. IUGR Concurrance of first trimester infection with events of cardiac organogenesis and subsequent identification of ventriculoseptal defect. Bb cultured from fetal liver of stillborn infant and confirmed w H5332 monoclonal antibody. Silver stains revealed spirochetes in myocardium, placenta, liver and brain.	Macdonald et al; 1987/1989

		Immunofluorescence revealed spirochetes in heart, adrenal gland, placenta +mid-brain	
1986/1989	(Case 3) stillbirth 23 weeks. No medical history for Lyme or Tickbite. Mother was seroneg for Bb	B. burgdorferi was identified in tissue by indirect immunofluorescence.	Macdonald, 1986/1989.
1989	(Case 10) intrauterine death at 25 weeks. No infections noted for mother, was nonreactive for Bb.	Autopsy revealed intraventricular septal defect without additional internal anomalies. Bb was identified in autopsy tissue by indirect immunofluorescence.	Macdonald, 1989
2009	Mother was treated for (EM) Lyme in first trimester. Stillbirth reported 29 weeks.	Stillbirth reported at 29 weeks. Borrelia garinni (strain 840) was isolated from the placenta by PCR.	Hulinska et al, 2009

Other reported cases of stillbirth/Intrauterine fetal death associated with maternal Lyme disease

1 case intrauterine fetal death at 20 weeks (treated mother)

- Culture and IFA of placenta and fetal tissues negative for Bb.

1986	Mother treated with oral PCN for ten days after onset of EM week 6 pregnancy followed by stiff neck and headache one week later. IFA 1:512 positive to Bb. At 20 weeks intrauterine fetal death was documented by ultrasound.	The placenta was hypoperfused and membranes exhibited autolytic change. Microscopic exam exhibited autolysis of fetal tissues and an immature placenta with presence of syncytial and cytotrophoblastic elements. There were no inflammatory elements. Culture and IFA of placenta and fetal tissues were negative for Bb.	Markowitz et al; 1986

1 case stillbirth in untreated mother

- Culture/PCR of fetal tissue/placenta not performed

2010	Untreated mother: her first visit to clinic was 4 days after stillbirth at 5 months gestation when a 30cm EM noted.	Stillbirth 5 months gestation. No other details given but author mentions 'placentas and offspring were not tested for Borrelia by PCR or culture in our study'	Lakos, 2010

Citations:

1. Markowitz LE, Steere AC, Benach JL, Slade JD, Broome CV. Lyme Disease During Pregnancy. *JAMA.* 1986;255(24):3394–3396.
2. Maraspin V, Cimperman J, Lotric-Furlan, S et al. Erythema migrans in pregnancy. Wein Klin Wochenschr (1999) 111/22-23:933-940.
3. MacDonald AB. Human fetal borreliosis, toxemia of pregnancy and fetal death. Zentralbl Bakt Mikrobiol Hyg A. 1986 Dec;263(1-2):189-200.
4. MacDonald A, Benach J, Burgdorfer W. Stillbirth following Maternal Lyme Disease. New York State Journal of Medicine vol 87, Nov 1987.
5. MacDonald A. Gestational Lyme Borreliosis. Implications for the fetus. Rheum Dis Clin North Am. 1989 Nov;15(4):657-77
6. Hulinska D, Votypka J, Vanousova D, Hercogova J, et al. Identification of anaplasma phagocytophilum and Borrelia Burgdorferi sensu lato in Patients with Erythema Migrans Folia Microbiol.54 (3), 246-256.
7. Lakos, A., & Solymosi, N. (2010). Maternal Lyme borreliosis and pregnancy outcome. International Journal of Infectious Diseases, 14(6), e494–e498. doi:10.1016/j.ijid.2009.07.019.

Miscarriage

"The data accumulated to date indicate that Lyme disease represents a serious risk factor in pregnancy: it increases the likelihood of miscarriage, has a teratogenic effect on the fetus in intrauterine infection and increases the indicators of perinatal mortality."

Elsukova L, Korenberg E, Kozin G. The Pathology of Pregnancy and the Fetus in Lyme disease. Meditsinskaia parazitologiia i parazitarnye bolezni, Oct, 1994. *translated from Russian

"Vertical transmission of B. Burgdorferi has been demonstrated, and there are anecdotal reports of Lyme disease during pregnancy complicated by birth defects, miscarriages, stillbirths and neonatal deaths."

Bracero LA, Wormser GP., et al. Prevalence of Seropositivity to the Lyme disease Spirochete during Pregnancy in an Epidemic area: A preliminary report. Journal of Maternal-Fetal Investigation (1992) 2:265-268.

"In a prospective study of abortuses in an area endemic for Lyme disease four cases of fetal borreliosis were described with B. burgdorferi isolated from fetal liver.33 This observation suggests that B. burgdorferi may be an etiologic agent in fetal demise of uncertain cause. The risk to infants of asymptomatic women with positive serologies for Lyme disease has been explored through analysis of cord blood for anti-B. burgdorferi antibodies. No association was noted between the presence of anti-B. burgdorferi antibodies in cord blood and the occurrence of congenital malformations, although seropositive babies tended to have a lower birthweight by 150grams. The development of these infants warrants further observation, especially since in another spirochetal infection, congenital syphilis, abnormalities are not always evident at birth."

Trock DG, Craft JE, Rahn DW. Clinical manifestations of Lyme disease in the United States. Conn Med. 1989. June;53(6):327-30.

'There is little doubt that the minute filterable form of bacteria move from the mother's capillaries to those of the fetus. This has been documented by MacDonald. Congenital syphilis has long been documented in textbooks, but congenital Lyme disease has been acknowledged only recently. Often, only one fraternal twin acquires the infection. Unfortunately, Borrelia burgdorferi attacks multiple tissues of the fetus, which may result in fetal loss. This is true even when the mother lacks circulating antibody to the organism to suggest her infection. Obviously, her antibody is tied up in immune complexes.'

Mattman LH. Cell Wall Deficient Forms. 3rd Edition. Chapter 37: The Placenta. CRC Press Taylor & Francis Group, 2001.

"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."

U.S Department of Health and Human Services. National Institutes of Health. Lyme Disease, The Facts, The Challenge. NIH Publication No. 03-7045 (April 2003) and NIH Publication No. 05-7045 (May 2005).

8 cases of miscarriage w Bb identified in fetal tissues:

- **3 cases Bb was identified by immunofluorescence in fetal tissue**
- **1 case spirochetes identified in culture**
- **1 case Bb identified w immunohistochemistry using monoclonal antibodies**
- **1 case Borrelia identified by electron microscopy and monoclonal antibodies**
- **1 case Bb identified in fetal tissue and placenta by PCR**

1987	Miscarriage in early pregnancy due to Lyme disease	'In a still unpublished case of a miscarriage due to Lyme disease in early pregnancy, **Borrelia burgdorferi was isolated from the liver, spleen and kidneys of the fetus**.'	Neubert, 1987
1989	(Case 2: Fetal Lyme borreliosis with miscarriage 19 week gestation) No maternal recall of tickbite or EM rash. Severe toxemia of pregnancy in week 17. Post partum serology for Bb negative at 2 labs.	Autopsy revealed **Bb was in fetal tissue by indirect immunofluorescence.**	MacDonald, 1986, 1989
1989	(Case 4: Fetal Lyme borreliosis with miscarriage at 15 weeks gestation) Uneventul first trimester of pregnancy. Postpartum Bb serology was negative.	Autopsy revealed spirochetes in fetal liver and in placenta. No inflammation in fetal viscera. **Bb was identified in tissue by indirect immunofluorescence** .	MacDonald, 1986, 1989
1989	(Case 7: Fetal Lyme Borreliosis with miscarriage 17 weeks gestation) 2 weeks prior mother had experienced vaginal bleeding and cramping. Post partum Bb serology negative.	Autopsy revealed hydrocephalus and spirochetes identified in **fetal brain by indirect immunofluorescence**.	Macdonald, 1989

1989	(Case 8: Fetal Lyme Borreliosis with Miscarriage at 16 weeks gestation) 2 weeks prior, mother experienced vaginal bleeding, abdominal cramps and low grade fever. Post partum Bb serology negative	Autopsy revealed **spirochetes in fetal brain** with immunohistochemistry **using monoclonal antibodies,** no malformations noted. No inflammation noted in viscera.	MacDonald, 1989
1989	(Case 9: Fetal Lyme Borreliosis with Miscarriage at 12 weeks gestation). Mother had history of two past pregnancy losses at 8 and 26 weeks gestation but neither fetus had been examined histologically.	Culture of fetal viscera in BSK revealed **spirochetes in fetal kidney**. No spirochetes were identfied in fetal viscera using immunohistochemistry.	MacDonald, 1989
2003	Mother was diagnosed with Lyme disease prior to Pregnancy. Sero + IgG WB. Antibiotic treatment prior to pregnancy Miscarriage 18wks	Miscarriage 18wks ; **PCR Bb positive placenta and fetal tissues** at MDL labs	Horowitz, 2003
2008	Pregnant woman with disseminated Lyme borreliosis with EM/arthralgia/paresthesia Treated with oral PCN for 5 days week 10 and retreatment week 14, positive LB serology	15 weeks Intrauterine fetal death. **Borrelia like organisms in ultrathin sections of placenta detected using monoclonal antibody H9724** against flagellin. (description from Maraspin, 2020).	Hercagova, 2008; Maraspin, 2020

Miscarriage associated with Maternal Lyme disease

Note: In one case below (Cielsielski), culture and stain was negative. All other cases combined, 20 cases, placentas/fetal tissue not tested for Bb by PCR or culture, therefore uncertain of Bb involvement.

1987	Woman acquired LD at 4 wks gestation had a missed abortion at 13 weeks.	Missed abortion at 13 weeks. 'Cultures and stains have not documented Bb as the etiology.'	Cielsielski et al., 1987
1988	Bb specific antibody was detected in a group of 6 of 49 (12.2%) of patients with a spontaneous abortion, compared to 3/49 term pregnancies. Test used was IFA (indirect immunofluorescence). A titre of specific IgG greater than or equal to 1:64 was considered positive.	4/6 reported a tickbite in a period ranging from 6-36 months prior to the abortion. 1/6 reported skin lesions and symptoms 1/6 reported antimicrobial treatment for other reasons following tick bite and prior to abortion. In term pregnancy group, none remembered a tickbite or EM and all delive healthy full term infants. **No mention of testing placentas/abortion material for Bb in these cases** but authors state: 'Necessity for routine serological screening of pregnant patients living in endemic areas has been suggested and seems to be supported by our data, given the frequency of cases in which the early infection symptoms were presumably misdiagnosed.' 'Parrafin sections of placental tissues and abortion material from every seropositive or clinically suspected case should be examined by indirect immunofluorescence and silver stain, to evaluate transplacental transmission.'	Carlomagno Et al, 1988
2010	6 patients with diagnosed Lyme disease with spontaneous abortion. Treatment status uncertain in these cases.	'Pregnancy loss most often occurred when the infection was acquired in the first weeks of pregnancy. Five of the pregnancy losses occurred in the 8th week of gestation and one in the 13th week. 'We have no information regarding any morphological exams done on these pregnancy losses.' '**Placentas and offspring were not tested for Borrelia by PCR or culture in our study.** Therefore, it cannot be concluded that the adverse outcomes were a result of Borrelia invasion of the fetus or placenta.'	Lakos et al, 2010
2020	8 cases of fetal death/miscarriage reported in larger series of pregnant patients diagnosed with EM rash in pregnancy and subsequently treated with antibiotics. 'Pregnant women were enrolled at the gestation week when they were diagnosed with EM and	Case 1 (1998); 11 weeks. Case 3 (2002); 16 weeks Case 4 (2008); 10 weeks. Case 6 (1997); 10 weeks Case 8 (2008); 10 weeks. Case 10 (2010); 10 weeks Case 11 (1993); 9 weeks. Case 18 (2009) 12 weeks '**we did not demonstrate the direct detection of borreliae in fetal tissue or umbilical blood, etc., which is a substantial limitation of the present study**, we do not know whether a relatively favorable outcome	Maraspin et al, 2020

	left the study at delivery or at the gestation week of an unfavorable event.'	of pregnancy is the result of our efficacious antibiotic treatment or a consequence of very rare or perhaps even non-existent borrelial involvement in the offspring.'	

Citations:

1. MacDonald AB. Human fetal borreliosis, toxemia of pregnancy and fetal death. Zentralbl Bakt Mikrobiol Hyg A. 1986 Dec;263(1-2):189-200.
2. MacDonald A. Gestational Lyme Borreliosis. Implications for the fetus. Rheum Dis Clin North Am. 1989 Nov;15(4):657-77.
3. Neubert, U. (1987): Erythema migrans in der Gravidität. Hautarzt; 38: 182-183.
4. Ciesielski, CA., Russell H., Johnson S, et al. Prospective Study of Pregnancy Outcomes in Women with Lyme disease. Abstract #39. 27th Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC), New York, 1987.
5. Carlomagno, G., Luksa, V., Candussi, G., Rizzi, G. M., & Trevisan, G. (1988). Lyme Borrelia positive serology associated with spontaneous abortion in an endemic Italian area. Acta Europaea fertilitatis, 19(5), 279–281.
6. Horowitz R, Yunker LL. Lyme Disease and Pregnancy: Implications of Chronic Infection, PCR testing and Prenatal Treatment Case Presentation. 16th International Scientific Conference on Lyme Disease and other Tick-Borne Diseases. June 7, 8, 2003.
7. Hercogova J, Vanousova D. Syphilis and borreliosis during pregnancy. Dermatol Ther. 2008 May-Jun;21(3):205-9.
8. Lakos, A., & Solymosi, N. (2010). Maternal Lyme borreliosis and pregnancy outcome. International Journal of Infectious Diseases, 14(6), e494–e498. doi:10.1016/j.ijid.2009.07.019 https://pubmed.ncbi.nlm.nih.gov/19926325/
9. 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(8):2364.

Lack of Inflammation in Fetal Tissues with Bb invasion

'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. The chorionic villi of the placenta show an increase of 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. **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**."

Duray PH, Steere AC. Clinical pathologic correlations of Lyme disease by stage. Ann N Y Acad Sci 1988;539:65-79

'Tissue inflammation is absent in fetuses with transplacentally acquired Bb infection.'

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

Cortical blindness and cardiac abnormalities have been described in fetuses after infection of the mother with B. burgdorferi during the early stages of pregnancy. However, no inflammatory infiltrates were found in the organs of these infants (Schlesinger et al. 1985; Weber et al. 1988).

De Koning J., Duray PH. Histopathology of Human Lyme borreliosis. In: Weber K, Burgdorfer W (eds) Aspects of Lyme Borreliosis. Springer-Verlag Berlin Heidelberg 1993. ISBN-13:978-3-642-77616-8

'Figure 7-9: Single B. burgdorferi spirochete in the spleen of a newborn infant whose mother had gestational Lyme borreliosis during the first trimester. Neonatal borreliosis is not associated with the degree of inflammatory cell responses seen in adult cases.'

Duray, P. Histopathology of Human Borreliosis. In: Chapter 7. In: Coyle PK. (ed) Lyme disease. Mosby Year Book, 1992. p. 49-58.

Cases of congenital Lyme disease have reported autopsy findings whereby *B. burgdorferi* spirochetes were identified in fetal/infant tissue specimens with either a minimal or lack of inflammatory infiltrates or cell response. See descriptions below:

Findings	Citation
"An autopsy of the infant showed widespread congenital cardiovascular abnormalities. Tubular hypoplasia of the ascending aorta and aortic arch, marked endocardial fibroelastosis and a persistent left superior vena cava draining into the coronary sinus was found. **There was no evidence of inflammation, no necrosis or granuloma formation in the heart or other organs.** The placenta was not available for study. Paraffin block sections of the viscera were stained later by a modification of the Dieterle method. A few spirochetes, morphologically compatible with the Lyme disease spirochete were found in the spleen, renal tubles and bone marrow."	Schlesinger et al, 1985
"**Routine sections of fetal tisues showed mild autolysis and no significant inflammation.** Placental tissues showed rare plasma cells in isolated villi. S pirochetes were identified by immunofluorsence in the fetal myocardium, adrenal gland, and subarachnid space of the midbrain, and silver stains disclosed rare spirochetes in the myocardium, placenta, liver and brain."	MacDonald Et al, 1987
Immunohistologic examination of cerebral tissue and matrix of brain for leukocyte antigen was negative. **No significant inflammation found in any organ including heart, liver, brain and kidney.** A small perivenous hemorrhage with minor aggregates of leukocytes was detected in pons. Lungs showed extreme congestion, microscopic edema and a small amount of amniotic fluid **without inflammatory signs**. Cardivascular system showed no malformations. Bb spirochetes identified in neonate brain and liver. Bb identified in paraffin sections of infant brain using monoclonal antibody H5332. Placenta not available for study	Weber et al, 1988

Citations:

1. Schlesinger PA, Duray PH, Burke BA, Steere AC and Stillman MT. Maternal-Fetal transmission of the Lyme disease spirochete, Borrelia Burgdorferi. Ann Intern Med. 1985;103(1):67-8
2. MacDonald A, Benach J, Burgdorfer W. Stillbirth following Maternal Lyme Disease. New York State Journal of Medicine vol 87, Nov 1987.
3. Weber K, Bratzke H, Neubert UWE et al. Borrelia Burgdorferi in a newborn despite oral penicillin for Lyme borreliosis during pregnancy. Pediatric Infectious Disease Journal Vol 7, No 4, 286-289, 1988

Minimal inflammatory response despite *B. burgdorferi* spirochetal presence has also been reported in experimental studies of hamsters infected intraperitoneally, beagle pups/fetuses infected with Bb in-utero, from biopsy samples from human brain tissue and in a case of latent Lyme neuroborreliosis where the organism was cultured and isolated from the cerebral spinal fluid of a patient without accompanying inflammatory changes.

- **Bb in Hamsters without inflammation:** Duray PH, Johnson RC. The histopathology of experimentally infected hamsters with the Lyme disease spirochete, Borrelia burgdorferi. Proc Soc Exp Biol Med. 1986 Feb;181(2):263-9

- **Bb in Neonatal Pup tissues without inflammation**. Gustafson JM, Burgess EC, Wachal MD, Steinberg H. Intrauterine transmission of Borrelia burgdorferi in dogs. Am J Vet Res. 1993 Jun;54(6):882-90. PMID: 8323057.

- **Bb in Human brain w/o inflammation:** Pachner, AR., Duray P, Steere AC. Central nervous system manifestations of Lyme disease. Arch Neuro. Vol 46, 1989. 790-795.

- **Bb in CSF w/o inflammation**: Pfister HW., Preac-Mursic V., Wilske B et al. Latent Lyme neuroborreliosis: Presence of Borrelia burgdorferi in the cerebrospinal fluid without concurrent inflammatory signs. Neurology 39, August, 1989

In congenital syphilis, spirochetal invasion of fetal tissue with Treponema pallidum without a corresponding inflammatory response has similarly been reported:

- Stowens, D. Pediatric Pathology. Chapter 14: Diseases Caused by Spirochetes (p. 185-203). 1959, The Williams and Wilkins Company.

- Harter C, Benirschke K. Fetal syphilis in the first trimester. Am J Obstet Gynecol. 1976 Apr 1;124(7):705-11. doi: 10.1016/s0002-9378(16)33340-3. PMID: 56895.

One expert in congenital syphilis hypothesized that this phenomenon occurs as the result of a human fetus being 'immunologically incompetent' to respond to foreign antigen in early gestation thus resulting in an inability to mount an immunologic response to a foreign organism.

- Silverstein, A. Congenital Syphilis and the Timing of Immunogenesis in the Human Fœtus. *Nature* **194,** 196–197 (1962). https://doi.org/10.1038/194196a0
- Silverstein, A. The immunologic modulation of infectious disease pathogenesis. Friedenwald Lecture, 1973. Invest Ophthalmol 13: 560 – 574, 1974.

Borrelia burgdorferi identified in Placenta

"At the time of childbirth, the placenta should be examined for histologic abnormalities and for spirochetes, as in congenital syphilis.'

Schelsinger PA, Duray PH, Burke BA, Steere AC and Stillman MT. Maternal-fetal transmission of the Lyme disease spirochete, Borrelia burgdorferi. Ann Intern Med. 1985;103(1):67-8.

"There is no placental protection or barrier that protects the fetus from the spirochete once the microbe has entered the maternal bloodstream. Therefore if we seek the truth, we must seek the spirochete directly by pathologic study of available tissues from the products of conception."

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

"If you suspect that Lyme disease has caused a patients miscarriage, stillbirth or neonatal death, your lab may be able to culture the spirochete from the placenta or infant's organs. Fixed tissues prepared with special stains may also reveal spirochetes, which can exist in small numbers."

Williams, CL., Strobino BA. Lyme disease transmission during pregnancy. Contemporary Ob/Gyn, June 1990. Pg. 48-54.

17 cases Bb identified in Placenta by PCR in treated pregnancies.

1993 (1 case)	Mother had been **treated** for serologically proven Lyme disease over a period of one year before pregnancy.	Baby/Child: Child was diagnosed with Lyme disease in neonatal period proven by ELISA 1:512 Placenta: **PCR identification of Bb in placental tissues**	Spector et al, 1993
2003 (1 case)	Lyme diagnosis prior to pregnancy. Sero + IgG WB. **Extensive Treatment prior to pregnancy.** Miscarriage 18wks	Miscarriage 18wks **PCR Bb positive placenta and fetal tissues at MDL labs**	Horowitz et al, 2003
2007 (2 cases)	13 pregnant patients with EM during pregnancy, **treated in pregnancy.** Maternal blood, umbilical cord blood and placenta were examined during childbirth. Borrelia was detected in umbilical cord blood and placenta by direct and indirect methods in 3 cases.	Case 2: **positive genome and suspected plasmid in placenta** along w **electron microscope detection in placenta** Case 3: suspected genome and plasmid in umbilical cord blood and **positive genome w suspected plasmid in placenta.**	Vanousova et al, 2007
2009 (1 case)	Mother was **treated for (EM)** Lyme in first trimester. Stillbirth reported 29 weeks.	Borrelia garinni (strain 840) was isolated from the placenta by PCR.	Hulinska et al, 2009
2011 (12 cases)	Pregnant women with EM rash in first trimester **treated with antibiotics.**	In 2008 :5 placentas, 2009: 5 placentas, 2010: 2 placentas. **Bb DNA detected by PCR and/or electron microscopy**. Culture performed in 2 cases and histology.	Hulinksa et al, 2011

2 cases Bb identified in Placenta by PCR in treatment uncertain pregnancies of asymptomatic, seronegative mothers.

1996 (2 cases)	60 placentas in asymptomatic women with ELISA pos or equivocal serology were tested by silver stain, and if positive by PCR in a prenatal screening program. In women w placental spirochetes, no maternal history of tick bite, EM or symptoms of Lyme disease noted. Uncertain if women were treated, treatment not mentioned in study.	3/60 placentas identified spirochetes by Silver staining **PCR confirmed Borrelia burgdorferi in 2/3 placentas** 3 women had negative syphilis serology, all had equivocal ELISA, 2 had negative WB, one had equivocal WB by CDC criteria. **These mothers w Bb positive placentas would be considered seronegative by CDC two-tier testing criteria.** • **'The significance of placental spirochetes is unknown.'** • **'presence of Bb spirochetes in plaenta implies fetal transmission.'**	Figueroa et al, 1996

4 cases Bb identified in placenta of untreated pregnancies: Immunofluorecence/Silver stains

1987/1989 1 case	**(Case 1) 40 week term stillborn infant**. Mother had EM rash in first trim. Not treated. Seropositive for Bb at 2/3 labs.	Bb cultured from fetal liver of stillborn infant and confirmed w H5332 monoclonal antibody. **Silver stains** revealed spirochetes in myocardium, **placenta,** liver and brain. **Immunofluorescence** revealed spirochetes in heart, adrenal gland, **placenta** +mid-brain	Macdonald et al; 1987/1989
1989 1 case	**(Case 4: Fetal Lyme borreliosis with miscarriage at 15 weeks gestation)** Uneventul first trimester of pregnancy. Postpartum Bb serology was negative.	Autopsy revealed spirochetes in fetal liver and **in placenta.** No inflammation in fetal viscera. Bb was identified in tissue by **indirect immunofluorescence** .	MacDonald, 1989
1989 1 case	**(Case 11: Fetal Lyme borreliosis presenting as neonatal sepsis at term pregnancy)** A 19 yr old woman delivered a term baby who developed respiratory distress in firs hour of life.	Infant developed respiratory distress in first hour of life, treated with IV antibiotics. **Examination of placenta revealed rare B. burgdorferi spirochetes.**	MacDonald, 1989
1989 1 case	**(Case 12: Fetal Borreliosis with Toxemia of Pregnancy and Neonatal Sepsis).** 26 yr old woman had onset of toxemia at 37 weeks. Infant was healthy at birth but shortly after developed respiratory distress, hypoglycemia and fever.	Infant developed respiratory distress shortly after birth, treated with antibiotics for sepsis NYD. At request of attending pediatrician, placenta was re-examined for spirochetes by **Warthin starry silver impregnation**. **Many spirochetes were found in the placenta**.	MacDonald, 1989

4 cases Bb identified in placenta of treated pregnancies: Staining/Monoclonal Antibody

1989 1 case	**(Case 13): Maternal Lyme Borreliosis with Persistent Placental Spirochetosis Despite Oral Penicillin Therapy in Second Trimester.** 28 year old woman diagnosed with Lyme borreliosis in second trimester with EM rash on back. Took 500mg oral Pen VK for 15 days and EM rash faded on day 8. One month later complaints of dizziness, sinus tachycardia was diagnosed. Maternal Bb antibody negative. Retrospective interview disclosed that 2 weeks before delivery, patient sought medical attention due to tick attachment. A 13 by 13 erythematous patch non consistent with erythema migrans was identified by the physician.	Healthy baby was delivered. Serology tests were negatve for antibodies to Bb in maternal and infant umbilical cord blood from IFA and ELISA methods. Culture of the placenta in BSK medium yielded motile spirochetes resembling borrelia species which could not be subcultured. Silver stain impregnantion yielded spirochetes in placental villi. Infant was treated with oral penicillin with probenecid after delivery. Child appeared well in several follow-up visits.	MacDonald, 1989

1993 1 case	34 year old patient with Lyme Borreliosis remained symptomatic despite seven months of therapy with oral antibiotics. She was subsequently **treated with further courses of IV and oral antibiotic therapy**.	Post partum, **B. burgdorferi (Bb) was found to be present in the placenta by histologic staining.**	Burrascano, 1993
1994 1 case	35 year old woman was assessed by author as she had developed an EM one year earlier. She was given a short course of oral antibiotics followed by IV antibiotics. Over several months, her symptoms returned, her ELISA titer was elevated and she was **restarted on IV and oral antibiotics**. She discovered she was pregnancy and after a normal pregnancy delivered a healthy male infant.	The placenta was examined at Brigham and Women's Hospital in Boston, Massachusetts where **several spirochetes were noted in perivascular and intervillous spaces on modified Dieterle Silver stain**.	Patmas, 1994
2008 1 case	Pregnant woman with disseminated Lyme borreliosis with EM/arthralgia/paresthesia Treated with **oral PCN for 5 days week 10 and retreatment week 14**, positive LB serology.	15 weeks Intrauterine fetal death. **Borrelia like organisms in ultrathin sections of placenta detected using monoclonal antibody H9724 against flagellin.**	Hercagova et al, 2008; Maraspin et al, 2020

1 case Bb identified in placenta – identification method not described, maternal treatment not identified.

