Lyme and Pregnancy Webinar Supplemental Information: April 29, 2021.
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Maternal-fetal transmission of Bb, adverse pregnancy outcomes and congenital infection has been documented over the last 35 years since the pioneering case report by Schlesinger et al[1] was published in 1985, resulting in widespread notification of this alternate mode of transmission through epidemiological bulletins issued by the Centres for Disease Control[2] (CDC), World Health Organization[3] and Canadian Federal Health authorities.[4]

The CDC has recently updated their online public guidance to address the risk of maternal-fetal transmission of Bb.[5] Vertical transmission of Bb also been reported by the U.S. Tick-borne Working Group 2018 Federal Report to Congress[6] by the National Institutes of Health[7] and Government of Canada, Canadian Centre for Occupational Health and Safety.[8] Several medical experts have suggested that Bb be added to the list of microbes known to cause congenital and perinatal infections.[9] [10] [11]

The UK Royal Society of Obstetricians and Gynecologists[12] has listed Lyme disease as one of the infectious organisms which can cross the placenta leading to late intrauterine fetal death and stillbirth. The American College of Obstetricians and Gynecologists (ACOG) 1991 committee opinion acknowledges spirochetes can cross the placenta with resulting stillbirth,[13] and a 2003 review in the American Journal of Obstetrics and Gynecology (AJOG) also identifies Bb as etiologic for stillbirth.[14]

[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. https://pubmed.ncbi.nlm.nih.gov/4003991/
[2] MMWR. 'Lyme disease and cases occurring during pregnancy' Vol 34, No 25, June 28, 1985), pp. 376-378. https://www.cdc.gov/mmwr/preview/mmwrhtml/00000569.htm
[3] World Health Organization, Geneva. Weekly Epidemiological Record. No. 39. 26 September 1986. Page 297-304.
[4] Health and Welfare Canada. Lyme Disease in Canada. Canada Dis Wkly Report, June 4, 1988.
[5] U.S. Department of Health and Human Services. Centers for Disease Control and Prevention. Ticks and Lyme Disease: Pregnancy and Lyme Disease. Updated Jan 27, 2020. https://www.cdc.gov/lyme/resources/toolkit/factsheets/Pregnancy-and-Lyme-Disease-508.pdf Date accessed: July 7, 2020
[6] https://www.hhs.gov/sites/default/files/tbdwg-report-to-congress-2018.pdf (Best way to cite?)
[7] U.S. Department of Health and Human Services. National Institutes of Health. Lyme Disease, The Facts, The Challenge. NIH Publication No. 08-7045, July 2008.
[8] Canadian Centre for Occupational Health and Safety. Lyme Disease. June 2008. Date accessed: July 7, 2020. https://web.archive.org/web/20080602101953/http://www.ccohs.ca/oshanswers/diseases/lyme.html
[9] Stray-Pedersen, B. (1993). *New Aspects of Perinatal Infections. Annals of Medicine, 25(3), 295–300.* doi:10.3109/07853899309147878.
[10] Boyer SG, Boyer KM. Update on TORCH Infections in the Newborn Infant. Newborn and Infant Nursing Reviews, Vol 4, No 1 (March), 2004:pp70-80. https://www.medscape.com/viewarticle/472409
[11] Maldonado Y, Nizet V, O.Klein J, Remington J, Wilson C. Current concepts of Infections of the Fetus and Newborn Infant (Chapter 1). Found in Remington and Klein Infectious Diseases of the Fetus and Newborn Infant, 8th edition, 2015. https://www.elsevier.com/books/remington-and-kleins-infectious-diseases-of-the-fetus-and-newborn-infant/wilson/978-0-323-24147-2
[12] Late Intrauterine Fetal Death and Stillbirth. Royal College of Obstetricians and Gynecologists. Green-top Guideline No. 55, October 2010.
[13] ACOG Committee Opinion: Committee on Obstetrics: Maternal and Fetal Medicine. Lyme disease during pregnancy. Int J Gynecol Obset 1992, 39:59-60. https://pubmed.ncbi.nlm.nih.gov/1358705/
[14] Goldenberg, R. L., & Thompson, C. (2003). *The infectious origins of stillbirth. American Journal of Obstetrics and Gynecology, 189(3), 861–873.* doi:10.1067/s0002-9378(03)00470-8

Several animal studies have identified that vertical transmission of Borrelia burgdorferi can occur. [15] [16] [17] [18] Gustofen whose PhD dissertation[19] focused on vertical transmission in dogs and foxes states: '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.' A group of researchers from China[20] who identified and reported vertical transmission in naturally infected mice and rats state: 'in-utero transmission is a potential means by which the spirochete can be transmitted in a breeding population in the absence of a tick vector.'

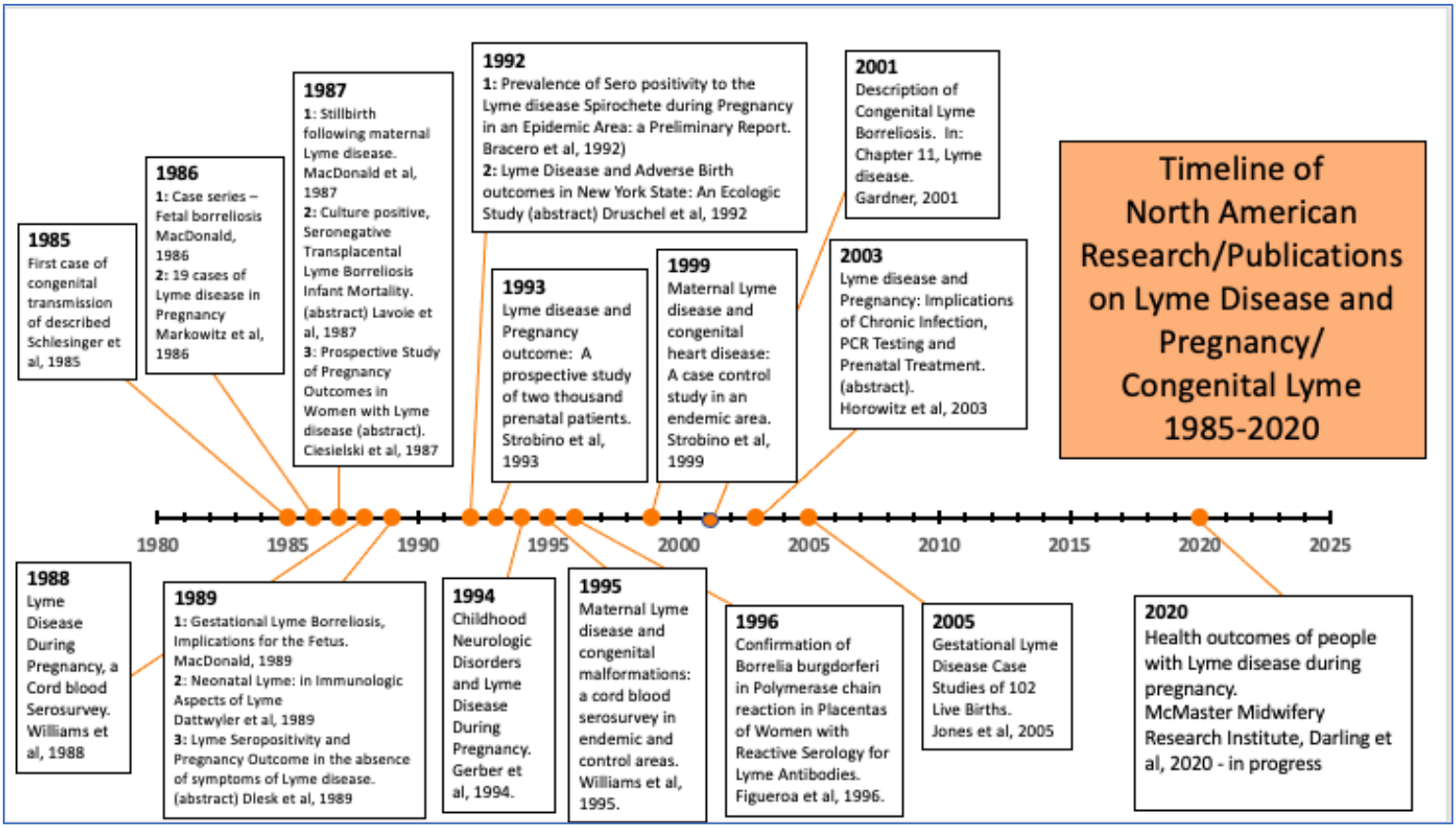
Case reports in humans also describe transmission of Borrelia burgdorferi from mother to baby[21] with outcomes ranging from miscarriage[22] and stilbirth,[23] [24] to cases of neontal death[25] [26] and congenital infection[27] [28] with multi-system clinical presentations.[29]