2002	Mother developed Lyme disease in the last month of pregnancy.	Borrelia burgdorferi **was identified in the placenta. (method of detection not identified)** 'The child did not develop clinical or laboratory manifestations of Lyme disease.'	Quershi et al, 2002.

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Histopathological Descriptions of Placenta

"Autopsy evidence for gestational Lyme borreliosis establish that spirochetes are in fetal or placental tissue. Such cases show that serological evidence is often lacking when maternal blood is tested for antibodies to Borrelia burgdorferi immediately after delivery of a living or dead fetus. Routine tissue studies with ordinary microscope techniques, namely hematoxylin and eosin stained sections, fail to provide clues that infection has reached the fetus because none of the autopsies to date has shown inflammation in the tissues which contained Bb.

In each of the previosuly published cases, a strong index of suspicion was the sole cause for the intricate and exhaustive medical investigation specifically directed toward the subtle clinical and histopathologic evidence of Lyme borreliosis and it spirochetal agent Bb. Patient and diligence are required if the histopathologist is to succedd in visualizing Bb with oil immersion magnification. There are many potential pitfalls and there are many opportunities to fail when looking for the spirochete."

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

"Parrafin sections of placental tissues and abortion material from every seropositive or clinically suspected case should be examined by indirect immunofluorescence and silver stain, to evaluate transplacental transmission."

Carlomagno, G., Luksa V., Candussi G., Rizzi GM., & Trevison, G. (1988). Lyme Borrelia positive serology associated with spontaneous abortion in an endemic Italian area. Acta Europaea fertilitatis, 19(5), 279-281.

"Uterine involvement in stage II Lyme borreliosis is a significant factor in pregnancy since it may result in transplacental transmission of B. burgdorferi to the fetus. The amount of Hofbauer cells may be increased in the villi of the placenta. An inflammatory infiltrate may or may not be present. One of us recently encountered cases of decidual necrosis with inflammation in patients with intrauterine infection due to B. burgdorferi (de Koning unpublished data)."

De Koning J., Duray PH. Histopathology of Human Lyme borreliosis. In: Weber K, Burgdorfer W (eds). Aspects of Lyme Borreliosis. Springer-Verlag Berlin Heidelberg 1993. ISBN-13:978-3-642-77616-8.

'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. **The chorionic villi of the placenta show an increase of Hofbauer cells as in luetic placentitis**. Inflammatory changes of fetal or changes are not as pronounced as in the adult, but cardiac abnormalities, including intracardiac septal defects have been seen. 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."

Duray PH, Steere AC. Clinical pathologic correlations of Lyme disease by stage. Ann N Y Acad Sci 1988;539:65-79.

Mother treated with oral PCN for ten days after onset of EM week 6 pregnancy followed by stiff neck and headache one week later. IFA 1:512 positive to Bb. At 20 weeks intrauterine fetal death was documented by ultrasound.	The placenta was **hypoperfused and membranes exhibited autolytic change. Microscopic exam exhibited autolysis of fetal tissues and an immature placenta with presence of syncytial and cytotrophoblastic elements.** **There were no inflammatory elements.** Culture and IFA of placenta and fetal tissues were negative for Bb.	Markowitz et al; 1986
Case 1: **(Fetal Lyme Borreliosis with Ventriculoseptal Defect)** Mother had EM rash in first trimester Not treated. Seropositive for Bb at 2/3 labs.	Bb cultured from fetal liver of stillborn infant and confirmed w H5332 monoclonal antibody. **Silver stains** revealed spirochetes in myocardium, **placenta,** liver and brain. **Immunofluorescence** revealed spirochetes in heart, adrenal gland, **placenta** +mid-brain	Macdonald et al; 1987/1989
(Case 4: Fetal Lyme borreliosis **with miscarriage at 15 weeks gestation)** Uneventul first trimester of pregnancy. Postpartum Bb serology was negative.	Autopsy revealed spirochetes in fetal liver and **in placenta.** No inflammation in fetal viscera. Bb was identified in tissue by **indirect immunofluorescence.**	MacDonald 1989.
(Case 11 in publication) **Fetal Lyme Borreliosis Presenting** **as Neonatal Sepsis at Term Delivery**	Examination of placenta revealed **rare Bb spirochetes** **in otherwise normal appearing villi.**	MacDonald, 1989

(Case 12: Fetal Borreliosis with Toxemia of Pregnancy a Neonatal Sepsis). 26 yr old woman had onset of toxemi 37 weeks. Infant was healthy at birth but shortly after developed respiratory distress, hypoglycemia and fever.	Infant developed respiratory distress shortly after birth, treated with antibiotics for sepsis NYD. At request of attending pediatrician, placenta was re-examined for spirochetes by **Warthin starry silver impregnation**. **Many spirochetes were found in the placenta**.	MacDonald, 1989
(Case 13): Maternal Lyme Borreliosis with Persistent Placental Spirochetosis Despite Oral Penicillin Therapy in Second Trimester. 28 year old woman diagnosed with Lyme borreliosis in second trimester with EM rash on back. Took 500mg oral Pen VK for 15 days and EM rash faded on day 8. One month later complaints of dizziness, sinus tachycardia was diagnosed. Maternal Bb antibody negative. Retrospective interview disclosed that 2 weeks before delivery, patient sought medical attention due to tick attachment. A 13 by 13 erythematous patch non consist with erythema migrans was identified by the physician.	Healthy baby was delivered. Serology tests were negatve for antibodies to Bb in maternal and infant umbilical cord blood from IFA and ELISA methods. Culture of the placenta in BSK medium yielded motile spirochetes resembling borrelia species which could not be subcultured. **Silver stain impregnantion yielded spirochetes in placental villi.** Infant was treated with oral penicillin with probenecid after delivery. Child appeared well in several follow-up visits.	MacDonald, 1989
60 placentas in asymptomatic women with ELISA pos or equivocal serology were tested by silver stain, and if positive by PCR in a prenatal screening program. In women w placental spirochetes, no maternal history of tick bite, EM or symptoms of Lyme disease noted. Uncertain if women were treated, treatment not mentioned in study.	3/60 placentas identified spirochetes by Silver staining PCR confirmed Borrelia burgdorferi in 2/3 placentas 3 women had negative syphilis serology, all had equivocal ELISA, 2 had negative WB, one had equivocal WB by CDC criteria. These mothers w Bb positive placentas would be considered seronegative by CDC two-tier testing criteria. **'The significance of placental spirochetes is unknown.'** **'presence of Bb spirochetes in placenta implies fetal transmission.'** **Rare silver-positive spirochetes were seen in the villi. Other sections revealed the same organism in the inter-villous (maternal) space.**	Figueroa, 1996
Mild early Congenital Lyme borreliosis: (Patient number 23) See description above	Placenta: **Focal chorioamnionitis and subchorionic nodules were found.**	Gardner, 2001
Severe Early Congenital Lyme borreliosis: (Patient number 24) See description above	Placenta: **Pathologic examination of the placenta showed chronic fibrosing villitis.**	Gardner, 2001

Note by Dr. Gardner:

"Placental histopathology of two of my cases of congenital Lyme borreliosis consisted of focal acute chorioamiontis, focal calcification, marked congestion and a 2.5 cm subchorionic nodular infarct in one term placenta following first trimester treated Lyme disease (patient 23), as well as focal chorionic villous edema, chronic fibrosing villitis, fibrin deposition betwee between villi, syncytial knots and marked congestion in the other 34-week placenta following second-trimester treated gestational Lyme disease (patient 24)."

'In a small number of gestational Lyme borreliosis placentas described, rare spirochetes may be found, and the histopathology may be either normal or abnormal. The focal chronic fibrosing villitis, nodular subchorionic villi, syncytial and trophoblastic features, and the suggestion of perivascular lymphoplasmacytic infiltrations are reminiscent of the pathology of syphilitic placentitis, just as the basic histopathologic lesion of Lyme disease, lymphoplasmacytic pervascular infiltration with vaculopathic damage, shows similarities with syphilis. A larger number of placentas must be studied histologically, using silver and B. burgdorferi specific IFA stains, and possibly with PCR and culture, before a definitive description of placental pathology in gestational Lyme borreliosis is found."

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Live Birth with Adverse Outcomes (possible or probable congenital Bb infection)

"Perinatal borreliosis of Lyme disease occurring in pregnancy may result in transplacental transmission of the spirochete and cases with adverse perinatal outcomes have been reported. Intrauterine fetal death, prematurity, cortical blindness, syndactyly, developmental delay and a vesicular rash were seen in 5 of 19 pregnancies in which mothers had clinical evidence of Lyme disease. Subsequent pregnancies in some of these cases were normal."

"In two case reports, first trimester maternal infection resulted in early neonatal death. These babies were born with cardiac malformation. Post-mortem examination showed Borrelia burgdorferi in most organs with minimal evidence of inflammation. The spirochete has been recovered from tissues of four early trimester abortuses, three of which had evidence of cardiac malformations."

"Although the association between congenital malformations and seropositivity was not found in a cord-blood study conducted in two cohorts of babies born in endemic and non-endemic areas, there were more low birth weight babies in the seropositive group.

"Taken together these data suggest that infection with B. burgdorferi during pregnancy poses a risk to the fetus."

Belani K, Regelmann WE. Lyme Disease in Children. Rheum Dis Clin North Am. 1989;15(4):679-689.

"Like syphilis, Lyme disease during pregnancy may be associated with congenital infection of the infant and resulting clinical illness. Several reports describe infants who died shortly after delivery, or were stillborn, to mothers who had Lyme disease during pregnancy (73-76). Spirochetes were found in autopsy specimens from some of these babies. Congenital heart defects and syndactyly have occurred in babies of mothers who had Lyme disease during pregnancy, but these associations are anecdotal (76)."

Nadelman RB, Wormser GP. A Clinical approach to Lyme disease. Mt Sinai J Med. 1990. May; 57(3):144-56

"Although the potential for B. burgdorferi to cause congenital disease has clearly been established, the frequency of transmission is not known. Furthermore, because of the chronic persistence of the organism in the untreated patient, it is not known whether patients who were infected prior to pregnancy can transmit the infection to the fetus. The answers to these questions will require large scale prospective studies. Analysis of case reports and small studies offers us a perspective and some tentative guidelines for the diagnosis and treatment of this infection during pregnancy."

Luft BJ, Dattwyler RJ. Lyme borreliosis. Curr Clin Top Infect Dis. 1989;10:56-81

'based on the apparent tissue tropism of *B. burgdorferi* in children and adults, neurologic or cardiac disease might be predicted as a consequence of congenital infections.'

Souza, IE., Bale JF., (1995). Topical Review: The Diagnosis of Congenital Infections: Contemporary Strategies. Journal of Child Neurology, 10(4), 271-282.

'The potential for congenital infections is recognized for syphilis, leptospirosis, and relapsing fever borreliosis.' Owing to the morphologic and antigenic similarities of Borrelia burgdorferi {Bb) to other spirochetal agents, recent concern has focused on the potential adverse effects of Lyme borreliosis (LB) during pregnancy. The early and late transplacental transmission of Bb has been documented in over 30 pregnancies all over the world, and fatal and adverse results have been reported, but no distinct pattern of teratogenicity has yet been described. Affected mothers may deliver normal healthy infants, but sometimes Bb infection during pregnancy can result in abortion, stillbirth, preterm delivery, intrauterine growth retardation, congenital malformations, and manifestations in the newborn.'

Trevison G, Stinco G, Cinco M. Neonatal skin lesions due to a spirochetal infection: a case of congenital Lyme borreliosis? Journal of Dermatology, 36, 677, 1997.

'Whenever we come across the need to decode a complex clinical picture of progressive damage to the central nervous system, we face the dilemma, the possibility of congenital neuro-borreliosis.'

Lazebnik T, Zal'tsman P. A Case of Congenital Neuroborreliosis. St Petersburg Medical Academy of Postgraduate Education, St. Petersburg, Russia. 2005.

"The bacteria permeate through the placental barrier and intensively multiply in fetal and neonate tissues. The effects of intrauterine infection involve either fetal death or numerous, atypical developmental malformations (for example in the nervous and cardiovascular systems as well as in bones, muscle and skin). These malformations have influence on the infants' condition and prognosis."
"The definition of Lyme disease as a disease with high variability of symptoms can be applied not only to adults, but also to its congenital form in neonates infected in a transplacental way."

Silwa, L. Teratogenic effects of the bacteria Borrelia sp. on the fetuses of pregnant women with Lyme disease. Nowa Medycyna 4, 2011. *translated from Serbian

15 cases Intrauterine Lyme infection/Fetal borreliosis/Congenital Lyme with adverse outcomes.

Year	Maternal History	Infant/Baby History	Citation
1986	No recall of tick bite or EM rash Asymptomatic mother Untreated pregnancy, later found to be seropositive Bb IgG.	Baby delivered at 37 weeks with neonatal onset of: Multi-system inflammatory disease in infant. Maculopapular skin rash, Hepatosplenomegaly Hypertrophy of heart, anemia Fever accompanied by recurrent infections – enteritis, bronchitis, rhinitis, cystopyelitis Delayed growth and development, head enlargement, wide fontanel, protruding eye balls, conjunctivitis, blepharitis, enlargement of cervical, axillary and inguinal lymph nodes, itchy maculopapular rash. Elevated IgG ELISA titers repeatedly identified in child's serum which decreased w antibiotic therapy 'It cannot be ruled out that our patient developed this specific syndrome as a self-propagating response after an intrauterine infection with Lyme disease spirochetes.''The neonatal onset suggests a prenatal infection.'	Lampert et al, 1986
1989	**(Case 11: Fetal Lyme borreliosis presenting as neonatal sepsis at term pregnancy)** A 19 yr old woman delivered a term baby who developed respiratory distress in first hour of life.	Infant developed respiratory distress in first hour of life, treated with IV antibiotics. Examination of placenta revealed rare B. burgdorferi spirochetes.	MacDonald, 1989
1989	**(Case 12: Fetal Borreliosis with Toxemia of Pregnancy and Neonatal Sepsis).** 26 yr old woman had onset of toxemia at 37 weeks. Infant was healthy at birth but shortly after developed respiratory distress, hypoglycemia and fever.	Infant developed respiratory distress shortly after birth, treated with antibiotics for sepsis NYD. At request of attending pediatrician, placenta was re-examined for spirochetes by Warthin starry silver impregnation. Many spirochetes were found in the placenta.	MacDonald, 1989
1989	Mother infected in second trimester. Treated for Lyme. Seronegative. 'The mother, who was asymptomatic, had been treated with oral antibiotics and did not have diagnostic levels of antibodies to Bb at time of parturition.'	Baby was born with neurologic dysfunction. Spinal tap on neonate reveals serological evidence of antibodies specific to borrelia in CSF.	Dattwyler et al, 1989
1992	No maternal tick bite, no EM Asymptomatic, Maternal serology revealed significantly increased IgM titer and slightly increased IgG. Untreated pregnancy	3 day old newborn diagnosed with sepsis and treated with antibiotics. No other details given. Increased IgM and IgG Bb antibodies in infant blood and CSF. Negative for syphilis and mononucleosis. 'highlights the dilemma that we are in an effort to prevent congenital borreliosis. An orientation on the symptoms of the expectant mother is not sufficient because the infection is often asymptomatic, but this does not exclude bacteremia and infection of the fetus.'	Horst, 1993
1994	Maternal tick bite, EM, flu like symptoms in 1968, was not treated. Later developed arthritis, cranial neuritis, meningitis, depression. Had Bb positive immunoblot	A son was born in 1969, at birth suffered from several minor abnormalities. He was generally weak, had recurrent episodes of fever. Extreme irritability and depression. Was diagnosed w Lyme disease by immunoblot.	Gasser et al, 1994.
Note: 4 cases below reported by Dr. Tessa Gardner are directly from the medical reference textbook Infectious Diseases of the Fetus and Newborn Infant, 1995, 2001.			
1995 /2001	**Mild early Congenital Lyme borreliosis:** (Patient number 23) Mother developed small 1 cm erthematous patch after a tickbite to her groin after lake visit. One month later conceived, developed a flu like illness and at 3 weeks gestation an	Infant was normal at birth except for sacral dimple and bilateral inguinal adenopathy. Normal pediatic opthamology examination Normal brain stem auditory evoked response evaluation Normal head ultrasound, Normal EKG Normal chest, long bone xrays Normal complete blood count Blood and cerebral spinal fluid negative for EIA Bb antibody	Gardner, 2001

	asymptomatic rash on her trunk accompanied by low grade fever and later two erytematous patches with central clearing. Maternal EIA to Bb was initally negative at presentation at 4.5 weeks gestation, became positive at 5.5 weeks, remained positive through 12 weeks, negative at delivery. Mother was treated immediately at 4.5 weeks with IV ceftriaxone 2 g daily but developed severe diarrhea and switched to oral PCN for remaining 2 weeks. In vitro lymphocyte proliferation assay for Bb was positive at 16 weeks gestation, at delivery + 1 month	In vitro lymphocyte proliferation assay for Bb positive on cord blood and infant blood at 1 month but lower at one month. After positive LPA test, infant treated with IV ceftriaxone 100mg/kg daily for two weeks and developed intensly erythematous generalized maculopapular rash on day 6 of treatment which resolved despite continuation of treatment. Inguinal adenopathy resolved by end of antibiotic therapy. Infant remained clinically well at 15 months and continued well at almost six years of age.	
1995, 2001	**Mild Early Congenital Lyme borreliosis:** (Patient number 26) At 17 weeks gestation mother sustained tick bites while camping. At 18 weeks developed an 10 by 5cm EM 'bullseye' rash that lasted 3 weeks and spontaneously resolved. Between 20-28 weeks experienced low grade fever, myalgias, stiff neck, fatigue, dizziness, photophobia and migratory polyarthralgias of knees. At 23-26 weeks had rash reoccurance. At 28 weeks tood oral erythromycin for 10 days and symptoms resolved. She heard about Lyme disease and started on oral cefuroxime from 33 weeks to delivery. Her urine positive for Lyme antigen at commercial lab at 32 weeks. At delivery maternal blood negative by polyvalent Lyme EIA. Blood obtained 1 day post-partum was positive by Bb in-vitro lymphocyte proliferation assay (LPA). After delivery, recurrance of headache, photo-phobia, flu-like symptoms and knee arthralgias was treated with oral doxycycline for one month. Long term followup information not available.	Infant was normal at birth except for small retinal hemorrhages with white centers. Normal brain stem auditory evoked response Normal EKG Normal 2D echo Normal complete blood count and liver enzyme panel Cordblood and infant blood on day 1, 2.5 weeks and 7 weeks seronegative by polyvalent EIA Bb antibody. Blood on first day was positive by in vitro LPA for Bb. At 2.5 weeks infant was listless and slept more than expected. Cerebral spinal fluid revealed slight lymphocytic pleocytosis, slightly elevated protein and normal glucose. MRI scan of brain was normal Complete blood count normal, liver enzymes normal. Slight hyperbilirubinemia noted, retinal lesions spontaneously resolved. Infant was treated with IV ceftiaxone 75mg/kg for 4 weeks, developed a 'pale'spell on day 2 of therapy, became more active and alert on day 3 and was completely well by completion of therapy. Long term follow-up not available.	Gardner, 2001
	Note from Dr. Gardner re: cases 23 and 26. Two mothers both had gestational erythema migrans with systemic symptoms both were treated with antibiotic therapy during pregnancy Mothers who have been treated with antibiotics for gestational Lyme borreliosis **may be seronegative** by antibody assays at delivery or in the peripartum period and they may be positive by the Bb specific LPA.	Infants were clinically normal at birth except for minor manifestations of congenital Lyme borreliosis. **Infant #1** – born to mother with gestational Lyme treated within 2 weeks of onset – had sacral dimple (unclear significance) and inguinal adenopathy and rash. **Infant #2** – born to mothers with symptoms of gestational Lyme borreliosis persisting for 10 weeks before antibiotic therapy had evidence of mild neurologic symptoms, transient retinal lesions, mild lymphocytic meningitis, and mild hyperbilirubinemia. Both infants **had episodes representing Jarisch-Herxheimer reactions** shortly after initiation of ceftriaxone therapy and had resolution of their manifestations of early congenital Lyme borreliosis by end of antibiotic therapy. Infants were **negative for polyvalent EIA Bb antibody at delivery and positive by Bb specific LPA**.	Gardner, 2001

1995, 2001	**Severe Early Congenital Lyme borreliosis:** (Patient number 24) 34 yr woman suffered a tickbite at 6.5-12.5 weeks gestation. Was treated with oral amoxicillin 250mg TID for 10-14 days for sinusitis and flulike symptoms at 5-7 weeks and at 20-22 week gestation. Mother remained clinically well following delivery and was seronegative for polyvalent EIA Bb antibody at one week, 9 months and 10 months after delivery. She was also negative for Bb LPA at 9 and 10 months.	Routine fetal sonogram at 17 weeks was normal Second fetal sonogram at 24 weeks because of decreased amniotic fluid showed marked intrauterine growth retardation. Fetal blood sampling at 24.5 weeks showed normal chromosomes nd no evidence of intrautrine viral infection. Infant was delivered by C-section at 34 weeks. **Placenta:** Pathologic examination of the placenta showed chronic fibrosing villitis. Infant was small for gestational age (1050 g, 34 weeks) Low Apgar score 'blueberry muffin rash' Profound thrombocytopenia that required platelet transfusions Hepatomegaly and hyperbilirubinemia Meconium ileus that required enemas Severe dilated cardiomyopathy with biventricular dysfunction and low voltage on electrocardiogram that required intensive cardiopulmonary support with intubation, mechanical ventilation and pressors. Transient patent ductus arteriosus **Additional abnormalities included:** Pilondial dimple, flexion contractures of large joints (knees, hips, elbows) Longitudinal striations and dense sclerotic transvere metaphyeal sutures Full fontanelle Bilateral inguinal adenopathy **Testing:** Head ultrasound revealed diffuse punctate increased parenchymal echogenecity Skull xrays showed no calcifications Liver enzymes normal Brain stem auditory response evaluation was normal **Diagnosis: Neuroborreliosis** Infant was intially thought to have culture negative bacterial sepsis and was treated with IV ampicillin and gentamycin for 6 days but failed to improve and continued to require platelet transfusions and intenseive cardiovascular support. Because of maternal history of tick bite, the possibility of congenital Lyme borreliosis was raised and IV ceftriaxone 100mg/kg/day was added on the seventh day and continued for 1 week. Within 24 hours, platelet count stabilized, pressors discontinued and infant began to recover. Spinal fluid on day 6 revealed elevated protein but no pleocytosis. Dense sclerotic transverse metaphyseal bands present in all the long bones during the first week gradually resolved during ceftriaxone therapy. Extensive evaluation for bacterial and viral causes of this fulminant sepsis was unrevealing. Negative polyvalent EIA Bb antibody Infant was discharged at 2 months in good condition. By 9 months baby demonstrated growth retardation, mild developmental delay, mild lower extremity spasticity and persistently small head circumference. The possibility of congenital Lyme borreliosis was considered. At 9 months but not 10 months she was found to have polyvalent EIA Bb antibody. At 9 and 10 months she had a positive Bb in vitro LPA At 9 and 10 months further evaluation included a normal spinal fluid with no detectable Bb antibody, normal EKG, normal complete blood count, slightly elevated liver enzymes and MRI scan of brain that showed left parietal parenchymal lesions of increased T2 signal.	Gardner, 2001

		Treated with IV ceftriaxone (75mg/Kg for 3 weeks for neuroborreliosis). Subsequently improved and exhibited normal growth and development at follow-up at 2.5 yrs age. **<u>Authors note:</u>** This mother-infant pair illustrate the presentation of severe early congenital Lyme borreliosis as fulminant neonatal sepsis; the need to **consider Lyme borreliosis in the differential diagnosis of culture negative sepsis**; the need to include optimal IV antibiotic therapy for Lyme borreliosis such as third generation cephelosporins, if Lyme disease is considered. This case also **indicates the failure of short courses of oral therapy in the prevention of severe congenital Lyme borreliosis** and need for more aggressive antibiotic therapy of gestational Lyme disease. The unusual finding of sclerotic transverse metaphyseal bands in the long bones, which faded during IV ceftriaxone in this infant and in one other infant (case 25) with congenital Lyme borreliosis may eventually prove to be a useful diagnostic finding in severe congenital Lyme borreliosis. The initial clinical presentation of this infant resembles the description by Lampert (1986) of the infant with infantile multisystem inflammatory syndrome who has later found to have chronic Lyme borreliosis as well as the description of some reported infants who had fulminant early congenital Lyme sepsis (Weber, 1988), (MacDonald, 1989), (Lavoie, 1987) although this infant did not have the severe cardiac malformations found in some of these patients.	
1995, 2001	**Late Congenital Lyme Borreliosis** (Patient number 25) 35 year mother of five children visited a tick infested farm with entire family for two weeks every summer from 1988-1990 and had occasional tick bites during that time. During the first 6 weeks of next pregnancy developed a flulike illness that progressed to pneumonia and was associated with nonpruritic non tender, vesiculobullous and even purulent round or oval skin lesions on her legs. She was treated with almost continuous antibiotic therapy for the first 10 weeks gestation, initially oral erythromycin for 7 weeks, followed by cefaclor for 3 days, IV cefuroxime for 4 days and oral cephalexin for 2 weeks then oral cefixime for 10 days at 12-13 weeks. The large erythematous skin lesions intermittently reappeared during the second and third trimesters She developed progressive arthralgias and arthritis of her hips, knees and lower back By time of her delivery, in Dec 1990 she was unable to walk without stooping over. The skin lesions, polyarthralgias and polyarthrtis recurred after delivery and continued intermittently for 4 months post partum; she also noticed headaches, fatigue, and short term memory lapses. In March 1991, the history of maternal gestational illness and tick exposure was discovered on routine questioning during hospitalization of the then 3 month old infant for severe failure to thrive.	**Infant:** Born at 37 weeks gestation, normal birth weight of 3490g and was considered normal at birth but developed neonatal hyperbilirubinemia and nursed poorly. Was treated with intravenous ampicillin and third generation cephalosporin for suspected sepsis and urinary tract infection at 1 week of age, developed a generalized erythematous maculopapular rash thought to be an allergic reaction. Bilateral inguinal hernias were repaired at 1 month Oral cefaclor given for otitis media at 2 months His mother noted he became increasingly limp and restless, held his neck to the right, slept almost all day and fed poorly. He presented at 2.5 months of age for infectious disease evaluation to look for possible congenital infection because of failure to thrive, developmental delay, growth retardation, and gastroesphogeal reflux with recurrent vomiting and recurrant aspiration pneumonias. Was found to have hepatomegaly, erythematous abdominal and distal extermity tough maculopapular rash, lethary, marked proximal hypotonia, distal hyperreflexia and hypertonia, jitteriness, alternating exotropia, and some dysmorphic features consisting of cupped ears, upturned nose, small chin, a unilateral simian crease and pectus excavatum. Collecting system was slightly dilated and the kidneys slightly small Transverse metalyseal bands in the long bones MRI brain scan normal Brain stem auditory evoked response normal Spinal fluid unremarkable Chromosone analysis normal Underwent fundoplication and feeding gastotomy because of inability to swallow without aspiration and exotropia was surgically corrected. Evaluation for possible congenital infection was initially unrevealing and spinal fluid and serum were both negative for polyvalent EIA antibody to Bb. Because of presence of metaphyseal bands (which were reminiscent of an earlier infant with Lyme borreliosis) the maternal gestational history and the maternal Lyme seropositivity the diagnosis of late congenital Lyme borreliosis was still considered. Both infant and mother were found to have positive responses in the Bb burgdorferi in-vitro LPA. The child received a total of 7 weeks of IV ceftriaxone (100mg/kg/day) between 2.5-7 months and showed dramatic improvement in neurologic function.	Gardner, 2001

	A part of the evaluation of the infant for possible congenital infection, maternal blood was sent and found to be seropositive for polyvalent EIA Bb antibody. The mother was treated with oral doxycycline 100mg twice daily and showed initial improvement of the lesions, was changed to IV ceftriaxone 1 week later because of intesification of the skin lesions and recurrance of fever and arthralgias and was changed back to oral doxycycline because of development of a generalized erythematous nonpruritic maculopapular rash that was considered by the physcian to be an allergic reaction. The headache, memory liss, fatigue and skin lesions resolved after 6 weeks of doxycycline but the right hip arthritis, polyarthralgias persisted and 1.5 years later, she developed chronic palpebral conjunctivitis and distal paresthesias of her hands and was treated with several weeks of intravenous ceftriaxone with good clinical improvement. **Authors note:** The prolonged first trimester courses of oral antibiotics may have sufficiently stabilized the gestational spirochetal infection to allow the pregnancy to be carried to almost term.	When initial attemps were made to use a less aggressive and shorter course of IV ceftriaxone, he experienced relapse with evdience of loss of developmental milestones; finally after a total of 7 weeks of IV ceftriaxone followed by a 1 year course of oral amoxicillin from 7 months to 19 months of age, he remained clinically well and continued to progress to esspecially normal neurologic status by 3 years of age. He had gradual resolution of scaly erythematous maculopapular abdominal and distal extermity rash by completion of ceftriaxone therapy. He gradually improved neurologically, regained lost developmental milestones and resolved the majority of focal neurologic findings including the subtle right hemiparesis, mild proximal hypotonia and distal hyperreflexia by 2 years of age. At follow up at 3 years he remained well and was appropriate developmentally and was slowly learning to take food by mouth. At 8 years of age he had reached an almost age-appropriate developmental and intellectual level but developed regression of reading, spelling and vocabulary skills, a seizure disorder, and episodic unilateral kness and ankle arthritis with no additional Bb exposure. The arthrtis and deterioration of language skills responded to IV ceftriaxone. At 9 years, he has regained almost all lost language skills but exhibits delated dentition and structural dental anomalies. **Authors note:** This mother-infant pair illustrates the ability of Bb to cause severe progressinve neurologic deficits consistent with chronic neuroborreliosis and failure of oral erythromycin and oral cephalosporins to prevent these complications. The neurologic recovery of this patient during the prolonged course of antibiotic therapy and the near normalization of his developmental level by 3 years of age lend support for such prolonged therapy until it appears that maximum recovery of neurologic function has occurred. The later development of arthritis, seizure disorder and deterioration of language skills with no additional Bb exposure and improvement after antibiotic therapy are suggestive of a relapse of Lyme disease and provide support for the use of additional antobiotic therapy for such relapses. The infant reported by Markowitz and colleagues who was normal at birth and later developed cortical blindness may represent this type of clinical manifestation of congenital Lyme borreliosis.	
1997	32 yr mother no recall of any tick bite and no symptoms during pregnancy but had taken part in outdoor activities in area known to be endemic for LB. No suspicion of infection during pregnancy. Mother was asymptomatic Postpartum serum antibody to Bb (IFI) was slightly elevated - IgG seropositive (slightly high IgG 1:128, cutoff 1:64). Untreated pregnancy	**Infant:** Infant presents to Pediatric Dermatology with relapsing/remitting multiple annular erythematous patches, fever and lymphadenopathy which had started at 3 weeks of age. Initial infant serology 9 months (IFI, ELISA, WB negative) **BUT** B- Burgdorferi was isolated and detected by PCR from skin biopsy samples in seronegative baby. Baby was treated. Three months later popular lesions and bluish red color in legs noted (still negative by ELISA and IFI but WB IgG positive) Despite repeated courses of oral antibiotic therapy, lesions recurred four more times over the following 3 years and child was retreated each time (this suggests persistence of Bb infection). By age 4, no further lesions documented. Authors suggest a congenital borreliosis and cutaneous manifestations of congenital spirochetosis. Dermatlogic findings included stropulus on arms and legs, multiple annular erythema, bluish-red discoloration of legs.	Trevison, et al 1997
2005	Mother has tick Bite 1st Trimester, develops high fever, presumed flu. Untreated Pregnancy. After birth dx w tetraparesis, neuroborreliosis ALS. 'Whenever we come across the need to decode a complex clinical picture of progressive damage to the central nervous system, we face the dilemma, the possibility of congenital neuro-borreliosis.'	The child, at age 2 years 10 months developed knee bilateral knee pain, contractures of the hip, ECG abnormalities and tachycardia, polyneuropathy, psycho-emotional lability. Child SERONEGATIVE by standard test (ELISA) however was POSITIVE for Bb through PCR. Significant improvement noted with treatment. 'Here we describe a case of chronic stage neuroborreliosis in a 5 year old girl born by the mother who had suffered Lyme disease while pregnant with the clinical features of the disease appearing after her daughter was born'.	Lazebnik et al, 2005

2005	Mothers of children all had either untreated or partially treated Lyme disease, some as a result of a tick bite during pregnancy. Most often mothers were diagnosed prior to their children. A retrospective analysis of progression of symptoms revealed oftentimes symptoms were overlooked in children until they gradually progressed in frequency and severity. '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.'	Details of testing in one case given: Both amniotic fluid and cord-blood of one infant tested positive for Borrelia burgdorferi. **In 102 children with Gestational Lyme Borreliosis:** 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 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 et al, 2005
2005	No maternal tick bite no, EM Asymptomatic, sero + Untreated pregnancy	Infant girl born w hydrocephalus and gestational Lyme. At birth 41KDa and 75 kDa identified in infant IgM WB.	Onk et al, 2005
2012	Mother reported joint problems at the end of pregnancy, no other hx of Lyme disease. Mother had positive IgG EIA.	Baby developed erythema migrans rash two months after birth which lasted two weeks. No tick-bite or exposure to ticks in baby. Baby had positive ELISA IgG 3,773 and IgM 1,828, at the same time WB IgG was negative and WB IgM positive.	Zjevikova, 2012.

Live birth: Bb in cordblood identified by PCR

2 cases of Bb identified in cord blood by PCR in mothers of treated for EM in pregnancy.

2007	13 pregnant patients with EM during pregnancy, treated in pregnancy. Maternal blood, umbilical cord blood and placenta were examined during childbirth. Borrelia was detected in umbilical cord blood and placenta by direct and indirect methods in 3 cases.	Case 1: **suspected plasmid Bb by PCR in cordblood**; Case 2: positive genome and suspected plasmid in placenta along w electron microscope detection in placenta, Child 3: **suspected genome and plasmid in umbilical cord blood** and positive genome w suspected plasmid in placenta.	Vanousova et al, 2007

Live birth: Bb antibodies in cordblood

1 case of Bb IgG and IgM Antibodies identified in infant born to mother treated for Lyme disease.

2009	A pregnant woman (no.12) was treated for Lyme disease and had positive IgM and IgG to Ap and Bbsl in the blood after bearing twins.	One twin had positive IgG and IgM antibodies against Bb. No other information given.	Hulinska et al, 2009

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Human Cord Blood with IgM Antibody to 41KD Flagellar Antigen of Bb.

'The earliest IgM antibodies formed against antigens of B. burgdorferi are directed against a polypeptide with an M_r of 41,000 daltons. This poly-peptide has now been shown to be genus-specific (Borrelia) flagellin. Sequential western blot studies of sera from patients have shown that antibodies of the IgG class are first directed also to the 41-kDa flagellin.'

Coleman, J.L., & Benach, J.L. (1987). Isolation of antigenic components from the Lyme disease spirochete: their role in early diagnosis. The Journal of infectious diseases, 155(4), 756-765. https://doi.org/10.1093/infdis/155.4.756

Introduction	Methods	Results	Ref:
'Antibody to the 41kD flagellar antigen is found early in disease, but may also be found in non-exposed individuals.' 'It has been postulated that the detection off anti-borrelia antibody in presumably non-exposed populations may result from cross reactivity with other organisms, or perhaps represent subclinical infection.'	'Samples were obtained from umbilical cord after ligation, obtained from a random selection of healthy women delivering at the Guthrie clinic. All of the patients resided within our catchment area of north central Pennsylvania which is currently non-endemic for Lyme disease. There were no women with histories suggesting Lyme borreliosis. There was no known history of possible exposure to B. burgdorferi such as travel to high-rish environments in endemic areas.'	'We report here that the finding of an IgM anti-41KD reactivity in 29% of cord blood samples from patients in an area non-endemic for Lyme disease.' 'The results of this study demonstrate that some human cord blood samples contain detectible levels of IgM antibody to the 41kD flagellar antigen of Borrelia burgdorferi. These were not derived from maternal exposure and possible transplacental passage of organisms, since the mothers lived in a non-endemic area, had no symptoms consistent with Lyme disease and had negative IgG Western Blots. These antibodies must therefore be of fetal origin and most likely represent the detection of the germline encoded natural antibody to an exogenous antigen frequently encountered in the environment.' **'**The spectrum of cord blood IgM reactivities with other microbial antigens requires further definition.'	Cooke Et al, 1993
'We performed a prospective study to investigate the biological significance and diagnostic specificity of anti-p41 immunoglobulin (Ig)M antibodies against Borrelia burgdorferi.'	'Out of 72 cord blood analyzed, five sera reacted serologically with the p41 antigen, with one serum showing IgM reactivity against the p41 band in the Western Blot.'	'The combined observations that human cord blood contains IgM antibodies to the 41kD flagellar antigen of B. burgdorferi and that such antibacterial antibodies remain in the antibody repertiore into adulthood support the hypothesis that anti-p41 antibodies can occur as natural antibodies.'	Ulvestad et al, 2001

Citations:

Cooke, W. D., Orr, A. S., Wiseman, B. L., Rouse, S. B., Murray, W. C., & Ranck, S. G. (1993). Human cord blood contains an IGM antibody to the 41KD flagellar antigen of Borrelia burgdorferi. Scandinavian journal of immunology, 38(4), 407–409.

Ulvestad, E., Kanestrøm, A., Sønsteby, L. J., Jureen, R., Omland, T., Edvardsen, B., Lundervik, J., Kristoffersen, E., & van Dam, A. P. (2001). Diagnostic and biological significance of anti-p41 IgM antibodies against Borrelia burgdorferi. *Scandinavian journal of immunology*, *53*(4), 416–421.

Borrelia Burgdorferi identified by PCR in human breastmilk

"Although B. burgdorferi has never been identified from human milk, it may be prudent to advise lactating women who present with early Lyme disease (when the organism may be spreading hematogenously) to temporarily stop nursing. After several day on antibiotics, which presumably will eliminate blood-born spirochetes, nursing may be resumed."

Schell, W., Davis JP. Lyme Disease: A Clinician's Guide. State of Wisconsin, Department of Health and Social Services. Division of Health. Bureau of Community Health and Prevention. Section of Acute and Communicable Disease Epidemiology. January, 1989.

"There is also no direct evidence to date that nursing mothers infected with Lyme disease transmit infection through their milk. However, if a nursing mother is suspected of being infected, she should stop nursing her infant until she has had a complete course of antibiotic therapy. The infant should be observed for signs of infection and its blood tested for evidence of infection if illness develops."

CDC Prevention Guidelines Database. (Archive). Vector-Borne Diseases (Lyme disease, Japanese Encephalitis, Yellow Fever). Publication date 08/01/1991.

"It is well known that B. burgdorferi can cross the placenta and infect the fetus. In addition, breast milk from infected mothers has been shown to harbor spirochetes that can be detected by PCR and grown in culture."

Burrascano, JJ. Advanced Topics in Lyme Disease. Diagnostic hints and treatment guidelines for Lyme and other tickborne illnesses. Sixteenth edition, Copyright, October, 2008.

"Overall, even though the risk of transmission through breast milk is minimal, it cannot be excluded, and lactating mothers should be made aware of all possible risks."

Mylonas I. Borreliosis during pregnancy: a risk for the unborn child? Vector Borne Zoonotic Dis. 2011 Jul;11(7):891-8. doi: 10.1089/vbz.2010.0102.

'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. If the infection occurred during pregnancy and treatment has already been completed, an infant can breastfeed. If infection occurs postpartum or the diagnosis is made postpartum, infant exposure may have already occurred. Again, discussion with the mother or parents about withholding versus continuing breastfeeding is appropriate.'

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

2 cases of Bb identified in breast-milk of lactating women

1995	'In addition to urine, breast milk from two lactating women with erythema migrans was tested and also found reactive. Borrelia burgdorferi DNA can be detected with high sensitivity (91%) by a nested PCR in urine of patients with Lyme borreliosis.' "To our knowledge, this is the first report on the occurrence of B. burgdorferi DNA in the breast milk of women with EM. In one of these patients, Bb could be cultivated from a skin biopsy. The other, a mother with EM, had concomitant dizziness for two weeks; her six-month old baby had to be hospitalized because of undetermined fever and vomiting, which resolved spontaneously after some days."	Schmidt BL, et al, 1995.

Citation:

Schmidt BL, Aberer E, Stockenhuber C, Klade H, Breier F, Luger A. Detection of Borrelia burgdorferi DNA by polymerase chain reaction in the urine and breast milk of patients with Lyme borreliosis. Diagn Microbiol Infect Dis. 1995 Mar;21(3):121-8.

See page 39 for additional studies in animals re: Bb cultured from cow milk, transmission via milk, oral infection.

Animal Studies: Findings of Vertical Transmission of Borrelia burgdorferi

'If fetuses can be infected in-utero with B. burgdorferi, as suggested by Anderson et al. (1987), and if they can survive transplacental transmission, this may be a means of maintaining the spirochete in the rodent population in the absence of ticks.'

Burgess EC, Wachal MD, Cleven TD. Borrelia burgdorferi infection in dairy cows, rodents, and birds from four Wisconsin dairy farms. Vet Microbiol. 1993 May;35(1-2):61-77. doi: 10.1016/0378-1135(93)90116-o. PMID: 8362496.

'It is surprising that the evidence presented for transplacental transmission has received little notice by investigators. It would seem that the clinical and epidemiological implications, if significant, could have an impact on current thinking and measures taken to manage the disease.'

Gustafson, John Michael, Ph.D. The in utero and seminal transmission of Borrelia burgdorferi in Canidae. The University of Wisconsin - Madison, 1993. PhD Thesis

'Lyme disease spirochetes were isolated from the fetuses of Apodemus agrarious and white-bellied rats, confirming that Lyme disease spirochetes can be transmitted vertically through the placenta, which is of great significance for the maintenance and expansion of the natural foci of Lyme disease.'

Hou X. [Preliminary investigation on reservoir hosts of Borrelia burgdorferi in China]. Wei Sheng Yan Jiu. 1999 Jan 30;28(1):7-9. Chinese. PMID: 12712735.

'These results suggest that maternal-fetus transmission via the placenta and maternal-offspring transmission probably through contaminated saliva, colostrum or milk can occur.'

Ubico-Navas, SR. Experimental and epizootiologic studies of Lyme disease. Ph.D. Dissertation. Colorado State University, 1992.

A 1988 paper titled, *A model of the spread of Lyme disease in natural populations* by Dr. Ginsberg at the Center of Coastal and Environmental Studies at Rutgers University suggested that the efficiency of vertical transmission of Bb in small mammal hosts will increase the speed in which infection establishes in a new population.

Ginsberg, H.S. (1988). A Model of the Spread of Lyme Disease in Natural Populations. *Annals of the New York Academy of Sciences, 539*.

Animal	Evidence for Maternal-Fetal (Vertical) Transmission of Borrelia burgdorferi in mammals.	Ref:
Mice - 1987	''One culture was obtained from a fetus of a pregnant white footed mouse from which spirochetes also were cultured from spleen and kidney tissues.'	**1**
Mice - 1992	'Spirochetes were also isolated from tissues from three of four still-born pups from two different inoculated dams (Table 2) A total of 76% of all the surviving pups born to both inoculated and uninoculated dams had B. burgdorferi spirochetes in their tissues at time of necropsy" • 57% of the fetuses or still born pups from infected mothers were positive for Bb • 79% of pups born to inoculated dams and raised by uninoculated dams were positive for Bb. • 74% of the pups born to uninoculated dams and raised by inoculated dams were positive. • Pups born to uninoculated dams became infected after being switched to and nursed by an inoculated dam • 80% uninoculated dams became infected after caring for pups born to the inoculated dams. 'Unfortunately, it was not possible to separate transmammary transmission from direct contact transmission from infected mother to offspring. Surprisingly, the opposite direction of transmission from infected offspring to uninoculated mothers via contaminated urine, feces, or saliva and tissues was also observed.'	**2**
Mice - 1993	'One M. musculus and one P. leucopus from Farm 2 were pregnant at the time of capture. Spirochetes were cultured from 2/5 fetuses from the M. musculus and 1 of 2 fetuses from the P. leucopus. The spirochetes from all three cultures were positive by PCR analysis.	**3**
Mice -1995	'A sensitive PCR technique detected B. burgdorferi in the uteri of acutely infected mice but did not detect DNA in uteri of controls or chronically infected mice. Spirochete DNA was only rarely detected in fetal tissues.'	**4**
Mice - 1997	Phase one studies: Males were infected and immediately mated. The day of coital plugging was established as day 1 of pregnancy. The pregnant mice were then infected during early- [day 6-7 postcopulation (PC)], middle-(day 9-10 PC) and late- (day 12-13 PC) gestation periods. Period mice were sacrificed 6 days post infection. Fetuses and their placentas were harvested and cultured for nine weeks in SKB II. No Bb was detected by culture, thus, PCR was performed on the cultures for detection of Bb DNA. There were no appreciable differences observed in transmission rates among the three Bb strains, therefore, the data were pooled.	**5-6**

	Results: • In groups A and C combined, during early-gestation Bb was detected in 4/30 (13%) fetuses and 3/30 (10%) placentas. • During middle-gestation Bb was detected in 3/57 (5%) fetuses and 4/57 (7%) placentas. • No Bb was detected in fetuses or placenta during late-gestation period. • No Bb was detected in samples from group B. <u>Phase Two studies</u>: Mating pairs were assigned to groups A-D and were infected immediately prior to mating. The pregnancies were allowed to go to term and the pups were sacrificed at 1, 7, 14, and 21 days of age. The milk content of the stomach, sections from ear, skin, heart, liver, spleen, brain, bladder, and kidney of all pups were cultured for Bb. Milk was not cultured from sacrificed 21 day-old weanlings. Transmission to offspring was indicated when Bb was isolated from any tissue. Results: • Of 25 infected females, 2 (8%) transmitted Bb to their pups on day one via their milk. No transmission was detected via milk on days 7 or 14. • Among 49 infected females from groups A and C, 5(10.2%) transmitted Bb to their pups either in utero or intrapartum. Two of the transmissions were detected on day 1, two on day 7, and one on day 14. • From the 132 pups at risk for close contact infection in group B, 9 pups were infected resulting in a close contact transmission rate of 6.8%. <u>This transmission model suggests that Bb can be transmitted in utero.</u> Increasing the inoculum size and/or changing the route of inoculation to intrauterine or intra-amniotic may enhance infection rates. This model has the potential to be used to study intervention strategies for gestational LD.	
Mice/Rats 1999	'Vertical transmission of B.b. was confirmed with B.b isolated from foetuses of Apodemus agrarius + Rattus edwardsi. The results showed that Lyme disease spirochetes, B.b., might be naturally maintained in an enzootic cycle by transplacental transmission.'	**7**
Cows - 1988	'Transplacental transmission of B. burgdorferi was demonstrated in the cows. Bb was cultured from the blood of a newborn calf, and an aborted calf had antibodies to B. burgdorferi, indicating in-utero transmission. There is no in utero maternal transfer of antibodies in cows. The findings of spirochetes in the blood of a cow that aborted and the high antibody levels in cows aborting also indicate that B. burgdorferi infection may cause reproductive disease in cows.'	**8**
Cows - 1998	'3/15 (20%) calves were stillborn, two were spirochetemic and all showed evidence of disseminated Bb infection by detection of Bb by PCR in multiple tissues.' <u>Of liveborn neonatal calves:</u> • 2 calves were spirochetemic, IFA negative and negative by immunoblot. • Viable Bb was also cultured from placenta and uterine fluid of two cows. • None of the cattle at birth showed clinical signs commonly associated with Bb infection, indicating a subclinical infection. 'Bb DNA was detected in blood from adult cattle and their offspring at parturition indicating the calves were infected prior to parturition.' 'This study clearly demonstrates in-utero transmission of Borrelia burgdorferi from naturally infected cows to their calves.' "Detection of B. burgdorferi DNA from the tissues of stillborn calves, as well as spirochetemia in neonatal liveborn and stillborn calves, gives evidence for in-utero transmission of B. burgdorferi in naturally infected dairy cattle."	**9**
Horses - 1989	Pregnancy Outcome in 1986: 2 mares aborted or resorbed fetuses 3 foals died within days 2 mares had a live foal that survived, one of which was euthanized at one year due to neurologic disease. <u>Necropsy results:</u> Foal 1: Found dead next to placenta. Serum was antibody negative. Bb isolated from the kidney. Foal 2: (twin 1) euthanized at 2 days age as unable to stand. Serum demonstrated antibodies to Bb. Bb isolated from kidney and brain and Bb demonstrated in kidney tissue by IFA. Foal 3: (twin 2) died at 6 days of age. No lesions seen on histologic examination. Foal 4: healthy when born, mare's colostrum had antibody titer of 1:256 but serum was negative. At six months of age foal had difficulty stepping up. Was euthanized as a yearling. Bb was isolated from kidney and liver. "The demonstration of antibodies in the serum of Foal 2 and the isolation of spirochetes from Foal 1 suggest infection took place in-utero."	**10**

Dogs - 1993	10 female beagles inoculated intradermally w Bb. All were seronegative by IFA and WB before inoculation. 10 female control beagles inoculated w saline. Remained IFA-WB negative and their tissues and their pups remained negative by PCR and culture. Bred naturally. • 10 infected females did not manifest clinical signs or infection during gestation, but a suggestion of increased dystocias and fetal resorptions was apparent. • Of the 10 infected females, 8 delivered litters (3 to 7 pups) that had at least 1 neonatal or 6-week-old pup with B burgdorferi DNA-positive tissues (by PCR). • Spirochetes were cultured from tissues from pups of 2 litters. • Four pups of 3 separate litters (a stillborn, a neonate that survived to 30 minutes of age, a 20-hour-old, and a 48-hour-old) had B burgdorferi-positive tissues (by PCR), and the 20-hour-old pup was also culture-positive, indicating intrauterine infection. • Further evidence of intrauterine exposure was the presence of IgM antibodies to B burgdorferi detectable by western blot in 3 of 7 one-day-old pups that did not receive colostrum, indicating a primary immune response. • Pups that became infected, but they did not manifest clinical signs of infection, inflammatory response,or increased mortality • Intrauterine infection with B burgdorferi is a mechanism by which pups can become infected in the absence of a vector. "Eight of 8 SI females that had litters delivered pups in which at least 1 had PCR detectable B burgdorferi DNA including 3 pups under 1 day of age (1 stillborn pup, and 1 that died at 30 minutes of age from female SI 3, and a 1 day old pup from SI female 10), providing evidence of in utero transmission."	**11, 12**
Dogs - 1993	"The finding of B burgdorferi specific DNA sequences by PCR in tissues from fetuses from 3/7 litters from females artificially inseminated with semen from spirochete inoculated males demonstrates that B burgdorferi can be transmitted in semen and that in utero infection of the fetuses occurs. These findings indicate that infected male dogs can transmit the organism to females during natural breeding. This could provide a means by which developing fetuses can become infected."	**11**
Foxes - 1993	• 'Transplacental transmission of Borrelia burgdorferi was demonstrated in 2 foxes from a Wisconsin fox ranch.' • 'Spirochetes were cultured from the tissues of 4 neonatal kits from fox vixen 1 and from a stillborn and a neonatal kit from fox vixen 2.' • 'Isolates from the liver and blood of one kit from vixen 1 were identified as B burgdorferi by indirect immunofluorescence using the H5332 monoclonal antibody specific for the 31 KDa protein.' • 'B burgdorferi specific DNA sequences were also detected in tissues from 2 kits in the vixen 1 litter and from 3 in the vixen 2 litter using polymerase chain reaction (PCR).' • 'The brain from vixen 1 and the spleen from vixen 2 also contained PCR detectable spirochetal DNA sequences.' • 'Both vixens were negative for antibodies using the indirect immunofluorescent antibody (IFA) test (a titer of 1:64 or less), but both had IgG antibodies to the 41 KDa and the 34 KDa B burgdorferi proteins by Western blot.' "Transplacental transmission of B burgdorferi to fox kits was found to occur in 2 naturally infected vixens. This conclusion was based on the finding of spirochetes and PCR detectable B burgdorferi specific DNA sequences in tissues of 4 neonatal kits immediately destroyed by one vixen at birth and in tissues from a stillborn and 2 neonatal kits from the other vixen. "	**11**
Coyotes - 1989	Coyotes from southern Texas were sampled for antibodies to Bb from 1980-1986. Coyote fetuses, adult coyote kidneys were cultured for Bb in 1986. Bb was isolated from kidneys of 1/5 coyote fetuses - the mother was seronegative. 'The case of an antibody negative coyote having a Bb culture positive fetus might suggest a localized infection in the reproductive tract or that the female was infected recently and had insufficient time to develop antibodies.' 'This could mean that a survey for Bb infection using the presence of antibodies alone as the method of detection may underestimate the prevalence of infection.' "These findings show that Borrelia sp. (most probably B. burgdorferi) infection has been present in coyotes in Webb County, Texas, since 1984 and that transplacental infection can occur in infected coyotes."	**13**

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Lack of Vertical Transmission of Borrelia burgdorferi in rodent models

Year	Vertical transmission NOT found	Other findings/notes	Citation
1990	'Infection did not affect reproduction or development of young born from infected dams, nor did spirochetes appear in the tissues of neonates.'	'Mice were susceptible to oral infection and transmitted infection to each through through direct contact.'	Wright SD, Nielsen SW. Experimental infection of the white-footed mouse with Borrelia burgdorferi. Am J Vet Res. 1990 Dec;51(12).
1991	'Five pregnant adult female Lewis rats were inoculated i.p. with spirochetes at 4 days gestation. Adult females seroconverted or had positive spleen cultures at 20 days gestation, placentas and fetuses were culture negative.'	'Venereal transmission from seven infected females or six infected males to uninfected rats of the opposite sex was not demonstrated.'	Moody KD, Barthold SW. Relative infectivity of Borrelia burgdorferi in Lewis rats by various routes of inoculation. Am Trop Med Hyg 44:135, 1991.
1991	'all 14 mother mice examined produced infected ticks and exhibited serum antibodies to Bb. However non of 28 offspring produced infected ticks and only a few had evidence of circulating antibody.'	In a separate experiment, no young CD-1 mice, born of infected mothers had IgM antibody to B. burgdorferi.'	Mather TN, Telford SR III, Adler GH. Absence of transplacental transmission of Lyme disease spirochetes from reservoir mice (Permyscus leucopus) to their offspring. J Infect Dis 164:564, 1991.
1999	These experiments support the notion that the LD spirochete, B. burgdorferi, is not transmitted transplacentally, venereally, or via contact with urine or feces from infected hamsters.	However, although the hamster model is an excellent system to explore various tick/Borrelia relationships, experimental data derived from it should be used cautiously in extrapolating to the murine model in nature.	Woodrum JE, Oliver JH. Investigation of Venereal, Transplacental, and Contact Transmission of The Lyme Disease Spirochete, Borrelia burgdoferi, in Syrian Hamsters. J. Parasitol., 85(3), 1999 p.426-430.