Since 1999, (over 20 years), there has been a lack of government funded research exploring maternal-fetal transmission of Borrelia burgdorferi in North America. The last NIH funded research on this issue was published in 1996 [30] and identified Borrelia burgdorferi by PCR in placentas of a small subset of women without history of tickbite or objective clinical manifestations of Lyme with borderline to negative serology. Researchers at that time recommended further investigation: '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.' Clearly, the prevalence, incidence, clinical spectrum and potential long-term health consequences of infants exposed to Lyme in-utero must be further examined.[31]

[15] Burgess EC, Gendron-Fitzpatrick A, Mattison M. Foal mortality associated with natural infection of pregnant Mares with Borrelia burgdorferi. In Proceedings, 5th Int Conf Equine Infectious Dis, 1989, 217-220.
[16] Ubico-Navas, SR. Experimental and epizootiologic studies of Lyme disease. Ph.D. Dissertation. Colorado State University, 1992.
[17] Liebstein M. M., Khan M. I., Bushmich S.L. Evidence for in utero transmission of Borrelia burgdorferi from naturally infected cows. J Spirochetal Tick-Borne Dis 1998; 5(4):54-62.
[18] Gustafson JM, Burgess EC, Wachal MD, Steinberg H. Intrauterine transmission of Borrelia burgdorferi in dogs. AM J Vet Res. Vol 54, No. 6, June 1993.
[19] Gustafson, John Michael, Ph.D. The in utero and seminal transmission of Borrelia burgdorferi in Canidae. The University of Wisconsin - Madison, 1993. PhD Thesis.
[20] Khanlin W, Zhefu Z, Hongying W, Xuexia H, et al. Preliminary investigation on reservoir hosts of borrelia Burgdorferi in China. Journal of Hygiene Research. 1999 Jan 30;28(1):7-9.
[21] 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. https://europepmc.org/article/med/3130607
[22] Horowitz RI. Lyme disease and pregnancy: Implications of chronic infection, PCR testing, and prenatal treatment. In Proceedings of the 16th International Scientific Conference on Lyme Disease & Other Tick– Borne Disorders, Hartford, CT, USA 2003 Jun (pp. 7-8).
[23] MacDonald, A. Lyme borreliosis. Implications for the Fetus. Rheum Dis Clin North Am. 1989;15(4):657-77. https://pubmed.ncbi.nlm.nih.gov/2685924/
[24] Maraspin V, Cimperman J, Lotric-Furlan S, Pleterski-Rigler D, Strle F (1999) Erythema migrans in pregnancy. Wien Klin Wochenschr 111:933–940.
[25] Lavoie PE, Lattner BP, Duray P. H et al. Culture positive, seronegative, transplacental Lyme borreliosis infant mortality (abstract no W/TH-P-92). In: Abstracts (book 2) of the 4th International Conference on Lyme borreliosis, 1990. Stockholm, Sweden, p 128.
[26] 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. https://pubmed.ncbi.nlm.nih.gov/4003991/
[27] Trevisan G, Stinco G, Cinco M. Neonatal skin lesions due to a spirochetal infection: a case of congenital *Lyme borreliosis*? Int J Dermatol. (1997) 36:677–80. https://pubmed.ncbi.nlm.nih.gov/9352409/
[28] Dattwyler R, Volkman D., Luft B. Immunologic aspects of Lyme borreliosis. Review of Infectious Diseases Vol 11(6) 1989. https://pubmed.ncbi.nlm.nih.gov/2682961/
[29] 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.
[30] 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.
[31] Bale, James F.; Murph, Jody R. (1992). Congenital Infections and the Nervous System. Pediatric Clinics of North America, 39(4), 669–690.

State of the art science is required to investigate the research gaps and complexities of this alternate mode of transmission and will require a collaborative multi-disciplinary, multi-stakeholder 'relay-team' approach, which values an integrative model of bringing together patients with lived experience, front-line clinicians, clinical researchers and scientists to collectively identify, propose and carry out further investigation.

Timeline of North American Research/Publications on Lyme disease and pregnancy and congenital Lyme.



Researchers/Clinicians recommend additional research and prospective studies:

Many past researchers and investigators have highlighted the necessity and importance of large-scale prospective studies as a critical next step.

	Research Recommendations	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
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.'	9
2020	The literature on "Congenital Lyme" is at present incomplete due to lack of intensive investigations, and lack of longitudinal follow up of exposed infants, as has been done for another spirochete, syphilis. There is no doubt that congenital infection occurs with Borrelia; whether a congenital syndrome occurs as a result of this *in utero* infection remains to be further investigated.	10

Research Recommendations – 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. 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.

10. 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.