Additional Studies in animals of interest re: Bb in milk, transmission via milk, oral infection

Animal studies have revealed Bb in milk and colostrum in infected cows

1988	Colostrum was collected at time of calving and milk samples taken by hand into tubes. 1/3 cow colostrums were Bb culture positive tested by immunofluorescence using a monoclonal antibody H5332 followed by FITC conjugated anti-mouse sera to ensure identification.	Burgess, 1988
1998	Bb was identified in the colostrum of 4/12 cows by PCR.	Leibstein et al, 1998
2000	In a 2.5 year cow with severe disease – history of poor appetite, distended joints and difficulty rising after birth. Noted erythema, warmth, swelling and hypersensitivity of the ventral skin of the udder. Sample of milk of the right forequarter was positive for B burgdorferi sensu stricto DNA.	Lischer et al, 2000

Experimental studies identified transmission of Bb via milk of infected females to their pups (mice)

1996	'Of 25 infected females, 2 (8%) transmitted Bb to their pups on day one via their milk.'	Altaie et al, 1996

Case of a cat seroconverting after ingesting milk from Bb infected Cow

1988	'A cat fed 4ml of milk from an affected cow seroconverted for B. burgdorferi.'	Post et al, 1988

Experimental studies mice (demonstrating oral transmission of Bb)

1990	'Oral induction of infection was tested by dropping 0.1 ml of BSK medium containing approximately 100,000 spirochetes into the open mouths of 4 hand-held mice. After receiving their oral dose, each mouse was put in a separate cage and blood collected every other day for 20 days. Sections of liver, kidney, and spleen were obtained for histologic examination and the remainder of the organs were placed in culture medium for isolation of spirochetes.' 'Three of the four mice receiving the oral inoculum of live spirochetes began producing antibodies by the third day after exposure. All 3 infected mice maintained titers throughout the experiment. Spirochetes were observed in the kidneys, liver, and spleen of 2 of the mice examined by tissue IFA but they were not observed in organs examined by modified Steiner silver stain. Infected mice did not have changes in activity, nor were clinical signs observed or spirochetes isolated from tissue homogenates.' 'Mice were susceptible to oral infection and transmitted infection to each other through direct contact.'	Wright, Nielsen, 1990
1992	'Oral induction of infection was attempted by exposing 5 male and 5 female weanling white mice to a culture of B. burgdorferi. Water bottles were removed for a period of 15 hours, after which the animals were given a bottle filled with liquid containing 105 spirochetes/ml of a diluted BSK culture of B. burgdorferi (NY90-14). Five control weanling mice were exposed to sterile BSK. Mice readily drank the culture media containing live spirochetes as well as the sterile BSK. Skin biopsies from the ear and blood samples were obtained weekly starting 1 week PI for the period of the study. Samples of blood, eye, ear and heart tissue were obtained at necropsy and cultured for the isolation of spirochetes.' 'B. burgdorferi spirochetes were isolated from all 10 mice receiving oral inocula of live spirochetes. Spirochetes were observed by darkfield microscopy in cultures of ear (30%), liver (50%), spleen (30%), kidney (60%), bladder (80%), eye (70%), and heart (50%) following necropsy of these mice at 42 days PI (Figure 5) . No spirochetemias were observed in any of these animals (Table 4). There was no statistically significant difference in the infection rate between orally inoculated and needle inoculated mice (Figure 6).' 'Experimental oral inoculation of white mice with B. burgdorferi produced infections in internal organs; spirochetes were isolated from different organs from each of the orally-inoculated mice.'	Ubico-Navas, 1992

Citations:

1. Leibstein MM, Khan MI, Bushmich SL. Evidence for in-utero Transmission of Borrelia burgdorferi from Naturally Infected Cows. Journal of Spirochetal and Tick-borne Diseases. Vol 5, Fall/Winter, 1998: 54-62
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Comparisons between Lyme disease and Syphilis

"**Syphilis and Lyme borreliosis have similar etiologic, clinical, and epidemiologic characteristics**. Both are multisystem infectious disorders spread worldwide. Their clinical course can be divided into three stages and as to spirochetal origin, antibiotic therapy is similar too. Taxonomical relationship of Treponema and Borrelia could explain also congenital manifestations well-known in syphilis and suggested in borreliosis."

Hercogova J, Vanousova D. Syphilis and borreliosis during pregnancy. Dermatol Ther. 2008 May-Jun;21(3):205-9. doi: 10.1111/j.1529-8019.2008.00192.x. PMID: 18564251.

'Ixodes-borne borreliosis is an infection with a potentially long-lasting course. **The parallels to syphilis are striking.** Both diseases may start with a primary lesion at the site of the spirochetal inoculation (ECM and primary sclerosis, respectively). The early manifestations resolve spontaneously, but a spirochetemia and signs and symptoms from different organ systems (the skin, nervous system, hearts, joints and bone) may develop. In both diseases, long asymptomatic periods (latent periods) may occur and be followed by new manifestations. In some patients, the infection ends with spontaneous cure, and in others persistent infection occurs. If antibiotic therapy is not given, the spirochetes may survive in the body for many years.'

Asbring, E., Hovmark, A. Cutaneous Manifestions in Ixodes-borne Borrelia Spirochetosis. International Journal of Dermatology. Vol 26(4). May 1987

"As our understanding of Lyme disease has grown, **there has been increasing concern about its similarities to syphilis** and the possibility of transmission to the fetus from an infected mother who is spirochetemic during pregnancy."

Adams FG. Connecticut Epidemiologist. Epidemiology Section. State of Connecticut Department of Health Services. Pregnancy and Lyme Disease. March 1989, Vol 9(2).

'There are many similarities between Lyme disease and syphilis. The major ones are their spirochetal etiology, the ability for the spirochetes to stay alive in human tissue for years, occurrence of clinical manifestations in stages, early disease in the skin and later in the brain, and susceptibility to antibiotic treatment. **Thus, one can assume that many of the lessons learned from the centuries of experience with syphilis will apply to Lyme disease**. One of these lessions that could be constantly borne in mind is that spirochetal disease of the brain can mimic many other neurologic diseases.'

Pachner, AR. Borrelia burgdorferi in the Nervous System: The New "Great Imitator". Annals of the New York Academy of Sciences, 539, 56-64, 1988.

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

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

"The **clinical picture is analogous in many ways to syphilis, another spirochetal infection**. Both are characterized by an initial skin infection and periods of latency followed by multi-system involvement that occurs in stages and mimics other diseases. Both can eventually cause progressive, debilitating neurologic disease." "The **course of Lyme disease, like that of syphilis is variable**. The response in untreated persons can range from no symptoms or only localized skin infection to severe and chronic involvement of multiple systems."

Steere, AC. (1993). Current Understanding of Lyme Disease. Hospital Practice (Office ed.), 28(4), 37-44. , April 15, 1993

'Borrelia burgdorferi, the spirochete causing the disease, appears **similar to another spirochete, Treponema pallidum, in its potential to survive in the untreated human host for prolonged periods of time and to cause disease in various organ systems,** in some instances after months or years of clinical latency.'

Pinger, R. R., Hamm, R. H., & Sinsko, M. J. (1989). Lyme disease: a review and an outlook for Indiana. *Indiana medicine: the journal of the Indiana State Medical Association*, *82*(4), 268–272.

"**Like syphilis, Lyme disease during pregnancy may be associated with congenital infection of the infant and resulting clinical illness**. Several reports describe infants who died shortly after delivery, or were stillborn, to mothers who had Lyme disease during pregnancy (73-76). Spirochetes were found in autopsy specimens from some of these babies. Congenital heart defects and syndactyly have occurred in babies of mothers who had Lyme disease during pregnancy, but these associations are anecdotal (76)."

Nadelman RB, Wormser GP. A Clinical approach to Lyme disease. Mt Sinai J Med. 1990. May; 57(3):144-56

"The past 4 years have seen a dramatic increase in the spectrum of tissue and organ damage attributed to Borrelia burgdorferi infection in humans. Lyme disease has now been shown to involve nearly every organ and organ system in both sexes. Initially thought to be a disorder beginning in the skin and progressing to involve the joints, **Lyme disease is now ranked as one of the great mimickers of other diseases, in a manner similar to that once ascribed to syphilis.**

Duray P.H. (1989). Clinical pathologic correlations of Lyme disease. Reviews of infectious diseases, Vol 11 Suppl 6, S1487-S1493

"The **clinical diversity of Lyme borreliosis is a formidable diagnostic challenge to the physician which is matched by the labyrinthine complexity if prenatal syphilis**. Three quintessetial paradigms from the literature of congenital syphilis appeared in the textbook by Stokes in 1945.

1: "Prenatal syphilis is a collection of rare events of interest to the connoiseur of the elegant art of medical investigative diagnosis."
2: "The diagnosis of syphilis in a dead fetus is just is as difficult as the diagnosis of syphilis in a living fetus."
3" "Never 'always', Never 'never..'"

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

"Experimental evidence has shown that **T. pallidum and B. burgdorferi can attach and move across endothelial cell monolayers.** The collective evidence for vascular injury in several spirochetal diseaes, may not be a coincidence, and this tissue could be the primary target for spirochetes as a site outside of circulation. That inflammation of the blood vessels occurs in several spirochetal diseases may be an indication that the organisms reside and even activate endothelium at least for a period of times leading to the production of injury."

Benach, JL., Coleman JL. Chapter 8. Overview of Spirochetal Infections. In: In: Coyle PK. (ed) Lyme disease. Mosby Year Book, 1993. p. 61--68

"**Clinically, Lyme disease is similar to other borrelial infections, most notably syphilis**, in that it involved multiple organ systems and progresses in stages. The first report of the maternal-fetal transmission of Lyme disease in 1985 and subsequent case reports provide evidence that transplacental passage of the spirochete can result in fetal infection. Some authors have suggested an increase in congenital malformations due to Lyme disease; however, this effect has not been proved conclusively to date. Because of the potential adverse fetal outcome and possible long-term maternal complications, it is important to understand the etiology, diagnosis and treatment of Lyme disease."

Alexander JM, Cox SM. Lyme Disease and Pregnancy. Infectious Diseases in Obstetrics and Gynecology 3:256-261 (1995).

"The present authors believe **the taxinomical relationship of T. pallidum and B. burgdorferi is responsible for a similar course of syphilis and lyme borreliosis including congenital infections**. Gestational Lyme borreliosis appears to be associated with a low rish of adverse pregnancy outcomes, particularly with appropriate antibiotic therapy. Further studies are needed to answer the question of a possible teratogenic effect of B. burgdorferi in humans."

Hercagova J., Vanousova, D. Syphilis and borrreliosis during pregnancy. Dermatologic Therapy, Vol 21, 2008, 205-209.

Similarities between Syphilis and Lyme disease

	Syphiis	Lyme Disease
Etiology	Spirochete – Treponema pallidum Can survive in tissue for years	Spirochete – Borrelia burgdorferi Can survive in tissue for years
General Course	Stages of early and late infection Wide spectrum of manifestations Subclinical latent infection	Stages of early and late infection Wide spectrum of manifestations Subclinical latent infection
Dermatologic	Primary: chancre at site of inoculation Secondary: syphilitic rash	Primary: erythema chronicum migrans at side of inoculation Later: Widespread cutaeous eruptions
Nervous System	Meningovascular syphilis Cranial nerve palsies Cerebrovascular accidents Syphilitic demylenation Radiculitis Meningomyelitis CMS perenchymatous inflammation Optic atrophy Argyll Robertson pupil Iritis, uveitis CSF pleocytosis Paralysis Dementa mental status changes	Meningovascular borreliosis Cranial nerve palsies Cerebrovascular accidents Demyelinating lesions in CNS and PNS Radiculitis Meningomyelitis Amyotrophy CMS perenchymatous inflammation Optic atrophy Argyll Robertson pupil CSF pleocytosis Paralysis Dementa mental status changes
Cardiac/vascular	Cardiovascular syphilis, arteritis	Myocarditis, vasculitis
Congenital/prenatal	Stillbirths Congenital anomalies	Stillbirths Congenital anomalies (eye, heart)
Other	Hepatitis Constitutional symptoms in second stage – Fever, headache, malaise, meningismus, generalized lymphadenopathy, mucocutaneous rash	Hepatitis Constitutional symptoms in second stage – Fever, headache, malaise, meningismus, generalized lymphadenopathy, rashes
Laboratory	Positive FTA-ABS False positive Lyme serology Circulating immune complexes	False positive FTA-ABS, negative RPR and VDRL Positive Lyme serology Circulating immune complexes
Treatment	Antibiotics (penicillin) Jarish-Herxheimer reaction	Antibiotics (tetracycline, penicillin) Jarish-Herxheimer reaction

Citation:

Table from: Lane KL., Parker JC. Lyme Disease: A confusing Multisystem Borreliosis. Southern Medical Journal. Vol 82(9), Sept 1989.

Syphilis in the mother

"Identifying asymptomatic infection, especially among pregnant women, through screening using laboratory tests and treatment of positive cases will prevent further transmission and adverse pregnancy outcomes and congenital syphilis."

WHO Guideline on Syphilis screening and treatment for pregnant women. World Health Organization 2017. https://apps.who.int/iris/bitstream/handle/10665/249572/9789241549806-eng.pdf

- **"**Syphilis is passed from person to person through direct contact with a syphilitic sore called a chancre. Transmission of the organism occurs during vaginal, anal or oral sex. Sores of primary syphilis occure about three weeks after contact, mainly on external genitals, vagina, cevix, anus or the rectum. They are often unrecognized in women because they can be asymptomatic."
- "Even without treatment both the primary and secondary lesions resolve and the infection enters a latent stage. Despite the lack of clinical manifestations, the infection can still be transmitted to the fetus." Tertiary syphilis may occur in a third of untreated pople, approximately 3-15 years after infection."(1)
- "Untreated syphilis in pregnancy leads to adverse outcomes among more than half of the women with active disease, including early fetal loss, stillbirth, prematurity, low birth weight, neonatal and infant death and congenital disease among newborn babies." (1)
- "Many people with syphilis do not have any symptoms or have only minor symptoms and do not realize that anything is wrong" (2)
- "In the prepenicillin era, when expression of the disease was much more dramatic, that it is today and only a few serological tests (of low sensitivity and specificity) were available, observations made by clinicians in the field of spphilis indicated that pregnancy affected the natural course of syphilis. As early as 1922, Moore wrote: 'The fact that women who bear syphilitic children often give no history of syphilis and present no signs of the disease (except a positive Wasserman reaction) has long been a common knowledge' and ' a woman infected at or shortly after the time of conception usually does not develop a chancre or secondary syphilis. When the infection takes place late in pregnancy, on the other hand, the usual couse of events follow(s), but is often much delayed.'" (3)
- "If a woman with a child younger than 1 year is diagnosed to have primary, secondary or early latent syphilis, that child should be fully evaluated for signs of congenital syphilis, tested serologically and treated accordingly. When a woman is treated for late syphilis, all her children should be evaluated. Only with adequate prenatal care and post-partum evaluation will congenital syphilis be prevented.' (4)
- "Prenatal screening remains the most important factor in identifying infants at risk for developing congenital syphilis and ideally results in diagnosis and treatment during pregnancy. Although the prevalence of syphilis is low in pregnant women, **the costs of undetected congenital syphilis are so high that screening may be cost-beneficial with prevalences as low as 0.005%."** (5)

Citations:

1. De Santis, M., De Luca, C., Mappa, I., Spagnuolo, T., Licameli, A., Straface, G., & Scambia, G. (2012). Syphilis Infection during pregnancy: fetal risks and clinical management. *Infectious diseases in obstetrics and gynecology*, *2012*, 430585. https://doi.org/10.1155/2012/430585
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4. Sanchez PJ, Wendel GD, Norgard MV. Congenital Syphilis associated with negative results of maternal serologic tests at delivery. Am J Dis Child 1991;145:967-9.
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Seronegativity in maternal syphilis despite fetal/infant infection

"Routine serologic testing of mothers during pregnancy and at delivery is essential to prevent congenital syphilis. However, limitations on the usefulness and reliability of such screening tests exist. Serologic test are poor diagnostic tools during the incubation or early primary stage of syphilis."

Sanchez PJ, Wendel GD, Norgard MV. Congenital Syphilis associated with negative results of maternal serologic tests at delivery. Am J Dis Child 1991;145:967-9.

Monif GRC, Williams BR, Shuman ST, Baer H. The problem of maternal syphilis after serologic surveillance during pregnancy. Am J Obstet Gynecol. 1973:117:268-270.

Al-Salihi, F. L., Curran, J. P., & Shteir, O. A. (1971). Occurrence of fetal syphilis after a nonreactive early gestational serologic test. *The Journal of pediatrics*, *78*(1), 121–123. https://doi.org/10.1016/s0022-3476(71)80275-5

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Bembry, W., Anderson, M., & Nelson, S. (2018). Congenital Syphilis: The Great Pretender Strikes Back. A Case Report. *Clinical pediatrics*, *57*(8), 992–996. https://doi.org/10.1177/0009922817738343

Treatment failure of Maternal Syphilis resulting in Congenital Syphilis

Sheffield, J. S., Sánchez, P. J., Morris, G., Maberry, M., Zeray, F., McIntire, D. D., & Wendel, G. D., Jr (2002). Congenital syphilis after maternal treatment for syphilis during pregnancy. *American journal of obstetrics and gynecology*, *186*(3), 569–573. https://doi.org/10.1067/mob.2002.121541

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Silva, S., Henriques, R., Gomes JP, Boreggo MJ, Afonso E. Could we miss congenital neurosyphilis? Lancet Infectious Diseases 2012;12:816.

(Mother was treated for syphilis during second trimester. At birth baby had a non-reactive RPR test, ELISA IgG-positivity and IgM negativity. Baby developed hypotonia, seizures and findings suggestive of neurosyphilis. Full neurosyphilis investigation for Treponema pallidum in cerebrospinal fluid with a real-time probe based PCR method and positive result was confirmed by a nested PCR and target sequencing. T pallidum was not detected in blood samples from the mother or newborn baby.)

Rawstron, S. A., & Bromberg, K. (1991). Failure of recommended maternal therapy to prevent congenital syphilis. *Sexually transmitted diseases*, *18*(2), 102–106. https://doi.org/10.1097/00007435-199118020-00009

Hardy JB, Hardy PH, Oppenheimer EH, Ryan SJ, Sheff RN. Failure of Penicillin in a Newborn With Congenital Syphilis. *JAMA.* 1970;212(8):1345–1349. doi:10.1001/jama.1970.03170210051008

Congenital Syphilis

"Congenital syphilis is now **rarely diagnosed on clinical grounds** primarily because of the serologic surveillance required by most states at the time pregnancy is diagnosed. This has eliminated much of the early fetal involvement which often manifested at birth. Even in the first year of life, less than 10 per cent of the cases are identified. The fact that organ pathology is not fully developed at birth emphasizes the necessity for early diagnosis and therapy."

Monif, GR., Willians BR, Shulman ST & Baer, H. (1973). The problem of maternal syphilis after serologic surveillance during pregnancy. American Journal of Obstetrics and Gynecology, 117(2), 268-270.

- "Congenital syphilis results from in utero infection of the fetus with Treponema pallidum, the causative organism of venereal syphilis. Congenital infections may present with clinical symptoms in the newborn period or infancy ("early" congenital syphilis) but **most infected infants have no clinical evidence of infection at birth. Infected but untreated newborns may not develop manifestations of disease until several months to years later** ("late" congenital syphilis)." (1)
- "Newborn infants with congenital syphilis may be severely affected, although **two-thirds show no clinical signs of infection at birth and are identified only by routine prenatal screening**."(1)
- "Because the fetus acquires T pallidum by hematogenous spread from the mother, no primary or chancre stage in the fetus occurs, and **widespread involvement is usual."** (1)
- "After fetal infection occurs, **any organ system can be affected because of widespread spirochetal dissemination**." (2)
- "**Congenital syphilis affects many different organ** systems and can have devastating effects on untreated infants and children."(3)
- "Congenital syphllis is usually divided into early congenital syphilis and late congenital syphilis. Clinical manifestations after birth are arbitrarily divided into early congenital syphilis at 2 years of age or less, and **late congenital syphilis in older children (but usually manifest near puberty)."** (3)
- "The **majority of infants born to mothers with untreated syphilis appear normal and have no clinical or laboratory evidence at birth**, but may develop manifestations of disease months to years later if left untreated."(4)
- "The **diagnosis of congenital neurosyphilis is difficult to establish since the majority of infants with congenital syphilis do not manifest any abnormalities on neurologic examination**.' (4)
- "Compared with conventional diagnostic testing, **the current T pallidum specific IgM tests are insensitive and inadequate for diagnosis of congenital syphilis**."(1)
- "No commercially available immunoglobulin M (IgM) test including the fluorscent treponemal antibody absorption (FTA-ABS)-IgM test or total IgM determination is recommended." (4)
- "The most common dilemma currently posed by syphilis in children is the management of asymptomatic infants born to mothers with positive serologic tests for syphilis. The clinician must assess the effectiveness of the maternal syphilis treatment regimen for adequatcy in treating infection in the fetus and must determine whether to treat a newborn infant who may harbor and infection that is not yet clinically apparent." (1)
- 'In the untreated congenitally asymptomatic infant, the organisms apparently vegetate in a commensal state until appropriate biological conditions that promote virulenceand pathogenicity develop.' (5)
- 'The congenitally infected child is at risk to go on to develop all the acquired neurosyphilis syndromes' (6)
- **'Evaluation of infants at birth remains problematic** since it is unknown how many asymptomatic babies who are at risk for congenital syphilis are truly infected. Ongoing studies that involve evaluation of Treponema pallidum-specific IgM, using Western Blots and EIAs and T. pallidum infection, using immunofluorescence, will help determine who has been infected. **However, even with IgM serology, physical examination, x-rays and lumbar punctures will be needed to evaluate these babies**.' (7)

Citations:

(1) Jenson, HB. Congenital Syphilis. Seminars in Pediatric Infectious Diseases, Vol 10, No 3 (July), 1999:pp 183-194.

(2) De Santis, M., De Luca, C., Mappa, I., Spagnuolo, T., Licameli, A., Straface, G., & Scambia, G. (2012). Syphilis Infection during pregnancy: fetal risks and clinical management. *Infectious diseases in obstetrics and gynecology*, *2012*, 430585. https://doi.org/10.1155/2012/430585

(3) Bembry, W., Anderson, M., & Nelson, S. (2018). Congenital Syphilis: The Great Pretender Strikes Back. A Case Report. *Clinical pediatrics*, *57*(8), 992–996. https://doi.org/10.1177/0009922817738343

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Congenital Syphilis – CDC Guidelines 1988

7.1.2 Microscopic Evaluation

The placenta and the umbilical cord may serve as excellent sites for the collection of specimens that can be examined by darkfield microscopy, immunofluorescence, H & E stains, or silver stains. Specimens from the placenta and umbilical cord should be microscopically examined for those infants born to mothers with reactive serologic results, when no histories are available, or when the placenta is hydropic. Additionally, all neonatal lesions should be examined for treponemes.

Treponemes seen in lesion material or in autopsy or biopsy sections by silver stain or darkfield, although considered definitive, may be confused in endemic areas with the Borrelia of Lyme disease. MATERNAL NONTREPONEMAL SEROLOGY MAY BE USED TO DIFFERENTIATE LYME DISEASE FROM SYPHILIS. The VDRL is uniformly nonreactive in Lyme disease.

An effort should be made to diagnose congenital syphilis in a stillborn whenever clinical findings or a maternal history suggests the possibility of untreated syphilis. Direct and histologic microscopic examinations of placenta, organs, and umbilical cord, as well as radiographic examinations of long bones, are helpful in postmortem diagnosis. The MHA-TP test can be used on the blood of a stillborn; blood can be obtained by direct cardiac punctures.

Centers for Disease Control. Guidelines for the Prevention and Control of Congenital Syphilis. MMWR 1988;37 (suppl no. S-1);1-13

Congenital Syphilis – CDC Current 2021 Guidelines 'Evaluation and Treatment of Neonates'

Retrieved from: https://www.cdc.gov/std/treatment-guidelines/congenital-syphilis.htm

Scenario 1: Confirmed Proven or Highly Probable Congenital Syphilis

Any neonate with

- an abnormal physical examination that is consistent with congenital syphilis;

- a serum quantitative nontreponemal serologic titer that is fourfold[§] (or greater) higher than the mother's titer at delivery (e.g., maternal titer = 1:2, neonatal titer ≥1:8 or maternal titer = 1:8, neonatal titer ≥1:32)[¶]; or
- a **positive darkfield test or PCR of placenta, cord, lesions,** or body fluids **or a positive silver stain of the placenta or cord.**

Recommended Evaluation

- CSF analysis for VDRL, cell count, and protein**
- Complete blood count (CBC) and differential and platelet count
- Long-bone radiographs
- Other tests as clinically indicated (e.g., chest radiograph, liver function tests, neuroimaging, ophthalmologic examination, and auditory brain stem response)

Recommended Regimens, Confirmed or Highly Probable Congenital Syphilis

- **Aqueous crystalline penicillin G** 100,000–150,000 units/kg body weight/day, administered as 50,000 units/kg body weight/dose by IV every 12 hours during the first 7 days of life and every 8 hours thereafter for a total of 10 days
- OR
- **Procaine penicillin** G 50,000 units/kg body weight/dose IM in a single daily dose for 10 days
- If >1 day of therapy is missed, the entire course should be restarted. Data are insufficient regarding use of other antimicrobial agents (e.g., ampicillin). When possible, a full 10-day course of penicillin is preferred, even if ampicillin was initially provided for possible sepsis (*648–650*). Using agents other than penicillin requires close serologic follow-up for assessing therapy adequacy

Suspected syphilis during pregnancy due to cross reaction by a Borrelia infection

Abstract:

"A weakly positive titre (1:20) in the Treponema pallidum haemagglutination test and a highly positive titre (1:1280) in the fluorescence Treponema antibody absorption test, but negative result for IgM antibodies, were found in the serum of a 23-year-old pregnant woman. The cardiolipin microflocculation test was at first borderline positive, but negative on repeat. In the absence of a history of syphilis tests for Borrelia antibodies were performed. Those for antibodies against B. burgdorferi were highly positive in the ELISA test (550 units), in the indirect Borrelia immunofluorescence test 1:1280 for IgG antibodies and 1:160 for IgM antibodies. In the Borrelia-specific indirect haemagglutination test, which measures both IgG and IgM antibodies, the titres were 1:640 to 1:1280. **These results confirmed the presence of an infection with B. burgdorferi and not with Treponema pallidum."**

Enders, G., Biber, M., Baier, R., Hlobil, H., & Wellensiek, H.J. (1988). Luesverdacht in der Schwangerschaft durch Kreuzreaktionen bei Borrelien-infecktion (Suspected syphilis in pregnancy due to cross reactions in Borrelia unfection). Deutsche medizinische Wochenschrift (1946), 113(39), 1511-1514. https://doi.org/10.1055/s-2008-1067843

Of note: the pregnant woman had no history of tick bite or typical symptoms of Lyme disease and a chronic Borrelia infection was suspected. Authors also state (translated from German): 'The following observation shows that positive syphilis results **can be simulated by a symptom-free Borrelia infection in individual cases** and that the exact diagnosis of syphilis or Borrelia infection can only be made with the aid of all previously known tests including those used in routine diagnostics.'

Epidemiological/Prospective Research Lyme disease and Pregnancy

Date	Type of Study/ Testing methods	Findings	Hx of Tickbite Or Lyme disease	Sub-clinical /past infection?	Adverse outcomes	Testing Baby?	Placenta	Long term F/U in babies	
1985	**Cord blood serosurvey** **Cord blood tested by Bb IFA or Bb ELISA** N= 463 infants (282 from endemic area + 166 control)	30 newborns (7.1%) had detectable(IgG) Bb antibody 26 (10.2%) endemic 4 (2.4%) non-endemic No association between congenital malformations and presence of Bb antibody.	2/30 cases Lyme disease had been documented in pregnancy	28/30	Infants w detectable antibody were lower birthweight, small for gestational age and some degree of neonatal jaundice (not statistically significant)	Cord blood at delivery In no cases was IgM antibody detected	No	No other testing in exposed infants.	**1**
1986-1988	**Prospective Cord blood serosurvey** Cord blood tested by **Bb ELISA** Designed to examine relationship between maternal exposure to Lyme and adverse pregnancy outcome Cord blood tested by Bb ELISA 2504 infants from endemic area 2507 control hospital Mothers were contacted during post-partum hospital stay by research nurse and asked to fill out questionnaire before discharge. F/U information was obtained by child's pediatrician at 6 months of age via mailed questionnaire.	In this study a positive serology and positive clinical history were not often present in same individual. (This could be because treatment can blunt the anibody response; hence a positive clinical history in absence of positive titre. Similarly cases can go undiagnosed becaue of absence of EM rash and resemble a flu like illness; hence a positive titre in absence of clinical dx. There also may be a larger proportion of women than has been identified in our study who had pas subclinical infection – women from endemic area with a seropositive cord blood who did not report past Lyme disease. Sample size limitations are considerable in this study. In order for any exposure to show a statistically significant 2.5 fold increase in their frequency of congenital heart defects, a sample of approx 2590 exposed subjects are needed. The findings of this study and our earlier population study taken together, indicate that having a past treated or untreated infection with Bb does not increase the risk of low birthweight, early fetal loss or congenital malformations as a whole. The effects of maternal infection around the time of conception or during pregnancy are not known. The effects of past infection on the risk of specific malformations or outcomes in early childhood are not known.	6 women dx w Lyme during pregnancy (all treated). 23 women reported pre-pregnancy Lyme disease and 91.3% treated. 67 women reported tickbite during pregnancy (25% had been treated)	20 infants had IgG positive cord blood samples but mothers did not have correspon ding clinical hx of Lyme disease.	Lyme disease **before** study: 2 (2/23 or 8.6%) infants born with malformations: One infant died of severe multiple congenital heart defects and the other had hydrocele and laryngomalaica**.** Lyme disease during pregnancy (1/6) (16.6%) one infant had hypospadias. Tick bite in pregnancy, 8/67 (12%) infants had congenital anomalies including ventricular septal defect, vesicoureteral block with reflux, hypospadias, inguinal hernia, laryngomalacia, haemangioma, genu varum, metatrsus adductus.	Cord blood at delivery In no cases was IgM antibody detected. 20 infants had IgG positive cord blood samples	No	At six months Pediatrician completed questionnair e on growth and development , medical issues, hospitalizati on. (68% endemic infants and 63% controls had f/u data) 'This study has limited follow-up with respect to long-term sequalae of prenatal exposure to Lyme disease. Developmen tal problems may not develop until after the first year of life.' Repeat testing on IgG pos infants not done.	**2**
Nov 1988-April 1990	**Prospective Serosurvey** Sample taken at first prenatal visit and at time of delivery. 2/3 of Samples tested by FIAX method for IgG and IgM antibodies. 1/3 were tested by ELISA as methods changed – see paper. Positive samples were further tested for IgM to determine if infection current as well as syphilis and rheumatoid factor. Self administered questionnaire at first prenatal visit. F/U data concerning pregnancy outcome came from on or more sources incl: midpregnancy interview, contact at hospital during delivery, a mailed questionnaire to the woman six months after expected date of delivery, pediatric and obstetric records.	11 women were seropositive at first prenatal visit (0.7%). 'we could not identify very early miscarriages, those that occurred before the first prenatal visit.' Maternal Lyme disease or increased risk of exposure not associated with fetal death, decreased birth weight, congenital malformations or prematurity Statistically significant associaion between past miscarriages and a history of tick bite. Significant association between having had a tick bite within 3 years of conception and congenital defects. (Whether the women had or had not been treated for tick bite did not alter the relationship). The nature of the relatioship between Lyme disease exposure and congenital malformations is not conclusive, primarily because of small numbers involved.	5/11 (45%) women had a history of Lyme disease in the past	6/11 (55%) no hx Lyme disease but seropos.	3/10 (30%) seropositive pregnancies had congenital anomalies 1: metatarsus adductus 2: stomach reflux 3: multiple major anomalies with Vater. One woman had negative serology at prenatal visit and experienced flu-like illness in second trimester of pregnancy, was untreated. At delivery both maternal and infant IgG antibody positive, but not IgM. At birth, baby was healthy and no problems up until one year of age. (no testing placenta or f/u testing noted in baby)		No	Information on babies was obtained from 6 month materal follow-up	**3**

1986 /87	**Serosurvey** IFA – threshold for IgG was 1:64, sera with >or= 1:64 were checked for IgM antibodies Blood samples taken from pregnant women and cord specimens from offspring collected at Department of Obstetrics, University of Zurich. Routine laboratory assessment of pregnant women included screening for syphilis by Treponema pallidum haemagglutination test. In second phase, records of mothers with Bb IgG titres > 1:64 were reviewed for symptoms compatible with Lyme disease and records of neonates checked. Detailed history in particular to Lyme disease was obtained from mothers and pediatricians. Clinical exam of children was carried out and serum samples drawn from children at that time.	15/1416 mothers seropositive but syphilis identified in 3/15, so 12/1416 seropositive for Lyme disease. Seroprevalence 0.85% Of 12 seropositve pregnancies: 8 were born at term 2 pretern 2 post-term <u>Adverse outcomes:</u> Hyperbilirubinemia (2 infants) Muscle hypotonia attributed to medication given to mother (1 infant) Underweight for gestational age (1 infant) Macrocephaly (1 infant) Supraventicular extrasystoles (1 infant) Ventricular septal defect (1 infant) One post-term infant was underweight for gestational age as consequence of chronic placental insufficiency (no inflammatory lesions of the placenta by histology) Child with cardiac defect (VSD) born to mother with tick bite during 1st trimester of pregnancy, followed by EM rash and recurrent arthralgia and headaches but was undiagnosed and untreated. Infant lacked specific antibodies at 10 months of age, thus authors sates placental transmission of spirochete seems unlikely although immunotolerance cannot be excluded.	<u>7/12 (58%) positive history</u> 5 women hx compatible with pregestational Lyme. 1 with EM 1 arthralgia 1 headaches 2 parasthesia In addition: 1 woman recalled tick bite before pregnancy 1 woman tick bite in first trimester w EM, not treated (showed evidence of clinically active Lyme disease)	<u>5/12 (42%) no history</u>	<u>7/12 children w adverse outcomes</u> Hyperbilirubinemia (2 infants) Muscle hypotonia attributed to medication given to mother (1 infant) Underweight for gestational age (1 infant) Macrocephaly (1 infant) Supraventicular extrasystoles (1 infant) Ventricular septal defect (1 infant)	Cord-blood specimens collected Children had titres within the range of one dilution step. None of the probands had specific IgM.	Mention of 1 placenta – see findings No mention of other placentas	At 9-17 months 11/12 children were re-examined, all children clinically healthy except for the infant w cardiac defect (born to mother w acute infection). IgM not detected in baby at 10 months. One other 9 month baby had a borderline titre of 1:64 (IFA) but no IgM detected.	**4**
1986?	Prospective study of Pregnancy outcomes in Women with Lyme disease. 17 women acquired LD while pregnant, definate LD cases by CDC criteria, all enrolled before delivery. All received antibiotics after LD was diagnosed.	5 women acquired LD in 1st trimester 8 in 2nd trimester 4 in 3rd trimester 15 delivered normal infants with no evidence of Bb as determined by cord blood IgM.	17/17	-	One missed abortion at 13 weeks, (cultures and stains have not documented Bb as etiology) A woman who acquired LD at 7 weeks delivered a child with syndactyly.	Cordblood IgM in all infants negative	No	No mention of long term f/u of infants. No repeat testing.	**5**
1987	Prospective and Retrospective 19 cases identified with onset between 1976 and 1984. 17 women had ECM 2 women didn't 2/19 had positive serology	(26%) 5/19 had adverse outcomes (3 treated, 2 not treated with antibiotics) 'Although B burgdorferi could not be implicated directly in any of the adverse outcomes, the frequency of such outcomes warrants further surveillance and studies of pregnant women with Lyme disease.' 1: intrauterine fetal death 20 weeks (culture and IFA of fetal tissue + placenta negative) 2: Prematurity at 36 weeks, jaundice at 4 days old. At 9 years, child had normal anatomic and functional development. 3: syndactyly. 4: cortical blindness and developmental delay. At one year of age child had no serum antibodies to Bb (CSF not tested). 5: petechial, vesicular rash and jaundice Infant treated with PCN for 10 days, no other common neonatal condition diagnosed. 'The rash in the infant born to mother with Lyme disease during labor may have been due to congenital Lyme disease but the case occurred before availability of Lab tests for Bb and microbiologic confirmation was not obtained.' In 4/5 cases w adverse outcome, babies were not tested for Bb at birth. Placentas were not examined for spirochetes.	19/19	-	intrauterine fetal death 20 weeks Prematurity at 36 weeks, jaundice at 4 days old. syndactyly cortical blindness and developmental delay petechial, vesicular rash and jaundice	Testing not done on any infants or children	1 placenta Tested and negative	Mention of one child well at 9 years of age.	**6**

1988	Retrospective case control study Blood samples from a series of 49 cases of spontaneous abortion (all but 4 during first trimester of pregnancy) and a series of 49 cases of term pregnancy were tested by IFA (a titre of specific IgG >/= 1:64 was positive.	Specific antibodies to Bb detectable at a titer ranging from 1:64-1:256 in 6/49 (12.2%) of the 49 spontaneous abortion group patients. 3/49 (6.12%) of term pregnancies were positive with titres ranging from 1:64-1:512. None of these patients remembered a tick bite or EM rash, all delivered healthy infants. 'Athought Bb could not be implicated directly as a cause of abortion, seropositive women were more frequently (12.2%) detected among the spontaneous abortion grup than among term pregnancy group. (6.12%).' 'these preliminary data confirm the necessity for further investigations on Lyme borreliosis complicated pregnancies. Necessity for routine serological testing of pregnant patients in endemic areas has been suggested and seems to be supported by our data, given the frequency of cases in which early infection symptoms were presumably misdiagnosed.' Authors recommend 'parafifin sections of placental tissues and abortion material from every seropositive or clinically suspected cases should be examined by indirect immunofluorescence and silver stain to evaluate transplacental transmission.	4/6 seropos patients from spontaneous abortion group reported a tick bite ranging from 6-36 months prior to abortion,	2/6 patients (spontaneous abortion group) reported no tick bite. 3/3 patients from control group with pos sera did not have recall of tickbite or symptoms	Three Infants from control group born to seropositive mothers were healthy, full term infants	No infants from control group tested for Bb.	No	No mention of f/u in infants born to seropositve mothers from control group	**7**
1988-1989	**Sero-survey** 638 women receiving antepartum care between July 1988 -June 1989 tested for antibodies to B. burgdorferi using the FIAX test. Reported sensitivity and specificity for this test 73% and 100% respectively. Patients with positive serology were also tested for syphilis, rheumatoid factor and ANA antibodies due to potential cross reactivity. Women with documented tick bites or thought to have active Lyme disease were treated with antibiotics. Patients with a positive serology who were asymptomatic did not receive antibiotic therapy, antibiotics were given after delivery.	1.1% - 7/638 women tested had a true positive Bb serology by FIAX method. Approx. 40% (3/7 women) had documented tick bites or active Lyme disease. Treated with antibiotics. No obstetrical complications. Approx. 60% (4/7) were asymptomatic, no history of tick-bite or associated clinical symptoms. NOT treated with antibiotics. 2/4 of asymptomatic mothers (50%) had adverse pregnancy outcomes. Adverse outcomes in the asymptomatic, untreated women could not be attributed directly to Lyme disease. Histologic studies from one case of placenta, membranes and cord revealed chorioamnionitis and funisitis although in this case, Staphylococcus aureus grew from placenta surface. Testing of placentas by culture, PCR and histologic examination for Bb was not mentioned.	40% (3/7 women) had documented tick bites or active Lyme disease.	60% (4/7) were asymptomatic, no history of tick-bite or associated clinical symptoms and 2/4 had adverse outcome	3 women with positive Lyme disease serology with a recent tick bite or clinical symptoms and received antibiotic treatment had good pregnancy outcomes. Of 4 untreated seropos women, 2/4 had chronic medical disorders that could adversely affect pregnancy outcome. **<u>Outcomes:</u>** 1: Premature rupture of membranes at 36 weeks (mother had Crohn's disease) but delivered healthy infant one week later 2: Preterm labor (28 weeks) associated with chorioamnionitis. Culture from fetal surface of placenta grew Staphylococcus aureus. 3: Intrauterine growth retardation and small for gestation (SGA) infant with 5 min Apgar score of 5 (mother was a drug abuser)	Not Done	Mention of 1 placenta – see findings No mention of other placentas	No mention of long-term follow-up of any infants	**8**
1989	**Sero-survey** Asymptomatic women were tested for anti-B burgdorferi antibodies (IFA) at first prenatal and post-partum visits. (Marshfield Clinic, Wisconsin) Outcome of pregnancy was recorded for each patient. According to Edly, investigators of this study planned to include 1,000 patients in the final report. However, no further data/report was published.	12% of asymptomatic pregnant women (14/116) were seropositive for Lyme – 12/116 had a miscarriage (10.3%) 1/12 seropositive women had a miscarriage (8.3%) Investigators preliminary conclusions were that asymptomatic Lyme disease does not have an important effect on outcome of pregnancy.	No	All IFA pos women were asymptomatic	1/12 seropositive women had a miscarriage (8.3%)	no	no	no	**9 + 10**

1989	7 year Retrospective analysis of perinatal autopsies performed from 1978-1985 and a three year prospective study of perinatal deaths	3/14 cases mothers had a history of tick bite/EM (Case 1, 13, 14) 1/14 cases mother had positive Bb IFA/EIA at 2/3 labs (Case 1) 11/14 cases presumed subclinical infection in mother (cases 2-12) 8/14 cases mothers negative by standard serology tests but spirochetes were still discovered in fetal tissue(Case 2-4, 7,8, 10, 13, 14 10/14 cases spirochetes or spirochetal fragments identified in fetal autopsy tissue including brain, heart, kidney, liver, heart and adrenal gland (Cases 1-10) 5/14 cases spirochetes identified in placenta 'It is my expectation that the spectrum of gestational Lyme borreliosis will expand into many of the clinical domains of prenatal syphilis.' '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.	3/14 cases mothers had a history of tick bite/EM (Case 1, 13, 14)	11/14 cases presumed subclinical infection in mother (cases 2-12)	2 cases of neonatal death noted (Case 5 and 6) Both babies died shortly after birth, both had multiple anomalies including heart defects. Spirochetes identified in fetal tissue. A separate study of SIDS cases revealed 2/10 SIDS cases showed spirochetes morphologically compatible with Bb in infant brain of infant male who died at 4 months and infant female who died at four months.	Case 13 cord blood negative by IFA and ELISA (mother had been treated for Lyme in pregnancy)	5/14 cases spirochetes identified in placenta	Mention of two infanst (case 12 and 13)	11
1996	Placentas of 60 asymptomatic women with a positive or equivocal ELISA for Bb antibodies were examined for spirochetes using a silver stain. Selected consecutively over a 6 month period of time from a prenatal screening program in Westchester County, New York – an area endemic for Lyme disease. At delivery, cord blood was tested with ELISA and Western Blot for Bb serology.	3/60 placentas (5%) with spirochetes identified by silver stain 2/3 pos for Bb by PCR No maternal history of tick bite or clinical symptoms of Lyme disease. No mention of maternal antibiotic treatment but authors make a point of stating 'none of the patients treated for syphilis had spirochetes in their placentas.' 2/3 asymptomatic women would be considered seronegative by two tier testing criteria (equivocal ELISA and negative WB) 1 asymptomatic woman had both an equivocal ELISA and WB 'The significance of placental spirochetes is unknown.' 'presence of Bb spirochetes in placenta implies fetal transmission' 'No relationship between the presence of placental spirochetes and the results of Lyme serology or the pregnancy outcome.' 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.	-	3/60 placentas of asymptomatic women revealed spirochetes.	-	Three babies born to mothers with placental spirochete were healthy at birth and negative Bb cord IgG and IgM WB	**See findings**	No long term F/U	12
2010	Review of cases of 95 women w Lyme borreliosis during pregnancy evaluated at the Center for Tick-Borne Diseases, Budapest, over the past 22 years. 'Placentas and offspring were not tested for Borrelia by PCR or culture in our study. Therefore, it cannot be concluded that the adverse outcomes were a result of a Borrelia invasion of the fetus or placenta.'	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. 'Our findings demonstrate a statistically significant association between untreated Lyme borreliosis and adverse pregnancy outcome.' Borrelia immunoblot from cord blood was performed on 74 infants, none showed IgM. All newborns born to mothers who were IgG at delivery were also IgG positive mirroring IgG pattern of mothers suggesting these antibodies maternal origin. 'Our results indicate that an untreated maternal Bb sl infection may be associated with an adverse outcome, although bacterial invasion of the fetus cannot be proven.'	All women diagnosed with Lyme disease	N/A	Adverse outcomes in 20 pregnancies included Miscarriage (6) Stillbirth (1) Prematurity (1) Cavernous hemangioma (4) Dysplasia coxiae (2) Pyloric stenosis (1) Cerebral bleeding (1) Neonatal Jaundice (2) Muscular hypotonia (1) Hypospadias (1) Skeletal anomaly (1)	IgM cordblood immunoblot of 74 infants negative	No	No mention of L/T follow-up in exposed babies/ Children No repeat testing of children at later intervals	13

2020	Prospectively acquired data From 304 cases of erythema migrans (EM) in pregnant women, diagnosed in the period 1990-2015 was assessed and compared with that in age-matched non-pregnant women. Patients were evaluated before commencing treatment with antibiotics, again two weeks later, and then at two, six, 12, and 18 months. At the first visit after delivery, detailed information about the birth and the infant was collected. A pediatrician monitored the babies at birth and after 6 months; however, several babies had more frequent and/or longer follow-ups. Frequency of unfavorable outcomes assessed.	Outcome of pregnancy was unfavorable in 42/304 (13.8%) patients: perterm birth in 22/42 (52.4%), fetal/perinatal death in 10/42 (23.8%) and/or anomalies in 15/42 (35.7%) Several patients had potential explanation(s) for the unfavorable outcome. 'Since we did not demonstrate the direct detection of borreliae in fetal tissue or umbilical blood, etc., which is a substantial limitation of the present study, we do not know whether a relatively favorable outcome of pregnancy is the result of our efficacious antibiotic treatment or a consequence of very rare or perhaps even non-existent borrelial involvement in the offspring.'	304 cases of EM rash in pregnancy	N/A	Adverse outcomes included: Miscarriage, Stillbirth, Prematurity Perinatal death (25 weeks) Respiratory Distress Syndactyly Neonatal Jaundice Ureteral stenosis, hydronephrosis, hydroureter Hypospadias Pulmonary stenosis Cerebral bleeding (ventricular and periventricular) Vesicoureteral reflux Atrial septal defect Ventricular septum defect extrasystoles Hearing deficit Open foramen ovale	No testing of infants	**No**	No details regarding long-term follow-up of children.	14

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Observations regarding epidemiological/prospective studies:

1. Epidemiological studies can only suggest an association (or lack thereof) of presence of infection and adverse outcomes. Findings are heavily influenced by maternal inclusion criteria and how thoroughly babies are evaluated/followed longitudinally for evidence of infection.
2. Several studies which identified adverse pregnancy outcomes did not test placentas, fetal tissue, products of conception for Bb, either provided limited or no information regarding long-term follow-up of exposed babies.
3. Most of the epi studies which look for patterns of adverse outcomes or congenital defects in endemic vs control groups - never tested the babies with IgG positive cord-blood/adverse outcomes, placentas or decidua using direct detection techniques such as PCR or culture and therefore could not draw any conclusions which would provide evidence of a possible causal link. Babies w IgG positive cord-blood were not tested at 12-18 months to see if IgG persisted (as by this time, passive maternal antibody would have waned).
4. In other infectious organisms passed transplacentally, babies are often asymptomatic at birth and only develop symptoms or detect malformations later on.
5. Using IgM as a marker of infection in a newborn is not a sensitive enough measure – and in all the epi studies done to date– this is the end-point – however, with an infant immune system being immature, IgM production may be delayed or even abrogated in the case of a mom being inadequately treated for Lyme during her pregnancy. Possible limitations/interpretation of negative cord blood IgM were not discussed in any Lyme and Pregnancy epi study as done in studies performed on other congenital infections.
6. If we look to other congenital infections, methodologies used to confirm infection include: silver staining or PCR of placenta or other tissue, immunohistochemistry, nucleic acid testing and reverse-transcription polymerase chain reaction. Babies are followed longitudinally, seen by various sub-specialists.

A paper published by authors in Tanzania, Africa, reported a serological survey conducted in a rural area of Dar Es Salaam which was testing for antibodies specific to Borrelia burgdorferi using an ELISA test specific for IgG and IgM antibodies to the Bb flagellum. The results were concerning as 19 out of 50 pregnant women (38%) had antibodies to Borrelia burgdorferi and 30 out of 100 blood donors (30%) had antibodies to Bb. Authors were calling for 'immediate efforts to conduct clinical, entomological and bacteriological investigations to confirm what extent Lyme exists in Tanzania'.

Mhalu F.S, Matre R. Serological evidence of Lyme Borreliosis in Africa: Results from Studies in Dar Es Salaam, Tanzania. East African Medical Journal, Vol 73, No 9, 1996.

A large sero-survey from Russia enrolled 1039 women during routine pregnancy check-ups. There was a seropositivity rate of 5.5% (57 of 1039 women). Authors stated they did further clinical and serological observations in cases of seropositive women and they also noted positive results in blood samples taken from umbilical blood in newborns. They also reported that histological and bacteriological study of placenta material had been undertaken and they were monitoring children of mothers with antibodies to the Lyme disease pathogen in their first year of life. They stated 'the data accumulated to date indicate that LD represents a serious risk factor in pregnancy: it increases the likelihood of miscarriage, has a teratogenic effect on the fetus in intrauterine infection and increases the indicators of perinatal mortality.' Authors stated that specific results from their studies would be analyzed in separate reports. It appears these reports were not published.

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Gestational Lyme with Healthy Pregnancy Outcomes – Case Reports

	Maternal History/Treatment	Outcome	Testing Baby	Placenta	F\U?	Citation
1986 3 cases	Three pregnant patients diagnosed with Lyme (EM) in 12th, 14th and 22 weeks gestation. All treated with Pen V 500mg QID for 21 days	All delivered full term, normal infants	No mention	No mention	No mention	Berger, 1986.
1987 1 case	Pregnant mother bitten by tick 24 week gestation, developed EM rash, no systemic symptoms. Tx: PCN	Gave birth at 39 weeks, healthy male infant.	Cord blood neg	Normal Placenta	No mention	Mikkleson, Palle, 1987.
1990 3 cases	3 pregnant women 1: uncomplicated EM – treated with oral PCN 2: EM multiple lesions + fever, treated 4 days IV PCN G and 10 days oral PCN. 3: neuroborreliosis treated w 14 days IV cefuroxime	Healthy newborns	No mention	No mention	No mention	Stiernstedt 1990.
1990 6 cases	6 pregnant patients with active Lyme borreliosis 2 EM (untreated), 2 carditis (IV antx), 1 facial palsy and TMJ (IV antx), 1 knee synovitis (not treated)	Normal outcomes	No Mention	No Mention	No Mention	Luger, 1990.
1991 1 case	Pregnant mother 27 weeks expanding EM rash, asymptomatic. Tx: with IV ceftriaxone for 21 days.	Healthy baby.	No mention	No mention	No mention	Schutzer, 1991.
1994 1 case	Pregnant mother developed EM at 36 weeks. Treated with amoxicillin for one month	Child was healthy	Neg EIA 6+9 mths	No inflammation Silver stain neg	No mention	Remy et al, 1994.
1998 1 case	Pregnant mother 25 weeks gestation, EM rash on abdomen, fever, shortness of breath. Treated with rifampin for Ehrlichiosis (dx PCR) and 21 days cefuroxime for Lyme. Amniotic fluid - tinged w meconium	'No evidence of disease in the child'	No mention	Placenta normal	No mention	Buitrago et al, 1998
1999 1 case	Pregnant mother developed unilateral facial palsy, one month after tick bites, no EM. Diagnosed with Lyme based on history and serological results. Tx: 2 weeks of IV ceftriaxone (2 G day) 14 days.	Two healthy children delivered by C-section	IFA + ELISA of cord blood neg	PCR negative	No mention	Schaumann et al, 1999
2002 1 case	Mother 3 month history of multiple expanding EM rash first trimester of pregnancy, no systemic symptoms, did not recall tick-bite. At 32 weeks Tx with IV PCN for 14 days. Positive IFA and WB IgG serology.	Healthy female infant delivered at 38 weeks	No mention	No mention	No mention	Tsai et al, 2002
2006 1 case	42 year old woman, developed L knee pain at 34 weeks gestation. No recall tick bite. Positive EIA and IgG/IgM WB. Started on oral amoxicillin. After delivery synovial fluid was positive by PCR for Bb	Weekly biophysical profile on infant, At 39 weeks labor induced, Baby healthy	Pos IgG Cordblood negative IgM cordblood	Silver stains negative for spirochetes	No Mention	Walsh et al, 2007
2012 1 case	Mother diagnosed with Borrelial lymphocytoma at 37 weeks pregnancy, had bitten bitten by tick two weeks prior. Serology positive by ELISA and IgM. Tx w amoxicillin for three weeks.	Healthy child	Serologic testing in newborn negative	No mention	No mention	Moniuszko et al, 2012
2015 1 case	Pregnant mother 28 weeks gestation - dx with Borrelia Miyamotoi (by PCR) and possible B. burgdorferi (ELISA and IgM immunoblot positive) coinfection. Tx w IV ceftriaxone 4 weeks.	Labor induced at 37 weeks, vaginal delivery, normal Apgar.	No mention	No mention	1 + 4 mth check-up normal	Hu et al, 2015
2017 1 case	Pregnant mother w low grade fever and EM rash 16 weeks gestation, progressed to headache, photophobia, large joint pain, periorbital cellulitis. Pos ELISA, LP negative for disseminated Lyme by gram stain, culture and PCR. Tx with 1 dose IV ceftriaxone 14 days oral cefuroxime.	21 week U/S normal fetal anatomy, no cardiac malformations. Vag delivery 41wk	No mention	No mention	No mention	O'Brien et al, 2017
2021 1 case	31 yr woman 6 months pregnancy, removed tick – a few days later developed fever, chills and headache. 2 neg SARS-COV PCR. Presumptive Dx Covid-19. C6 EIA pos, IgM WB band 41, 39, 23. Also PCR positive for anaplasmosis. Was treated with amoxicillin.	Spontaneous Vaginal Delivery, Healthy at birth	No Mention	No Mention	No Mention	Horowitz et al, 2021

Limitations: These case reports highlight healthy infant outcomes following maternal Lyme disease which was treated in most cases. Note that in a minority of cases testing on cordblood (2 cases) or infant (2 cases) is completed, there is no mention of long-term follow-up. In 3 of the cases there is mention of testing placenta by staining or PCR, and in 2 cases placenta is described as 'normal', (unsure if histology carried out). In only one case is there brief mention of follow-up in a baby at one and four months.

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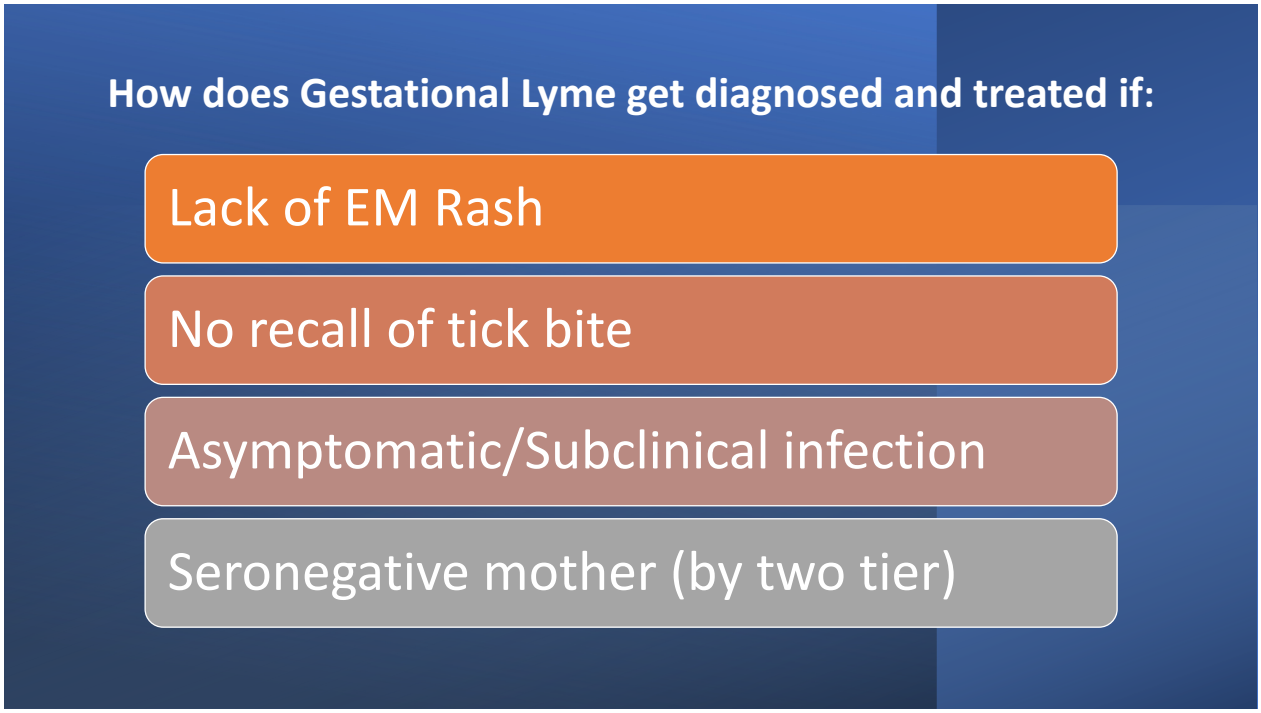
Complexities of Gestational/Congenital Lyme disease

"Acquiring Lyme disease during pregnancy continues to be cause for concern. Transplacental transmission of B. burgdorferi can occur and fetal deaths and malformations occurring after the mother became infected with the spirochete have been reported. A recent report documents transmission of B. burgdorferi from mother to fetus during the first trimester of pregnancy with resulting overwhelming, spirochetosis in the fetus and intrauterine death near term. **The need for rapid diagnosis and treatment of maternal infection may be critical for the prevention of fetal damage due to intrauterine fetal infection."**

Pinger, R. R., Hamm, R. H., & Sinsko, M. J. (1989). Lyme disease: a review and an outlook for Indiana. *Indiana medicine : the journal of the Indiana State Medical Association*, *82*(4), 268–272.



As this next section outlines, there are several complexities which have been identified in gestational and congenital Lyme disease.

These include:

- asymptomatic/subclinical Bb infection in pregnant women
- sero-negativity in mother and baby despite fetal/infant/placental infection
- treatment failure in pregnancy resulting in Borrelia findings in placenta/fetus/baby

If a pregnant person doesn't exhibit an erythema migrans rash, doesn't recall a tick-bite, doesn't have objective clinical symptoms associated with Lyme disease and/or is seronegative by two-tier serology, how would that person be diagnosed and treated for Lyme disease so as to prevent in-utero transmission of the spirochete?

How do you clinically diagnose Lyme disease infection in a pregnant person if there is no recall of a tick bite or erythema migrans rash?

'Patients with Lyme disease, which is caused by the tick-borne spirochete *Borrelia burgdorferi* may present during summer with systemic symptoms without the initial skin lesion erythema migrans.'

Steere, Allen C., et al. "Systemic symptoms without erythema migrans as the presenting picture of early Lyme disease." The American journal of medicine 114.1 (2003): 58-62.

"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.

Year	EM %	Comments	Cite
1977	**25%** 13/51	13 patients (25%) noted an erythematous papule that developed into an expanding, red, annular lesion.'	Steere et al, 1977
1986	**35%** 6/17	'17 cases of Lyme arthritis were documented by new serology among 220 referrals to the new pediatric rheumatology service at the State University of New York at Stonybrook. 'There was observation of tickbites in only 24% of the Lyme arthritis cases, (ECM) in 35% and of neurologic manifestations in 6%.'	Ross, Benach JL., 1986.
1986	**48%** 13/25	'more than half of these children had no history of ECM, significant prodromal illness, or tick bite. Inasmuch as ECM is so striking, it is unlikely to go unnoticed or be forgotten by the child or family members, even though the interval between rash and arthritis may be months. In the majority of cases, arthritis was the first sign of Lyme disease.'	Eichenfield et al, 1986
1987	**46%** 20/43	'Only twenty patients had a history of erythema chronicum migrans, the characteristic rash that precedes the arthritis, and for only nineteen children was there any recollection of having been bitten by a tick.'	Culp, Eichenfield, 1987
1987	**21%** 78/375	'Among 375 proven cases there were 78 with erythema migrans, 211 with neurological signs, 48 with Lyme arthritis and 36 with acrodermatitis.'	Wilske B, et al. 1987
1995	**9%** 6/69	Five children with neurologic findings also had erythema migrans (EM), and one had both EM and arthritis. 27% of children with neurologic abnormalities due to LD had a history of EM or arthritis.	Bingham et al, 1995
2010	**43%** 400/929	43% (400 persons) had the characteristic expanding rash (Erythema Migrans)	Report to Maine Legislature, 2010.
2012	**13%** 11/84	11/84 children diagnosed with confirmed neuroborreliosis had an EM rash.	Skogman, et al, 2012
2014	**40%**	While only 6.3% reported EM rash as the basis of their clinical diagnosis, 39.3% reported having a rash when they contracted the disease.	Johnson et al, 2014
2008	**51-87%**	Rates of EM reported from 1992-2006 in different US states. (Table 3)	Surveillance for Lyme Disease, 2008
2017	**18% 42/238**	238 children had Lyme disease. The diagnosis was made as follows: EM lesion alone n=27, EM lesion plus positive two tier serology n=15, positive two tier serology alone n=196.	Nigrovic et al, 2018

The table above identifies studies whereby EM rash was identified anywhere between 9-87% of the time. Note many of the studies in children (highlighted in green) identified a lower prevalence of EM lesions.

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EM rash and spirochetemia without other constitutional symptoms in pregnancy

2011	**Description of Study:**	**Findings:**	**Conclusion:**
	'Of 187 pregnant women diagnosed with previously untreated typical EM at the Department of Infectious Diseases at the University Medical Center Ljubljana, Slovenia, in the years 1994-2006, a total of 182 blood culture was performed. Borreliae were isolated from blood in 7 (4%) of 182 pregnant women. 5 (71%) isolates were typed as B. afzelii and 2 (29%) as B. garinii.'	'Borreliae were isolated from blood in 7 (4%) of 182 pregnant women. 5 (71%) isolates were typed as B. afzelii and 2 (29%) as B. garinii.'	'The findings of the present study on pregnant women with EM and borreliae isolated from blood indicate that the course and outcome of early LB is uneventful when pregnant women are treated with IV ceftriaxone and that outcomes of pregnancies is good.'

Note: 5 of 7 pregnant patients with EM had **no other local or systemic symptoms** accompanying the rash and Bb was isolated from blood culture, indicating patients were spirochetemic at time of blood-draw. This underscores the importance of early diagnosis and appropriate treatment in pregnancy as an asymptomatic EM rash might not be identified, or possibly misdiagnosed and/or considered a localized infection and thus not adequately treated.

Maraspin V., Ruzic-Sabljic, ER., Pleterski-Rigler D., Strle, R. Pregnant women with erythema migrans and isolation of borreliae from blood: course and outcome after treatment with ceftriaxone. Diagn Microbiol Infect Dis . 2011 Dec;71(4):446-8

Other cases of clinically silent early dissemination of Borrelia burgdorferi in patients with erythema migrans have been reported in Europe and North America.

1. Oksi, J., Marttila, H., Soini, H., Aho, H., Uksila, J., & Viljanen, M. K. (2001). Early dissemination of Borrelia burgdorferi without generalized symptoms in patients with erythema migrans. APMIS : acta pathologica, microbiologica, et immunologica Scandinavica, 109(9), 581–588. https://doi.org/10.1034/j.1600-0463.2001.d01-178.x
2. Wormser, G. P., McKenna, D., Carlin, J., Nadelman, R. B., Cavaliere, L. F., Holmgren, D., Byrne, D. W., & Nowakowski, J. (2005). Brief communication: hematogenous dissemination in early Lyme disease. Annals of internal medicine, 142(9), 751–755. https://doi.org/10.7326/0003-4819-142-9-200505030-00011
3. Maraspin, V., Ruzić-Sabljić, E., Cimperman, J., Lotric-Furlan, S., Jurca, T., Picken, R. N., & Strle, F. (2001). Isolation of Borrelia burgdorferi sensu lato from blood of patients with erythema migrans. Infection, 29(2), 65–70. https://doi.org/10.1007/s15010-001-0154-6
4. Goodman, J. L., Bradley, J. F., Ross, A. E., Goellner, P., Lagus, A., Vitale, B., Berger, B. W., Luger, S., & Johnson, R. C. (1995). Bloodstream invasion in early Lyme disease: results from a prospective, controlled, blinded study using the polymerase chain reaction. The American journal of medicine, 99(1), 6–12. https://doi.org/10.1016/s0002-9343(99)80097-7
5. Berger, B. W., Johnson, R. C., Kodner, C., & Coleman, L. (1994). Cultivation of Borrelia burgdorferi from the blood of two patients with erythema migrans lesions lacking extracutaneous signs and symptoms of Lyme disease. Journal of the American Academy of Dermatology, 30(1), 48–51. https://doi.org/10.1016/s0190-9622(94)70006-0

Asymptomatic/Subclinical Infection with Lyme disease

'Some infected persons have no recognized illness (i.e., asymptomatic infection determined by serologic testing), or they manifest only nonspecific symptoms (e.g., fever, headache, fatigue, and myalgia).'

'B. burgdorferi infection in the untreated or inadequately treated patient can progress to late-disseminated disease from weeks to months after infection.'

MMWR. Recommendations for the Use of Lyme Disease Vaccine. June 4, 1999 / Vol. 48 / No. RR-7

"In all probability, subclinical or asymptomatic infection with B. burgdorferi occurs. For this reason, many people who have never experienced signs or symptoms of Lyme disease will have measurable antibody to B. burgdorferi. This is especially problematic when attempting to clinically evaluate a patient from an area where Lyme disease is endemic, which includes most of Wisconsin.

Ultimately, decisions regarding whether to treat vaguely symptomatic or asymptomatic seropositive individuals will depend on the accuracy of serologic tests. Currently there is no clear consensus regarding the clinical management of persons who are identified to have elevated antibody titres to B. burgdorferi with questionable or absent clinical signs or symptoms.

There is a fear that these individuals have latent B. burgdorferi infection (with sequestration of the spirochete) and will subsequently develop manifestations of later stage Lyme disease such as central nervous system (CNS) involvement or acrodermatitis atrophicans (ACA). The occurance, manifestations and frequency of latent CNS involvement of Lyme disease are still not well defined."

Schell, W., Davis JP. Lyme Disease: A Clinician's Guide. State of Wisconsin, Department of Health and Social Services. Division of Health. Bureau of Community Health and Prevention. Section of Acute and Communicable Disease Epidemiology. January, 1989.

The management of asymptomatic persons found to be seroreactive for Lyme disease is an important unresolved issue for practitioners in endemic areas (Wormser et al., 2006). A comparison with syphilis, caused by Treponema pallidum, a spirochete that has evolved to persist in humans, is instructive: It is well recognized that patients with latent syphilitic infection are at risk of recrudescent disease, and, therefore, must be treated.

Radolf, J.D., Strle, K., Lemieux ,J.D., & Strle, F. (2021). (2021). Lyme Disease in Humans. Current issues in molecular biology, 42, 333-384.

Year	Asymptomatic/subclinical/latent infection	Citation
1984	'Of 15 persons with a history of LD at any time, 6 had titers of ~1:64, whereas 11 (6.8%) of the 161 participants with no clinical history also had elevated titers .'	Hanrahan et al, 1984
1986	'Of 121 asymptomatic residents who gave blood samples, 10 adults (8%) had high titers of IgG antibodies to the Lyme disease spirochete; these titers sometimes persisted for years. From 1981 to 1983, the estimated ratio of apparent-to-inapparent infection was 1:1. The high frequency of Lyme disease on Great Island underscores the need for surveillance and control programs.'	Steere et al, 1986
1987	'These data coupled with observations of Lyme disease presenting primarily with neurologic, cardiac, or arthritic manifestations indicate subclinical infection is common and untreated patients are at risk for late complications of the disease.'	Duffy, 1987
1991	Epidemiologic studies have revealed that 2% to 22% of people in endemic areas may seroconvert with no history of tick exposure or evidence of disease.	Ostrov, Arhreya,1991
1992	Western blot results were consistent with epidemiologic exposure to Bb and implied frequent asymptomatic infection among healthy adults living in or visiting areas endemic for Lyme borreliosis.' (7-15%).	Huycke et al, 1992
1992	'Borrelia burgdorferi infection may be asymptomatic. The proportion of patients with subclinical infection is not known but approximates 20%.'	Coyle, 1992
1993	'Asymptomatic and subclinical infection is probably common.'	Dennis, 1992
1992	'There is considerable evidence that patients undergo a latent phase of the disease. These patient lack clinical signs and symptoms but have elevated antibody titers usually of the immunoglobulin G (IgG) type.'	Weber et al, 1992
1991	'In population-based serologic surveys, the majority of individuals identified as having experienced infection with Bb cannot recall an illness compatible with Lyme disease. What percent of seropositive individuals represents false-positive tests and what percent reveals true infection with Bb that has not been ascertained. However, asymptomatic infection appears to be common.'	Buchstein et al, 1991
2003	Thus, the true frequency of asymptomatic infection with B. burgdorferi in the United States is probably 7% of cases of infection.	Steere et al, 2003

2001	Some new cases of Lyme disease begin with asymptomatic seroconversion. These individuals remain asymptomatic, appearing to have spontaneous cure, or they develop manifestations of disseminated (i.e.,secondary skin lesions, neurologic manifestations, cardiac abnormalities, musculoskeletal symptoms) or late (i.e., axonal polyneuropathy, encephalopathy, cognitive disorders, and intermittent or chronic large-joint, inflammatory, oligoarticular arthritis) Lyme disease as their initial clinical manifestation.	Rahn, 2001
2009	"The mere proof of an infection with borreliae is not sufficient, because the infection may not always result in illness. It appears that the proportion of symptomatic infections is much higher in the USA at about 90%, thank in Europe where fewer than 50% of infetions result in clinical illness."	Strle, Stanek, 2009
2012	'We show that asymptomatic infection with Bb occurred more frequently than clinical cases of Lyme disease.' 'In table 4 we found 11 participants with asymptomatic antibody positive and PCR positive urine, which confirmed that their urine contained B. burgdorferi DNA. This indicated that Bb DNA could be discharged from the body during asymptomatic infection. There were 11 PCR positive individuals among the serum antibody-negative cases.'	Tan et al, 2015

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1. Hanrahan JP, Benach Jl., Coleman JL, Bosler EM, Morse DL, Cameron Dl, Edelman R, Kaslow RA. Incidenceand cumulativefrequencyof endemicLymediseasein a community. 1 Infect Dis 1984;150:489-96
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Cases of Asymptomatic/Subclinical Infection in the Mother, fetus/placenta/baby infected.

"the most important concern of the obstetrician is the patient who is not treated for Lyme disease during pregnancy because it was not recognized as such or diagnosed."

Strobino B, Williams C, Abid S, et al. Lyme disease and pregnancy outcome: A prospective study of two thousand prenatal patients. Am J Obstet Gynecol, August 1993.

"We are unsure of the significance of seropositivity in asymptomatic women. These women could have chronic disease, prior resolved infection or false positive results."

Bracero LA, Wormser GP., et al. Prevalence of Seropositivity to the Lyme disease Spirochete during Pregnancy in an Epidemic area: A preliminary report. Journal of Maternal-Fetal Investigation (1992) 2:265-268.

'This case, 'highlights the dilemma that we are in an effort to prevent congenital borreliosis. An orientation on the symptoms of the expectant mother is not sufficient because the infection is often asymptomatic, but this does not exclude bacteremia and infection of the fetus.'

Horst, H.: Borrelia burgdorferi-Infektionen in der Schwangerschaft. In: Hassler, D. (Hrsg): Infection Taschenbuch Lyme-Borreliose. MMV. Medizin Verlag, Munchen 1992, 85-91.

'The possible effects of maternal infection before conception, as well as those of infection occurring during pregnancy, are of interest because so little is known about the persistence of the spirochete throughout the course of the disease. Although the disease can be treated and cured with antibiotics, it is possible that cases go untreated, are insufficiently treated, or are treated but recur anyway.'

Strobino BA, Williams CL, Abid S, Chalson R, Spierling P. Lyme disease and pregnancy outcome: a prospective study of two thousand prenatal patients. Am J Obstet Gynecol. 1993 Aug;169(2 Pt 1):367-74.

'the potential for B. burgdorferi to cause congenital disease has been clearly established', and 'because of the chronic persistence of the organism in the untreated patient, it is not known whether patients who were infected prior to pregnancy can transmit the infection to the fetus.'

Luft BJ, Dattwyler RJ. Lyme Borreliosis. Current Clinical Topics Infectious Disease. 1989; 10:56-81.

1986	Pregnant mother delivered a stillborn infant at 34 weeks. **Prenatal record negative for infections.** **No recall of tickbite and no symptoms suggestive of Lyme borreliosis.** no medication taken during gestation. Positive Bb IgG serology (IFA) negative syphilis testing Subsequently treated with doxycycline for three weeks after delivery six months later serology Bb negative.	33 week stillborn infant. Upon autopsy of fetus: cutaneous macerations, fluidothorax, ascites, hepatoplenomegaly. Histological examination of tissues revealed only mild predominantly perivascular lymphocytic infiltration. Clinically, congenital syphilis was suspected however maternal syphilis tests were negative and Bb IgG antibody tests (IFA) were positive. Spirochetes identified by darkfield microscopy in lung, liver and brain tissue specimens.	Maraspin et al; 1999
1986	**No recall of tick bite or EM rash** **Asymptomatic mother** Untreated pregnancy, later found to be seropositive Bb IgG.	Baby delivered at 37 weeks with neonatal onset of: Multi-system inflammatory disease in infant. Maculopapular skin rash, Hepatosplenomegaly Hypertrophy of heart, anemia Fever accompanied by recurrent infections – enteritis, bronchitis, rhinitis, cystopyelitis Delayed growth and development, head enlargement, wide fontanel, protruding eye balls, conjunctivitis, blepharitis, enlargement of cervical, axillary and inguinal lymph nodes, itchy maculopapular rash. Elevated IgG ELISA titers repeatedly identified in child's serum which decreased w antibiotic therapy 'It cannot be ruled out that our patient developed this specific syndrome as a self-propagating response after an intrauterine infection with Lyme disease spirochetes.''The neonatal onset suggests a prenatal infection.'	Lampert et al, 1986
1987	**Mother had no history of tickbite or EM rash**. Mother had been experiencing arthralgias And fatigue since experiencing horse fly	Infant healthy at birth (delivered by C section, died at 8 days) Admitted with profound lethargy leading to unresponsiveness, marked Peripheral cyanosis, systemic hypertension, metabolic acidosis, Myocardial dysfunction and abdominal aortic thrombosis.	Lavoie et al., 1987

	And mosquito bites while camping in Maine in 1971. Was seronegative by ELISA at Yale No cardioilpin antibodies found.	Bb cultured from infant frontal cerebral cortex. Silver stain confirmed infection in brain and heart.	
1989	Mother infected in second trimester. Treated for Lyme. Seronegative. '**The mother, who was asymptomatic**, had been treated with oral antibiotics and <u>did not have diagnostic levels of antibodies to Bb</u> at time of parturition.'	Baby was born with neurologic dysfunction. Spinal tap on neonate reveals serological evidence of antibodies specific to borrelia in CSF.	Dattwyler et al, 1989
1989	11 of 14 cases presumed subclinical infection in mother – or mention of tick-bite or Lyme disease. (cases 2-12)	Spirochetes identified in fetal tissue, placenta. See details of each case in above sections.	Macdonald, 1986/1989
1992	**No maternal tick bite, no EM** **Asymptomatic** Maternal serology revealed significantly increased IgM titer and slightly increased IgG. Untreated pregnancy	3 day old newborn diagnosed with sepsis and treated with antibiotics. No other details given. Increased IgM and IgG Bb antibodies in infant blood and CSF. Negative for syphilis and mononucleosis.	Horst, 1993
1997	32 yr mother no recall of any tick bite and no symptoms during pregnancy but had taken part in outdoor activities in area known to be endemic for LB. **No suspicion of infection during pregnancy.** **Mother was asymptomatic** Postpartum serum antibody to Bb (IFI) was slightly elevated - IgG seropositive (slightly high IgG 1:128, cutoff 1:64). **Untreated pregnancy**	**<u>Infant:</u>** Infant presents to Pediatric Dermatology with relapsing/remitting multiple annular erythematous patches, fever and lymphadenopathy which had started at 3 weeks of age. Initial infant serology 9 months (IFI, ELISA, WB negative) **BUT** B- Burgdorferi was isolated and detected by PCR from skin biopsy samples in seronegative baby. Baby was treated. Three months later popular lesions and bluish red color in legs noted (still negative by ELISA and IFI but WB IgG positive) Despite repeated courses of oral antibiotic therapy, lesions recurred four more times over the following 3 years and child was retreated each time (this suggests persistence of Bb infection). By age 4, no further lesions documented. Authors suggest a congenital borreliosis and cutaneous manifestations of congenital spirochetosis. Dermatlogic findings included stropulus on arms and legs, multiple annular erythema, bluish-red discoloration of legs.	Trevison, et al 1997
2005	**No maternal tick bite, no EM** Asymptomatic, sero + Untreated pregnancy	Infant girl born w hydrocephalus and gestational Lyme. VP shunt was placed on day 2 of life. At birth 41KDa and 75 kDa identified in infant IgM WB.	Onk et al, 2005
2012	Mother **reported joint problems at the end of pregnancy, no other hx of Lyme disease.** Mother had positive IgG EIA.	Baby developed erythema migrans rash two months after birth which lasted two weeks. No tick-bite or exposure to ticks in baby. Baby had positive ELISA IgG 3,773 and IgM 1,828, at the same time WB IgG was negative and WB IgM positive.	Zjevikova, 2012.

Attenuated symptoms in mother – studies in mice and humans

Lyme Disease:

'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

Pregnant women less often had ring-like EM despite similar duration of the skin lesion before treatment.'

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

'The probability of reporting constitutional symptoms systematically decreases with gestation week at diagnosis of EM (EM was diagnosed a median 7 days after the appearance of the skin lesion) and that women infected during the later stages of pregnancy report fewer constitutional symptoms compared with those infected during the early phases of pregnancy, who are more similar to non-pregnant women.'

'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.

Relapsing Fever Borrelia:

'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.

Cases of seronegative maternal infection despite fetal/placental borrelia infection.

'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.'

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

'Antibiotic therapy aborts the humoral response but a few spirochetes survive in protected niches where they later cause an attenuated syndrome with mild joint problems or subtle neurologic symptoms. Although the patient has not made detectable levels of antibody, there is often a cellular response that may be detected by the T-cell proliferative assay, currently only available in research laboratories.'

Steere A. C. (1993). Current understanding of Lyme disease. *Hospital practice (Office ed.)*, *28*(4), 37–44.

'serologic testing may not be the definitive diagnostic tool to determine if the fetus has been exposed in utero to B. burgdorferi, for serologic testing for Lyme disease is far from perfect.'

Edly SJ. Lyme disease during pregnancy. N J Med. 1990 Jul;87(7):557-60. PMID: 2200981.

"If a woman has had Lyme disease before coming pregnanct, carefully consider her current serologic status for both IgG and IgM antibodies, her history of antibiotic treatment and whether or not she has symptoms. If you think her disease may be persistent consider consulting with an infectious disease specialist to determine whether additional follow-up and treatment are indicated."

Williams, CL., Strobino BA. Lyme disease transmission during pregnancy. Contemporary Ob/Gyn, June 1990. Pg. 48-54.

Question: What about testing during pregnancy?
'False-negative serologic results are common during pregnancy; therefore serologic testing cannot be relied on in diagnosing LB during pregnancy.'

Ostrov, BE., Athreya, BH. Lyme Disease: Difficulties in diagnosis and Management. Pediatric Clinics of North America, Vol 38 (3); June 1991.

Clinical diagnosis is especially important since conventional laboratory diagnostic tests may be inadequate or require lengthy periods of times before a positive result occurs.'

Schutzer SE, Janniger CK, Schwartz RA. Lyme disease during pregnancy. Cutis. 1991 Apr;47(4):267-8. PMID: 2070648.

Cases of CDC negative (2) or equivocal (1) by two tier test, asymptomatic mothers Bb identified in placenta by Siver staining and/or PCR.

1996 (2 cases)	60 placentas in asymptomatic women with ELISA pos or equivocal serology were tested by silver stain, and if positive by PCR in a prenatal screening program. In women w placental spirochetes, no maternal history of tick bite, EM or symptoms of Lyme disease noted. Uncertain if women were treated, treatment not mentioned in study.	3/60 placentas identified spirochetes by Silver staining **PCR confirmed Borrelia burgdorferi in 2/3 placentas** 3 women had negative syphilis serology, all had equivocal ELISA, 2 had negative WB, one had equivocal WB by CDC criteria. **These mothers w Bb positive placentas would be considered seronegative by CDC two-tier testing criteria.** • **'The significance of placental spirochetes is unknown.'** • **'presence of Bb spirochetes in plaenta implies fetal transmission.'**	Figueroa et al, 1996

A 1996 study authored by Figueroa and colleagues studied sixty placentas of asymptomatic women with reactive Lyme serology using a silver stain. They confirmed identity of spirochetes as Bb by PCR. Authors Identified spirochetes using a silver stain in 3 of 60 placentas. 2 placentas with spirochetes were PCR positive for Bb, the third placenta not tested by PCR. Authors stated: ' the presence of these spirochetes in placental tissue implies fetal transmission.' The three women had equivocal ELISAS, were asymptomatic and had no known history of a tick bite. 2 of three women had negative Western Blot and one woman had an indeterminate WB.

There was no mention of antibiotic treatment in these women. Cord blood serology IgG and IgM was done in all 3 infants and was negative. The infants were described as having a 'normal perinatal outcome' but there was no mention of any longitudinal follow-up or re-evaluation of serological status at a later date. Authors concluded by emphasizing '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.'

They also highlighted that 'there was no relationship between the presence of placental spirochetes and the results of ELISA and Western Blot analysis.' Interestingly enough, Dr. MacDonald had previously made similar observations that maternal serology wasn't a practical indicator of Bb infection in the baby.

Cases of seronegative maternal infection despite fetal/placental borrelia infection

"Serovariable disease means that one laboratory will test an aliquot of your patient's serum and report that Lyme disease antibodies cannot be detected, but a second laboratory will test the same aliquot and detect antibodies at a significant titer.

A recent report of transplacental Lyme borreliosis illustrates such a situation. Maternal postpartum serum was strongly reactive by two independent methods (indirect immunofluorescence and enzyme-linked immunosorbent assay) at the Centers for Disease Control, the New York State Departments of Health but was non-reactive at the Yale School of Medicine. The mother had the diagnostic skin lesion, erythema migrans followed by arthritis. The fetus was stillborn. Spirochetes were obtained from cultures of fetal liver and heart, and spirochetes were found in fetal heart, brain, adrenal gland, placenta and other organs using a variety of histochemical methods (silver impregnation, immunohistochemistry and monoclonal antibody techniques)."

"There is much to learn about Lyme borreliosis. Our task will be less tedious if we heed the lessons of syphilis."

MacDonald, A. Ambiguous Serologies in Active Lyme Borreliosis. Journal of Clinical Neuro-ophthalmology (8)2:79-80, 1988.

Mother had no history of tickbite or EM rash. Mother had been experiencing arthralgias And fatigue since experiencing horse fly And mosquito bites while camping in Maine in 1971. **Was seronegative by ELISA at Yale** No cardioilpin antibodies found.	Infant healthy at birth (delivered by C section, died at 8 days) Admitted with profound lethargy leading to unresponsiveness, marked Peripheral cyanosis, systemic hypertension, metabolic acidosis, Myocardial dysfunction and abdominal aortic thrombosis. Bb **cultured** from infant frontal cerebral cortex. Silver stain **confirmed infection in brain and heart**.	Lavoie et al., 1987
(Case 2: Fetal Lyme borreliosis with miscarriage 19 week gestation) No maternal recall of tickbite or EM rash. Severe toxemia of pregnancy in week 17. **Post partum serology for Bb negative at 2 labs.**	Autopsy revealed Bb was in fetal tissue by indirect immunofluorescence.	Macdonald, 1986/ 1989
(Case 3) stillbirth 23 weeks. **No medical history for Lyme or Tickbite.** **Mother was seroneg for Bb**	B. burgdorferi was identified in tissue by indirect immunofluorescence.	Macdonald, 1986/ 1989.
(Case 4: Fetal Lyme borreliosis with miscarriage at 15 weeks gestation) Uneventul first trimester of pregnancy. **Postpartum Bb serology was negative.**	Autopsy revealed spirochetes in fetal liver and in placenta. No inflammation in fetal viscera. Bb was identified in tissue by indirect immunofluorescence .	Macdonald, 1986/ 1989.
(Case 7: Fetal Lyme Borreliosis with miscarriage 17 weeks gestation) 2 weeks prior mother had experienced vaginal bleeding and cramping. **Post partum Bb serology negative.**	Autopsy revealed hydrocephalus and spirochetes identified in **fetal brain by indirect immunofluorescence**.	Macdonald, 1989
(Case 8: Fetal Lyme Borreliosis with Miscarriage at 16 weeks gestation) 2 weeks prior, mother experienced vaginal bleeding, abdominal cramps and low grade fever. **Post partum Bb serology negative**	Autopsy revealed **spirochetes in fetal brain** with immunohistochemistry **using monoclonal antibodies,** no malformations noted. No inflammation noted in viscera.	Macdonald, 1989
(Case 10) intrauterine death at 25 weeks. **No infections noted for mother,** **was nonreactive for Bb serology**	Autopsy revealed intraventricular septal defect without additional internal anomalies. Bb was identified in autopsy tissue by indirect immunofluorescence.	Macdonald, 1989
Mild Early Congenital Lyme borreliosis: (Patient #26) **At delivery, maternal blood negative by polyvalent Lyme EIA.** Blood obtained 1 day post-partum was Positive by Bb in-vitro lymphocyte Proliferation Assay (LPA).	Cordblood and infant blood on day 1, 2.5 weeks and 7 weeks seronegative by polyvalent EIA Bb antibody. Blood on first day was positive by in vitro LPA for Bb.	Gardner, 2001

Cellular Immune Response to Bb in pregnancy/congenital infection

'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).'

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

'**A vigorus specific T cell response to B. burgdorferi is detectable early in the course of infection, often preceeding the development of a measurable humoral response.** The role that these immune responses play in the expression of the various clinical manifestations of this illness remains to be elucidated.'

Dattwyler, R.J, Volkman D.J et al. (1988). Specific immune responses in Lyme borreliosis. Characterization of T cell and B cell responses to Borrelia burgdorgeri. Annals of the New York Academy of Sciences, 539, 93-102.

'**The T-cell proliferative assay may be a helpful diagnostic test** in the small subset of patients with late Lyme disease **who have negative or indeterminant antibody responses by ELISA**.'

Dressler F., Yoshinari, NH., Steere, AC. The T-Cell Proliferative Assay in the Diagnosis of Lyme disease. Annals of Internal Medicine, 1991; 115:533-539.

'Several studies have been carried out on the role of cell-mediated immunity in Lyme disease and, specifically, the interaction between B. burgdorferi cells and the cellular elements of the immune system.'

'The stimulation index of T-cell responsiveness to whole borreliae has been used at one institution to confirm the diagnosis of Lyme borreliosis (57). **Some patients demonstrate a significant cell-mediated immune response to the borreliae when they have only borderline or slightly elevated antibody titers to the organisms** (57). Family members of Lyme disease patients have higher stimulation indices than unrelated controls, indicating either a hereditary predisposition or shared exposure to the infectious agent.' (152)

Barbour AG. Laboratory aspects of Lyme borreliosis. Clin Microbiol Rev. 1988;1(4):399-414. Doi:10.1128/CMR.1.4.399

Maternal blood serovariable by ELISA (treated with antibiotics) but positive Lymphocyte proliferation assay (LPA)

'Mothers who have been treated with antibiotics for gestational Lyme borreliosis **<u>may be seronegative</u>** by antibody assays at delivery or in the peripartum period and they may be positive by the Bb specific LPA.'

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.

(**Mild early Congenital Lyme borreliosis:** (Patient number 23) Mother developed small 1 cm erthematous patch after a tickbite to her groin after lake visit. One month later conceived, developed a flu like illness and at 3 weeks gestation an asymptomatic rash on her trunk accompanied by low grade fever and later two erytematous patches with central clearing. Maternal EIA to Bb was **initally negative at presentation** at 4.5 weeks gestation, **became positive at 5.5 weeks, remained positive through 12** weeks, **negative at delivery.** Mother was treated immediately at 4.5 weeks with IV ceftriaxone 2 g daily but developed severe diarrhea and switched to oral PCN for remaining 2 weeks. **In vitro lymphocyte proliferation assay (LPA) for Bb was positive at 16 weeks gestation, at delivery + 1 month**	Blood and cerebral spinal fluid negative for EIA Bb antibody. In vitro lymphocyte proliferation assay (LPA) for Bb positive on cord blood and infant blood at 1 month but lower at one month. Gardner, 2001	**Gardner, 2001**

Maternal blood is negative by ELISA (treated with antibiotics) but positive Lymphocyte proliferation assay (LPA), baby dx: congenital Lyme negative by ELISA, positive by LPA.

Mild Early Congenital Lyme borreliosis: (Patient number 26) At 17 weeks gestation mother sustained tick bites while camping. At 18 weeks developed an 10 by 5cm EM 'bullseye' rash that lasted 3 weeks and spontaneously resolved. Between 20-28 weeks experienced low grade fever, myalgias, stiff neck, fatigue, dizziness, photophobia and migratory polyarthralgias of knees. At 23-26 weeks had rash reoccurance. At 28 weeks tood oral erythromycin for 10 days and symptoms resolved. She heard about Lyme disease and started on oral cefuroxime from 33 weeks to delivery.Her urine positive for Lyme antigen at commercial lab at 32 weeks. **At delivery maternal blood negative by polyvalent Lyme EIA.** **Blood obtained 1 day post-partum was positive by Bb in-vitro lymphocyte proliferation assay (LPA).** After delivery, recurrance of headache, photo-phobia, flu-like symptoms and knee arthralgias was treated with oral doxycycline for one month. Long term followup information not available.	Cordblood and infant blood on day 1, 2.5 weeks and 7 weeks seronegative by polyvalent EIA Bb antibody. Blood on first day was positive by in vitro LPA for Bb.	Gardner, 2001

Infant with congenital infection is negative by Bb ELISA but positive by other tests

"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 sero-conversion by early antibiotic therapy. If the antibiotic therapy has been inadequate to eliminated the B. burgdorferi infection, these infants may present the dilemma of seronegative late Lyme borreliosis."

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.

32 yr mother no recall of any tick bite and no symptoms during pregnancy but had taken part in outdoor activities in area known to be endemic for LB. No suspicion of infection during pregnancy. Mother was asymptomatic Postpartum serum antibody to Bb (IFI) was slightly elevated - IgG seropositive (slightly high IgG 1:128, cutoff 1:64). Untreated pregnancy	**<u>Infant:</u>** Infant presents to Pediatric Dermatology with relapsing/remitting multiple annular erythematous patches, fever and lymphadenopathy which had started at 3 weeks of age. **Initial infant serology 9 months (IFI, ELISA, WB negative) BUT** **B- Burgdorferi was isolated and detected by PCR from skin biopsy samples in seronegative baby**. Baby was treated. Three months later popular lesions and bluish red color in legs noted (still **negative by ELISA and IFA but WB IgG positive** Despite repeated courses of oral antibiotic therapy, lesions recurred four more times over the following 3 years and child was retreated each time (this suggests persistence of Bb infection). By age 4, no further lesions documented.	Trevison, 1997
Mother has tick Bite 1st Trimester, develops high fever, presumed flu. Untreated Pregnancy. After birth dx w tetraparesis, neuroborreliosis ALS.	The child, at age 2 years 10 months developed knee bilateral knee pain, contractures of the hip, ECG abnormalities and tachycardia, polyneuropathy, psycho-emotional lability. **Child seronegative by standard test (Bb ELISA) however was POSITIVE for Bb through PCR.**	Lazebnik et al, 2005
Mild early Congenital Lyme borreliosis: (Patient number 23) Maternal EIA to Bb was initally negative at presentation at 4.5 weeks gestation, became positive at 5.5 weeks, remained positive through 12 weeks, negative at delivery. In vitro lymphocyte proliferation assay for Bb was positive at 16 weeks gestation, at delivery + 1 month	See section on congenital infection for more details: **Blood and cerebral spinal fluid negative for EIA Bb antibody** **In vitro lymphocyte proliferation assay for Bb positive on cord blood and infant blood at 1 month but lower at one month**.	Gardner, 2001

Mild Early Congenital Lyme borreliosis: (Patient number 26) At delivery maternal blood negative by polyvalent Lyme EIA. Blood obtained 1 day post-partum was positive by Bb in-vitro lymphocyte proliferation assay (LPA).	See section on congenital infection for more details: **Cordblood and infant blood on day 1, 2.5 weeks and 7 weeks seronegative by polyvalent EIA Bb antibody.** **Blood on first day was positive by in vitro LPA for Bb.**	Gardner, 2001
Late Congenital Lyme Borreliosis (Patient number 25) A part of the evaluation of the infant for possible congenital infection, maternal blood was sent and found to be seropositive for polyvalent EIA Bb antibody.	See section on congenital infection for more details: Evaluation for possible congenital infection was initially unrevealing and **spinal fluid and serum were both negative for polyvalent EIA antibody to Bb.** Because of presence of metaphyseal bands (which were reminiscent of an earlier infant with Lyme borreliosis) the maternal gestational history and the maternal Lyme seropositivity the diagnosis of late congenital Lyme borreliosis was still considered. Both **infant and mother were found to have positive responses in the Bb burgdorferi in-vitro LPA.**	Gardner, 2001

Maternal blood seronegative by ELISA (treated with antibiotics), infant seropositive, then seronegative by EIA but positive by Lymphocyte proliferation assay (LPA)

Severe Early Congenital Lyme borreliosis: (Patient number 24) 34 yr woman suffered a tickbite at 6.5-12.5 weeks gestation. Mother remained clinically well following delivery and was seronegative for polyvalent EIA Bb antibody at one week, 9 months and 10 months after delivery. She was also negative for Bb LPA at 9 and 10 months.	See section on congenital infection for more details: At 9 months but not 10 months she was found to have polyvalent EIA Bb antibody. At 9 and 10 months she had a positive Bb in vitro LPA At 9 and 10 months further evaluation included a normal spinal fluid with no detectable Bb antibody	Gardner, 2001

Treatment for Lyme disease in Pregnancy

"It is essential to realize that in the pregnant woman Lyme disease is a clinical diagnosis regardless of her serologic status. Because the precise risk to the fetus from an infected pregnant female is not yet clear, it is important to be aggressive in the diagnosis and management of Lyme disease. This is important not only for the fetus, but also for the mother."

Sicuranza, G., Baker DA. Lyme Disease in Pregnancy. Chapter 23. In: Coyle PK. (ed) Lyme disease. Mosby Year Book, 1993. p. 49-58.

"Instances of severe illness in infants following transmission from untreated mothers has already lowered the threshold for more aggressive treatment of pregnant women."

Kaslow RA. Current Perspective on Lyme Borreliosis. Grand Rounds at the Clinical Center of the National Institutes of Health. JAMA, March 11, 1992, Vol 267, No. 10

"The precise risk to the developing fetus of maternal Lyme disease during pregnancy is unknown although it is well documented that fetal infection can occur and may have deletrious outcomes including malformations and death. Since anecdotal experience has suggested that oral antibiotic therapy does not invariably protect the fetus, I prefer to use high-dose intravenous penicillin for pregnant women with active Lyme disease."

Wormser, GP. Treatment of Borrelia burgdorferi infection. Laboratory Medicine. Vol 21 (5), May 1990.

"Borrelial infection during pregnancy should promptly be treated with antibiotics in high dosages, in order to prevent maternal-fetal tranmission of borrelial organisms resulting in stillbirth or congenital infections of the newborn.

Neubert, U. Clinical Aspects of Infections with Borrelia burgdorferi. Zeitschrift fur Hautkrankheiten 64 (8) 649-656. Eingegangen am 13.10.1988.

"Transmission of B. burgdorferi from mother to fetus has been described, but appears to be extremely uncommon. The literature has suggested that proven vertical infections (which are rare) have been associated with pronounced, even fatal, abnormalities of the fetus and newborn. However, the evidence that LD in pregnancy can have adverse effects on pregnancy outcomes has been recently reviewed with the conclusion that no clear cut pattern of teratogenic effects or neonatal infection has been identified. Pregnant women should be treated in accordance with treatment recommendations for non-pregnant adults, with the exception that tetracyclines should be avoided because of their effect on fetal bones and teeth. The well appearing infant of a mother who has had LD probably needs no special evaluation or treatment."

Eppes, SC. Diagnosis, Treatment and Prevention of Lyme Disease in Children. Pediat Drugs, 2003:5(6):363-372.

"It is well known that B. burgdorferi can cross the placenta and infect the fetus. In addition, breast milk from infected mothers has been shown to harbor spirochetes that can be detected by PCR and grown in culture. The Lyme Disease Foundation in Hartford, CT had kept a pregnancy registry for eleven years beginning in the late 1980's. They found that if patients were maintained on adequate does of antibiotic therapy during gestation, then no babies were born with Lyme. My own experience over 20 years agrees with this. The options for treating the mother include oral, intramuscular, and intravenous therapy as outlined above. It is vital that peak and trough antibiotic levels be measured if possible at the start of gestation and at least once more during treatment."

Burrascano, JJ. Advanced Topics in Lyme Disease. Diagnostic hints and treatment guidelines for Lyme and other tickborne illnesses. Sixteenth edition, Copyright, October, 2008.

"Based on literature review and the data analyzed, a relationship between maternal infection with Borrelia burgdorferi and any adverse events on the fetus cannot be defined with certaintly. However, a reduced incidence of adverse events to the fetus of mothers with Lyme disease, promptly treated with antibiotic therapy, is certainly demonstrated. The recommendation is therefore to treat any pregnant woman suffering from Lyme disease with the correct antibiotic therapy, remaining confident that further studies can definitively clarify the correlation between adverse events at birth and infection with Borrelia burgdorferi. Therefore, in conclusion, following the worldwide guidelines, it is recommended to undertake antibiotic therapy with ceftriaxone in pregnant women with Lyme disease."

Conforti, C., Vezzoni R., Retrosi, C., Longone, M., Corneli, P., Magaton Rizzi, G., Nan., K., Di Meo, N., & Zalaudek I. (2020). Overview on the treatment of Lyme disease in pregnancy. Giornale italiano di dermotologia e venereologia: organo ufficiale, Societa italiana di dermatologia e sifilografia, 155(2), 220-222.

"Treatment of gestational Lyme is essential as data show reduced adverse outcomes in treated compared to untreated disease. Doxycycline should not routinely be used in pregnancy for Lyme disease, especially with proven alternatives, due to transient suppression of bone growth and staining of developing teeth. Amoxicillin is preferred in the absence of neurological manifestations (eg: Lyme meningitis) or arioventricular heart block. Ceftriaxone is typically reserved for patients with severe neurological or cardiac manifestations. One study noted a non-significant increase in adverse pregnancy outcomes, such as pregnancy loss, among orally treated (31.6%) compared to parenterally treated (12.1%) patients."

Gould AP, Winders HR, Stover KR, Bookstaver PB, Griffin B, Bland CM, Eiland LS, Murray M. Less coomon bacterial, fungal and viral infections: review of management in the pregnant patient. Drugs context. 2021;10:2021-4-3.

Adverse Outcome in Treated vs Non-Treated 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).
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(8):2364.	'The outcome of pregnancy was unfavorable in 42/304 (13.8%) patients (treated w IV ceftriaxone) preterm birth in 22/42 (52.4%) fetal/perinatal death in 10/42 (23.8%); anomalies in 15/42 (35.7%).'
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.'

Treatment Failure reported with Lyme disease and Pregnancy, Bb identified in fetus/placenta/baby

"Effective therapy to eradicate borreliae on both the maternal and the fetal side of the placenta is essential, as **peristent 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.

"Evidence for the transplacental transmission of the spirochete is derived from several case reports. These demonstrate that the spirochete can infect the fetus and that short-term antibiotic treatment of early stage Lyme does not necessarily prevent the fetus from becoming infected."

"The possible effects of maternal infection prior to conception are also of interest because little is known about the persistence of the spirochete throughout the course of the disease. **Although it can be treated and cured with antibiotics, cases can go untreated, or although treated, can recur anyway."**

Williams CL, Strobino B, Weinstein A, et al. Maternal Lyme disease and congenital malformations: a cord blood serosurvey in endemic and control areas. Paediatric and Perinatal Epidemiology 1995, 9, 320-330.

"Patients treated early in the course of infection are usually cured without sequelae; those with delayed or inadequate treatment may have continuing refactory complaints. **Infrequently, patients with continuing complaints have evidence of persisting infection**."

Dennis DT. Lyme disease. Dermatoepidemiology. Dermatologic Clinics. Vol 13(3), July 1995.

"Clearly, the early recognition and treatment of patients with Lyme disease decrease the risks of long-term complications, **but the benefit to the fetus of early maternal treatment is unknown**. Although serology is helpful after 3-4 weeks of infection, a clinical suspicion of disease and the recognition of signs and symptoms are the most important tools in establishing early diagnosis. The current recommendations emphasize close examination of the newborn for signs of intrapartum infection."

Alexander JM, Cox SM. Lyme Disease and Pregnancy. Infectious Diseases in Obstetrics and Gynecology 3:256-261 (1995).

Mother had tickbite, EM, seropositive. **Was treated with oral penicillin three times daily for a week**	Infant born initially healthy, died 23 hours later. **Bb spirochetes identified in neonate brain and liver.** Bb identified in paraffin sections of infant brain using monoclonal antibody H5332. Placenta not available for study	Weber et al, 1988
(Case 13): Maternal Lyme Borreliosis with Persistent Placental Spirochetosis Despite Oral Penicillin Therapy in Second Trimester. 28 year old woman diagnosed with Lyme borreliosis in second trimester with EM rash on back. **Treated with 500mg oral Pen VK for 15 days** and EM rash faded on day 8. One month later complaints of dizziness, sinus tachycardia was diagnosed. Maternal Bb antibody negative. Retrospective interview disclosed that 2 weeks before delivery, patient sought medical attention due to tick attachment. A 13 by 13 erythematous patch non consistent with erythema migrans was identified by the physician.	Healthy baby was delivered. Serology tests were negatve for antibodies to Bb in maternal and infant umbilical cord blood from IFA and ELISA methods. Culture of the placenta in BSK medium **yielded motile spirochetes resembling borrelia species which could not be subcultured. Silver stain impregnantion yielded spirochetes in placental villi.** Infant was treated with oral penicillin with probenecid after delivery. Child appeared well in several follow-up visits.	MacDonald, 1989
Mother infected in second trimester. Seronegative. 'The mother, who was asymptomatic, **had been treated with oral antibiotics** did not have diagnostic levels of antibodies to Bb at time of parturition.'	Baby was born with neurologic dysfunction. Spinal tap on neonate **reveals serological evidence of antibodies specific to borrelia in CSF.**	Dattwyler et al, 1989

Mother had tickbite and EM. Was **treated for Bb with phenoxymethyl penicillin 1 million IU TID for 10 days** and skin lesion disappeard. End of second trimester developed vertigo. Lumbar puncture Identified elevated concentration of proteins and leukocytes. Serologic tests for Bb positive. **Retreated with PCN BID for 14 days and symptoms improved.** At 32 weeks gestation delivered a female infant. seropositive. At follow-up after delivery, mother's serologic tests for Bb were negative.	Infant born at 32 weeks, died hours later. Autopsy of infant revealed hydrocephalus, fluidothorax, ascites but no malformations. **Darkfield microscopy revealed spirochetes in fetal lung, liver.** No attempt to culture spirochetes from fetal autopsy tissues.	Maraspin et al., 1999
34 year old patient with Lyme Borreliosis remained symptomatic despite **seven months of therapy with oral antibiotics.** She was subsequently **treated with further courses of IV and oral antibiotic therapy**.	Post partum, **B. burgdorferi (Bb) was found to be present in the placenta by histologic staining.**	Burrascano, 1993
35 year old woman was assessed by author as she had developed an EM one year earlier. She was given a **short course of oral antibiotics followed by IV antibiotics.** Over several months, her symptoms returned, her ELISA titer was elevated and she was **restarted on IV and oral antibiotics**. She discovered she was pregnancy and after a normal pregnancy delivered a healthy male infant.	The placenta was examined at Brigham and Women's Hospital in Boston, Massachusetts where **several spirochetes were noted in perivascular and intervillous spaces on modified Dieterle Silver stain.**	Patmas, 1994
Mother had been **treated for serologically proven Lyme disease** over **a period of one year before pregnancy**.	**Baby/Child:** Child was diagnosed with Lyme disease in neonatal period **proven by serology (ELISA 1:512) and PCR identification of Bb in placental tissues** At 7 years of age the child died because of cerebral complications of congenital Lyme borreliosis. The Histologic findings suggest that **pigmentary changes in the fundus in congenital Lyme disease are similar to those described in congenital syphilis**. Spirochetes were most likely transmitted from the mother to fetus transplacentally.	Spector et al, 1993
Pregnant woman with disseminated Lyme borreliosis with EM/arthralgia/paresthesia Treated with **oral PCN for 5 days week 10 and retreatment week 14**, positive LB serology.	15 weeks Intrauterine fetal death. **Borrelia like organisms in ultrathin sections of placenta detected using monoclonal antibody H9724 against flagellin.** (full description from Maraspin, 2020 – Table 4).	Hercagova et al, 2008; Maraspin et al, 2020

Frequency of Fetal/Neonatal Adverse Outcomes following Gestational Lyme disease

'based on the apparent tissue tropism of *B. burgdorferi* in children and adults, neurologic or cardiac disease might be predicted as a consequence of congenital infections.'

Souza, IE., Bale JF., (1995). Topical Review: The Diagnosis of Congenital Infections: Contemporary Strategies. Journal of Child Neurology, 10(4), 271-282.

"The literature shows that effects of congenital Lyme disease may be different, including symptoms like spontaneous abortion, fetal death, cardiovascular defects, cryptorchidism, urologic abnormalities, hypoplastic enamel, delayed psychomotor development, cavernous hemangioma, and dysplasia coxae."

Jasik KP, Okła H, Słodki J, Rozwadowska B, Słodki A, Rupik W. Congenital Tick Borne Diseases: Is This An Alternative Route of Transmission of Tick-Borne Pathogens In Mammals? Vector Borne Zoonotic Dis. 2015 Nov;15(11):637-44.

"Transplacental transmission of B burgdorferi in humans has been documented in association with adverse fetal outcomes"
"Studies in both human and animal models have established that B. burgdorferi can cross the placenta, presumably occurring during a period of spirochetemia." "Because gestational Lyme disease has been clearly linked to fetal loss in animal studies, the potential for a causal effect in human gestational LD exists."

Elliot D, Eppes S, Klein, J. Teratogen Update: Lyme Disease. Teratology 64:276-281, 2001.

'I feel that, having been associated with this type of research for a number of years, we have been obsessed way too long by looking for defects recognizable at birth. I am sure we have to get away from this and look beyond birth and beyond infancy into childhood for these children who may have been at risk during pregnancy.'
Dr. J.A Dudgeon - Department of Microbiology, The Hospital for Sick Children, London & Institute of Child Health.

Dudgeon, JA. Introduction. In: Elliott, K. M., Knight, J., Ciba Foundation, & ProQuest. (1973). *Intrauterine infections*. Elsevier.

"Many of the calculations of adverse outcomes became apparent only when all the available case information was compared, as each individual report of one or several cases represented too few cases from which to draw conclusions."

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.

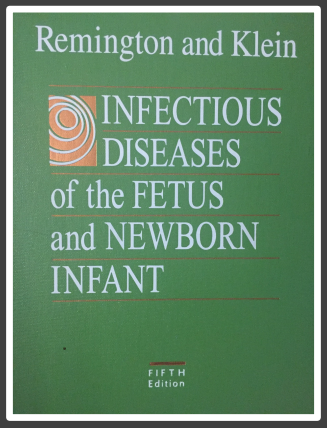
Frequency of occurrence of various types of fetal or neonatal adverse outcomes after Gestational Lyme (Table 11-3)

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

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.

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



Is cordblood IgM a suitable marker for identifying congenital Lyme infection?

Several US epidemiological studies on Lyme and Pregnancy relied on cord blood IgM as a stand-alone endpoint to identify congenital infection – as IgM does not cross the placenta and thus would originate from an infected infant. In all cases, of samples tested, a positive IgM was never reported. None of these studies identified the possible limitations of testing cord blood IgM in their discussion.

There are no studies which have studied the sensitivity and specificity of cordblood Bb IgM.

If one looks to research done in other congenital infections (as shown below), investigators provide caution about using IgM as a stand alone measure to rule out infection given issues with sensitivity.

In the case of congenital syphilis, the CDC currently recommends against commercially available IgM testing with an earlier report by CDC authors (Kaufman et al, 1974) identifying a false-negative rate that may exceed 35% in delayed-onset disease, thus insufficient for use as a screening test.

Kaufman RE, Olansky DC, Wiesner PJ. The FTA-ABS (IgM) test for neonatal congenital syphilis: A critical review. J Am Vener Dis Assoc. 1974 Dec;1(2):79-84. PMID: 4616027.

In the case of West Nile Virus: 'it is possible that in utero production of an antibody is impaired such that congenitally infected infants might fail to produce a sufficient WNV-specific antibody to be detected with standard assays, particularly if they were infected early in pregnancy. In such cases, and without the detection of viral RNA or antigen, the diagnosis of congenital WNV infection would need to be made based on clinical abnormalities, but without knowledge of the clinical spectrum of congenital WNV infection this is problematic' (O'Leary, 2006).

O'Leary DR, Kuhn S, Kniss KL, Hinckley AF, Rasmussen SA, Pape WJ, Kightlinger LK, Beecham BD, Miller TK, Neitzel DF, Michaels SR, Campbell GL, Lanciotti RS, Hayes EB. Birth outcomes following West Nile Virus infection of pregnant women in the United States: 2003-2004. Pediatrics. 2006 Mar;117(3):e537-45. doi: 10.1542/peds.2005-2024. PMID: 16510632.

Infection	Sensitivity of IgM serology
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)
Cytomegalovirus	'IgM antibody in neonates is of limited diagnostic value with a sensitivity ranging from 20-75%.' (3)
Chagas Disease	'Because the infected mother's antibody to *T. cruzi* can persist in her infant for up to 9–12 months, serologic testing is not useful for detecting congenital infection in newborn infants. Over time, the mother's antibody will disappear and children who are uninfected should be antibody negative by 9–12 months of age.' (4)
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. (5)

(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.
(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.
(4) CDC. Congenital Chagas Disease. https://www.cdc.gov/parasites/chagas/health_professionals/congenital_chagas.html
(5) CDC 2015 Guidelines for Syphilis: https://www.cdc.gov/std/tg2015/congenital.htm

How does one diagnose congenital Lyme disease?

"There is evidence to support the possibility that Bb may present clinically differently in congenitally infected versus vector-inoculated humans, and a review of similar chronic transplacental diseases in humans is instructive. **Common in congenital infection are 'silent' transfer, differential neonate illness presentation and a negative effect on later immune competence**. This information collectively suggests that silent or atypical birth presentation may be common, possibly resulting in delayed or complete lack of recognition of the transfer."

Harvey, W and Salvato, P. 'Lyme disease': ancient engine of an unrecognized borreliosis pandemic? Medical Hypothesis 60(5), 742-759, 2003.

"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 response because of attenuatin or prevention of sero-conversion by early antibiotic therapy. If the antibiotic therapy has been inadequate to eliminate the B. burgdorferi infection, these infants may present the dilemma of seronegative late Lyme borreliosis."

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.

"Clearly, the early recognition and treatment of patients with Lyme disease decrease the risks of long-term complications, but the benefit to the fetus of early maternal treatment is unknown. Although serology is helpful after 3-4 weeks of infection, a clinical suspicion of disease and the recognition of signs and symptoms are the most important tools in establishing early diagnosis. The current recommendations emphasize close examination of the newborn for signs of intrapartum infection."

Alexander JM, Cox SM. Lyme Disease and Pregnancy. Infectious Diseases in Obstetrics and Gynecology 3:256-261 (1995).

"After prenatal or postnatal exposure, an infant should be closely observed and empiric therapy considered if the infant develops a rash or symptoms suggestive of Lyme borreliosis. Treatment of mother and infant with ceftriaxone, penicillin, or amoxicillin is acceptable during breastfeeding relative to the infant's exposure to these medications. Doxycycline should not be administered for more than 14 days while continuing breastfeeding because of possible dental staining in the neonate. Continued surveillance for viable organisms in breast milk and evidence of transmission through breastfeeding is recommended." **Lawrence, RM. Transmission of Infectious Diseases Through Breast Milk and Breastfeeding. *Breastfeeding* (2011): 406–473. doi:10.1016/B978-1-4377-0788-5.10013-6**

"There is **substantial documentation to suggest a causal relationship between LD and stillbirths, congenital abnormalities, spontaneous abortion, low birth weight babies, prematurity and intrauterine fetal infection acquired from the mother**. An outcome of untreated LD arising from Mg^{++} deficiency could be pre-eclampsia (hypertension) or eclampsia (hypertension with seizures). Magnesium is often relied on to treat these problems. Women with LD in pregnancy can experience severe morning sickness, gestational diabetes mellitus and prominent flares of Lyme related symptoms. As both LD and Sudden Infant Death Syndrome are attended by sleep apnea, this should impel further research to determine if some babies with SIDS are actually suffering from LD. *Bb* can appear in the breast milk."

Bleiweiss, JD. (MD) When to Suspect Lyme. Personal Essay. 1994. http://cassia.org/essay.htm

Diagnostic criteria for other congenital infections cast a wide net beyond cord blood IgM, including PCR, diagnostic imaging, nucleic acid testing from various maternal samples including placenta and amniotic fluid, and neonate samples including saliva, CSF, peripheral blood and urine.

Testing/follow-up for an exposed infant could include:

- Direct and indirect testing methodologies including paired maternal/baby serology, culture, PCR and cellular response testing.
- 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.

Interim Guidelines needed for gestational and congenital Lyme disease:

"Whether or not to treat the newborn of a woman with Lyme disease depends on the case's circumstances and the pediatricians assessment of them. If there is any suggestion that the mother was not given adequate therapy, and especially if the infant shows any clinical signs of neonatal infection, the CDC recommends the same regimen as is used in congenital syphilis, usually IV or IM penicillin."

Williams, CL., Strobino BA. Lyme disease transmission during pregnancy. Contemporary Ob/Gyn, June 1990. Pg. 48-54.

'All cases of Lyme disease occurring during pregnancy should be reported and followed carefully for fetal abnormalities or developmental abnormalities occurring in infancy.'

Rahn DW. Lyme disease: clinical manifestations, diagnosis and treatment. Semin Arthritis Rheum. 1991. Feb; 20(4):201-18.

'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."

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*

'Can we expect to discover congenital manifestations of Lyme disease secondary to maternal-fetal transmission of B. burgdorferi? Answers to these and other perplexing questions will be forthcoming if those of us who have the opportunity to evaluate patients with Lyme disease continue to investigate and evaluate their skin lesions.'

Berger BW. Dermatologic manifestations of Lyme disease. Rev Infect Dis. 1989 Sep-Oct;11 Suppl 6:S1475-81.

'It has recently become apparent, however, that late neuroborreliosis may begin long after initial disease, following years of latent infection, 11 and 12 years after onset of disease, two children in this study were found to have subtle encephalopathy, with memory impairment, headache and fatigue accompanied by intrathecal production of antibody to the spirochete, a neurologic picture that is typical of lyme encephalopathy.'

Szer, I. S., Taylor, E., & Steere, A. C. (1991). The long-term course of Lyme arthritis in children. *The New England journal of medicine*, *325*(3), 159–163.

Interim Guidelines for the Evaluation of Infants Born to Mothers Infected with West Nile Virus During Pregnancy

West Nile Virus:

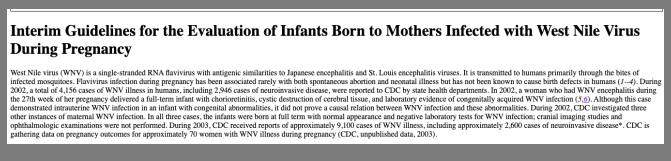
2002: First case of congenital WNV infection is identified and one case of possible transmission via breastmilk

Epidemiological and Prospective studies initiated.

December 2, 2003, CDC convened a meeting of specialists in the evaluation of congenital infections. Interim guidelines are established during that meeting.

2004: Interim guidelines are published for the Evaluation of infants born to mothers infected with WNV in pregnancy.

Guidelines provide clinicians with guidance on how clinical assessment, testing strategies, guidance around testing of placenta.



Interim Guidelines for the Evaluation of Infants Born to Mothers Infected with West Nile Virus During Pregnancy

West Nile virus (WNV) is a single-stranded RNA flavivirus with antigenic similarities to Japanese encephalitis and St. Louis encephalitis viruses. It is transmitted to humans primarily through the bites of infected mosquitoes. Flavivirus infection during pregnancy has been associated rarely with both spontaneous abortion and neonatal illness but has not been known to cause birth defects in humans (*1–4*). During 2002, a total of 4,156 cases of WNV illness in humans, including 2,946 cases of neuroinvasive disease, were reported to CDC by state health departments. In 2002, a woman who had WNV encephalitis during the 27th week of her pregnancy delivered a full-term infant with chorioretinitis, cystic destruction of cerebral tissue, and laboratory evidence of congenitally acquired WNV infection (*5*,*6*). Although this case demonstrated intrauterine WNV infection in an infant with congenital abnormalities, it did not prove a causal relation between WNV infection and these abnormalities. During 2002, CDC investigated three other instances of maternal WNV infection. In all three cases, the infants were born at full term with normal appearance and negative laboratory tests for WNV infection; cranial imaging studies and ophthalmologic examinations were not performed. During 2003, CDC received reports of approximately 9,100 cases of WNV illness, including approximately 2,600 cases of neuroinvasive disease*. CDC is gathering data on pregnancy outcomes for approximately 70 women with WNV illness during pregnancy (CDC, unpublished data, 2003).

https://www.cdc.gov/mmwr/preview/mmwrhtml/mm5307a4.htm

Interim guidelines for Evaluation of Infants born to Mothers Infected with Lyme disease during Pregnancy are **Needed**

Lyme Disease:

1985: First case of congenital Lyme infection is identified- followed by several more cases identified in this presentation.

Epidemiological studies initiated late 80's.

To date:

- **No longitudinal prospective studies in mother baby pairs** initiated in N. America despite many investigators calling for them to be done.
- **No clinical guidance/guidelines** regarding identifying, testing, treating exposed babies.
- Most **frontline clinicians aren't aware that maternal-fetal transmission** of Borrelia burgdorferi **is even possible**.
- Families are **unable to access appropriate diagnosis, treatment + support for infants suspected infected in-utero.**

Interim Guidelines needed for gestational and congenital Lyme disease:

Standardized clinical guidelines providing recommendations for diagnosis, treatment and follow-up of Lyme borreliosis for both mother and exposed fetus/infant have never been created.

Other zoonotic infectious diseases such as Zika and West Nile Virus **do have these guidelines**.

Interim guidelines could be developed based on evidence available to date and be updated as new research findings are reported. Without clear guidance, practitioners/clinicians may be uncertain of how to manage cases of gestational and congenital Lyme disease, which may lead to misdiagnosis or inadequate management.

A standardized assessment tool to guide clinical evaluation, treatment/management and follow-up of infants born to mothers with Lyme during pregnancy could include:

- Laboratory testing guidance
- Clinical Assessment Tools
- Treatment recommendations
- Recommendations for subspecialty consultation and support (cardiology, neurology, ophthalmology etc.)
- Recommendations for histological examination/ testing of placenta, umbilical cord tissue

Treatment guidelines for congenital syphilis could provide an interim framework that may have applicability to Lyme disease.

The 2022 US Tickborne Disease Working Group Report to Congress includes a section on Lyme disease and pregnancy and states:

> 'The development of evidence based interim clinical guidelines for Lyme disease in pregnancy are needed and could provide health care practitioners with resources and guidance in several important areas. These include (a) clinical evaluation and treatment of Lyme disease in pregnant persons; (b) evaluation of the fetus in pregnant persons with a Lyme disease diagnosis during pregnancy; (c) clinical evaluation and testing of infants born to persons diagnosed with Lyme disease during pregnancy; (d) recommended long-term follow-up for infants with possible congenital Lyme disease infection; and (e) recommendations for histological examination/ testing of placenta, umbilical cord, and/or products of conception or other autopsy samples. All of these guidelines could be updated with the emergence of new research or clinical findings.'

HHS Tickborne Disease Working Group Report to Congress 2022.
https://www.hhs.gov/sites/default/files/tbdwg-2022-report-to-congress.pdf

Congenital Syndrome – a realistic expectation?

With congenital Lyme, a specific pattern of teratogenicity such as microcephaly in Zika or Hutchinson's Triad in congenital syphilis has not been identified.

A collection of 'readily identifiable' symptoms or 'syndrome' has not been identified in babies exposed to Bb in-utero.
However: a heterogeneous range of adverse outcomes – often similar findings across studies has been documented including:

Cardiac, neurologic, urologic, musculoskeletal anomalies, respiratory distress, early onset sepsis, hyperbilirubinemia, prematurity, miscarriage, stillbirth and perinatal death.

Identification of a specific phenotype/syndrome associated with congenital Lyme infection would be helpful for diagnosis and treatment of affected infants but the lack of such a syndrome does not preclude congenital infection and a reliance on a such a syndrome may miss cases.

According to Wicher et al, in congenital syphilis, in the post-penicillin era, an attenuated, less obvious clinical presentation in infants is observed and a large percentage of congenitally infants born to untreated mothers with syphilis are asymptomatic and appear healthy without evidence of infection at birth but if left untreated, may develop later stages of the disease months to years later.

With congenital *T. cruzi* (Chagas' disease) – vertical transmission is clearly acknowledged however:

- 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.**

Wicher V, Wicher K. Pathogenesis of maternal-fetal syphilis revisited. Clin Infect Dis. 2001 Aug 1;33(3):354-63. doi: 10.1086/321904. Epub 2001 Jun 25. PMID: 11438902.
MMWR: Congenital Transmission of Chagas Disease — Virginia, 2010. July 6, 2012 / 61(26);477-479

Intergenerational congenital infection with Lyme disease?

"The ability of long-term survival of B. burgdorferi s.l. in tissues and spreading of spirochetes in the body despite antibiotic treatment can contribute to intergenerational infection of Lyme disease. Weber et al. (1988) found B. burgdorferi in human neonatal brain and liver, although the mother had been treated with an orally administered penicillin for Lyme disease during early pregnancy."

Jasik KP, Okla H, Slodki J, Rozwadowska B, Slodki A, Rupik W. Congenital Tick Borne Diseases: Is This An Alternative Route of Transmission of Tick-Borne Pathogens in Mammals? Vector Borne Zoonotic Dis. 2015 Nov;15(11):637-44.

I often hear this question asked by families who have concerns that Lyme disease has been passed unchecked through the generations. I think this is a viable question which can only be answered by further research.

One animal model in congenital syphilis is of interest in this respect.

'The transmission of congenital syphilis was studied in a 4-generation guinea pig family with 10 litters and 38 offspring. By use of one or all of the following tests (ELISA-IgM, polymerase chain reaction, and rabbit infectivity), **transplacental infection was demonstrated through 5 litters and up to 4 generations.** Twenty-eight (93%) of 30 animals were positive by >/=1 test, and 2 (7%) were negative by 1 or 3 tests. While transmission of the pathogen appeared to be unaffected by the maternal acquisition of immunity, **signs of smoldering infection in the young was suggested by the decline in humoral responses in successive progeny and** by unusual rabbit infectivity test results. With each pregnancy there was a remarkable booster in the maternal humoral response, which dropped significantly prior to term.'

Wicher, K., Baughn, R. E., Abbruscato, F., & Wicher, V. (1999). Vertical transmission of Treponema pallidum to various litters and generations of guinea pigs. *The Journal of infectious diseases*, *179*(5), 1206–1212. https://doi.org/10.1086/314718.

Researchers calling for Prospective studies in Mother-Baby Pairs

	Prospective Longitudinal Investigation of mother baby pairs exposed to Lyme disease is needed.	Ref
1986	"the frequency of adverse outcomes reported here warrants further surveillance and epidemiologic and laboratory studies of pregnant women with Lyme disease."	1
1989	"Additional research is needed to **define the exact risk of transplacental transmission of Lyme disease,** the clinical consequences of such transmissions and the appropriate management of these cases."	2
1989	"Although the potential for B. burgdorferi to cause congenital disease has clearly been established, the frequency of transmission is not known. Furthermore, because of the chronic persistence of the organism in the untreated patient, it is not known whether patients who were infected prior to pregnancy can transmit the infection to the fetus. The answers to these questions will **require large scale prospective studies**.'	3
1994	"A large, **prospective longitudinal investigation of pregnant women with Lyme disease** that utilizes sensitive measures for both the diagnosis of Lyme disease and the identification of neurologic disorders could help to determine the precise incidence of Lyme disease during pregnancy, the rate of transplacental transmission of B. burgdorferi, and the full implications of transplacental transmission for the infant."	4
1990	"There is an **obvious need for controlled studies of large numbers of patients** to determine conclusively the effect, if any of Lyme disease infections during pregnancy. Unfortunately, there are many difficulties faced by the investigator, not the least of which is that serologic testing of the mother and fetus may not be an accurate reflection of the presence or absence of B. burgdorferi infection."	5
1996	**Long-term follow-up of infants born to mothers with placental spirochetes** is needed to determine what effect, if any, placental spirochetes may have on the development and health of these individuals.	6
1997	'As the disease is uncommon and anomalies less common, **larger epidemiologic studies are required for a definitive resolution** to the question of fetal risks with perinatal infection.'	7
2001	'Determination of true risk to the fetus and infant of maternal gestational Lyme disease **requires prospective studies of all pregnancy outcomes of gestational Lyme disease**, long-term follow-up of live-born products of these pregnancies and improved diagnosis of Lyme disease in affected fetuses, placentas and infants.'	8
2010	"Ideally a **prospective, multicenter study should be conducted** enrolling sufficient numbers of women, in order to adequately address these research questions."	9
2018	'additional research using currently accepted methods of LD diagnosis, an improved understanding of LD, and larger sample sizes (**e.g. via large multi-center observational studies) is needed to more adequately explore** possible effects of gestational LD and further investigate potential risk factors.'	10
2020	The literature on "Congenital Lyme" is at present incomplete due to lack of intensive investigations, and l**ack 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.	11

Citations:

(1) Markowitz LE, Steere AC, Benach JL, Slade JD, Broome CV. Lyme disease during pregnancy. JAMA. 1986 Jun 27;255(24):3394-6.

(2) Cartter M, Hadler J, Gerber M, Mofenson L. Lyme Disease and Pregnancy. Connecticut Medicine. Volume 53 (6), June 1989.

(3) Luft BJ, Dattwyler RJ. Lyme Borreliosis. Current Clinical Topics Infectious Disease. 1989; 10:56-81.

(4) Gerber M, Zalneraitis E. Childhood neurologic disorders and Lyme disease during pregnancy. Pediatric Neurology Vol 11(1), 1994.

(5) Edly S. Lyme Disease During Pregnancy. New Jersey Medicine. Vol 87 (7), July 1990.

(6) 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.

(7) Silver HM. Lyme disease during pregnancy. Infect Dis Clin North Am. 1997 Mar;11(1):93-7.

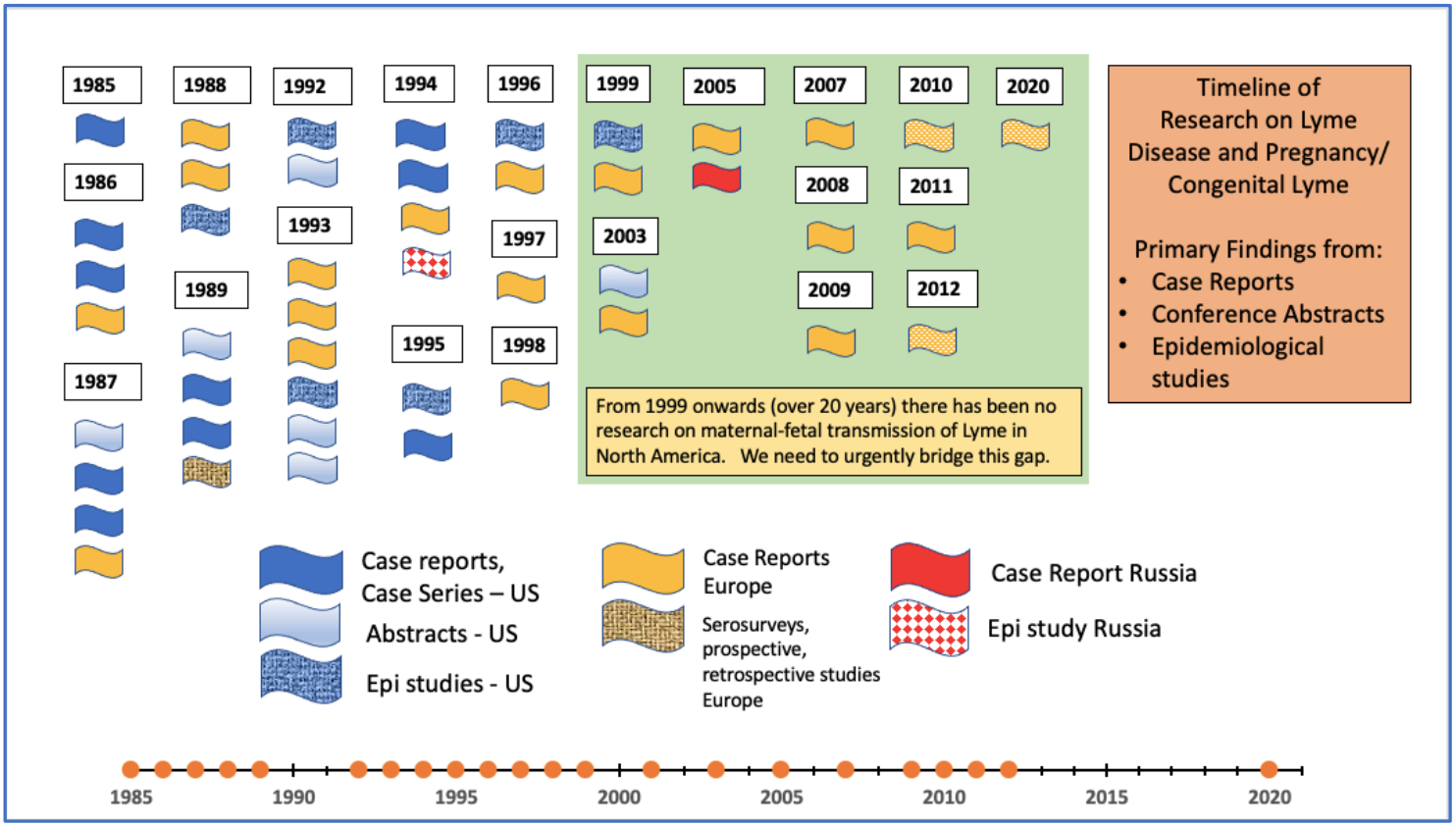
(8) Gardner T. Infectious Diseases of the Fetus and Newborn Infant. In: Remington JS, Klein JO, editors. Lyme Disease, Chapter 11. 5th ed. Philadelphia, PA: The W.B. Saunders Co.;2001. pp. 519-641.

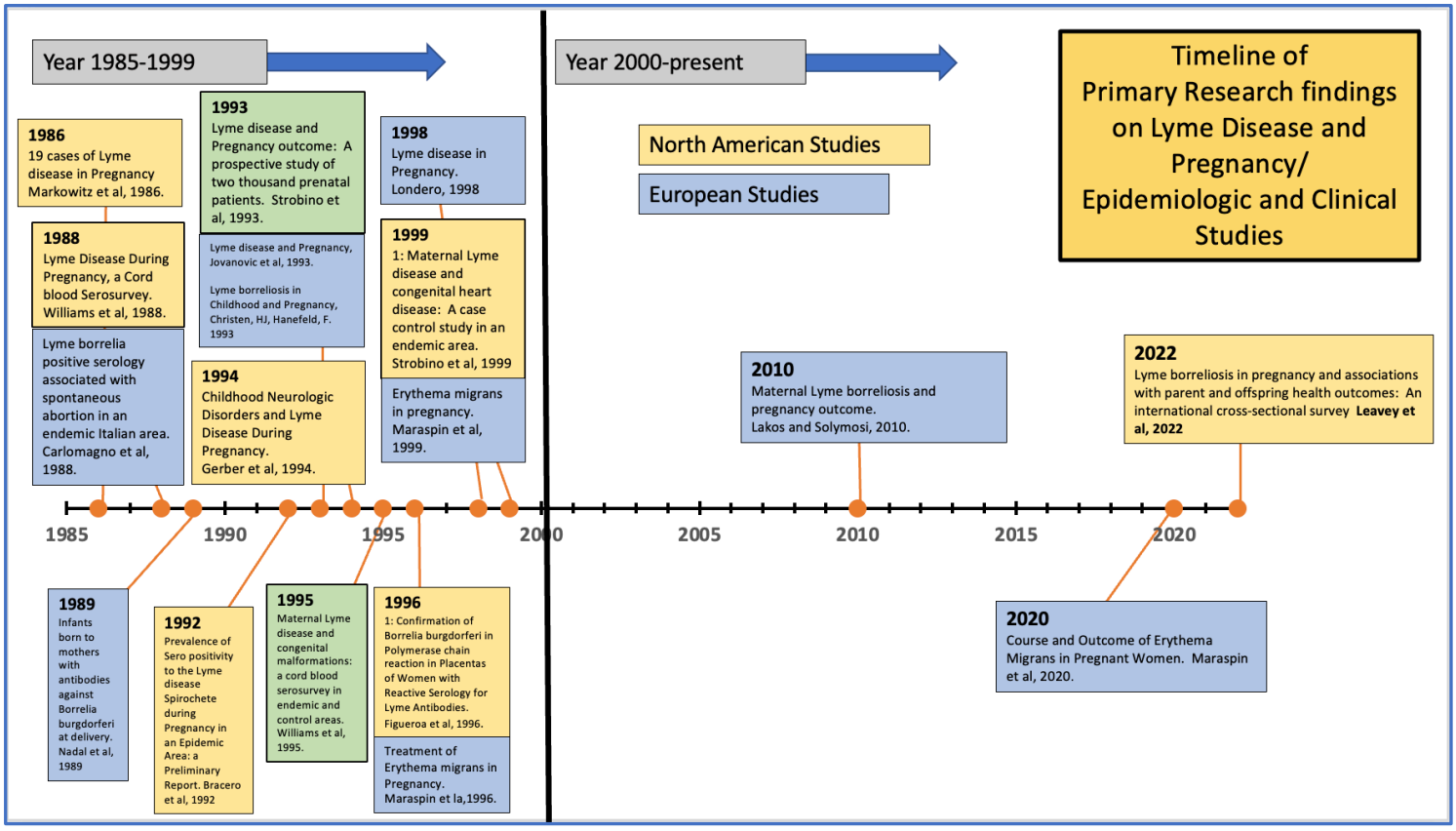
(9) Lakos A, Solymosi N. Maternal Lyme borreliosis and pregnancy outcomes. Inf J Infect Dis 2010;14:e494-e498.

(10) Waddell LA, Greig J, Lindsay LR, Hinckley AF, Ogden NH (2018) A systematic review on the impact of gestational Lyme disease in humans on the fetus and newborn. PLoS ONE 13(11): e0207067.

(11) Lambert JS. An Overview of Tickborne Infections in Pregnancy and Outcomes in the Newborn: The Need for Prospective Studies. *Front Med (Lausanne)*. 2020;7:72. Published 2020 Mar 6.

Timeline of Research on Lyme Disease and Pregnancy – 1985- Present





Research Solutions

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

Lyme and Pregnancy Registries: National/State/Provincial.

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

Developing care plans for neonates at potential risk for congenital or intrapartum infection.

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

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

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 disease.