Lyme and Pregancy Registry:

A Lyme and Pregnancy registry needs to be re-initiated to inform epidemiological surveillance and collect important data. This should be accompanied with the formation of a biobank/biorepository with samples from mother baby pairs such as placentas, amniotic fluid, cord-blood, serum, urine, breastmilk and other tissue which could be accessed by researchers for further investigation. This kind of information could inform the creation of a surveillance and clinical case definition for congenital Lyme.

Opportunity:

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

Pregnancy Registry

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

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

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

CDC: Lyme Disease 01/01/1991

Interim Guidelines for Lyme and Pregnancy:

Interim guidelines for the evaluation, treatment and follow-up of infants born to mothers with Lyme during pregnancy needs to be developed. These could systematically guide and assist frontline clinicians caring for pregnant patients with Lyme and with babies who may have been exposed to Lyme in-utero.

This guideline would identify appropriate laboratory testing, assessment tools, treatment recommendations and recommendations for histological evaluation of samples such as placentas and cord tissue. It could be modified as more data accumulates but would serve as a necessary starting point.

Of note, a similar guideline was initiated by the CDC after the first case of transplacental transmission of West Nile Virus was first identified. https://www.cdc.gov/mmwr/preview/mmwrhtml/mm5307a4.htm

Cases reporting maternal-fetal transmission of Borrelia burgdorferi /spirochetes/borrelia species to offspring and/or placenta ranging between 1985-1987.

Year	Case	Method Bb identified in placenta/fetus/infant/child	Ref
1985	Maternal Tickbite **1st trimester** + EM rash. Untreated Pregnancy Seropositive mother. Infant born at 35 weeks, died at 39 hours	**Bb identified in fetal autopsy tissue by. Silver stain.** Spirochetes morphologically compatible with Bb were identified in spleen, renal tubules/kidney and bone marrow. Later MacDonald identified Bb in myocardium with IHC.	1
1986	Four cases of fetal borreliosis – in all four cases no infections were diagnosed in mothers. Maternal toxemia noted in two cases.	**Spirochetes were cultured from fetal liver** in four stillborn human fetuses, three of whom demonstrated congenital malformations of the heart or great vessels. Spirochetes were identified in paraffin embedded formalin fixed fetal tissues in each case using IFA.	2
1986	No tick bite no, EM Asymptomatic, sero + Untreated pregnancy Multi-system inflammatory disease in infant.	Multi-system inflammatory disease in infant. Elevated IgG ELISA titers repeatedly identified in child's serum which decreased w antibiotic therapy	3
1986	No maternal recall of tick bite, no symptoms suggestive of Lyme borreliosis, untreated. Delivered stillborn fetus at 33 weeks. Positive IFA, negative for syphilis.	**Spirochetes seen by darkfield examination** of the lung, liver and brain tissue specimens. No attempt to culture spirochetes was done in autopsy tissues.	3
1986	Maternal tick bite and EM rash in 1st trimester. Treated for Lyme (two separate courses). Serologic testing for Bb positive. Delivered premature infant at 32 weeks, died shortly after.	Autopsy revealed hydrocephalus, a fluidothorax, ascites but no malformations. **Dark-field microscopy of lung and liver tissue showed spirochetes**. No attempt to culture spirochetes was done in autopsy tissues.	4
1987	Maternal Tickbite **1st trimester** + EM rash. Untreated Pregnancy, Seropositive mother. Stillborn delivered at term	**Bb cultured from fetal liver** 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	5
1987	No maternal recall tick-bite, no EM Subclinical infection. Untreated Seronegative mother. Infant healthy at birth, died at 8 days.	Upon autopsy Borrelia Burgdorferi was **cultured from a frontal cerebral cortex.** Silver stain of brain and heart confirmatory of tissue infection	6

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 AB. Human fetal borreliosis, toxemia of pregnancy, and fetal death. Zentralbl Bakteriol Mikrobiol Hyg A. 1986 Dec;263(1-2):189-200.

3. Lampert, R. Infantile multisystem inflammatory disease: another case of a new syndrome. Eur J Pediatr (1986) 144:593-596.

4. Maraspin V, Cimperman J, Lotric-Furlan, S et al. Erythema migrans in pregnancy. Wein Klin Wochenschr (1999) 111/22-23:933-940.

5. MacDonald A, Benach J, Burgdorfer W. Stillbirth following Maternal Lyme Disease. New York State Journal of Medicine vol 87, November 1987.

6. 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

Cases reporting maternal-fetal transmission of Borrelia burgdorferi /spirochetes/borrelia species to offspring and/or placenta ranging between 1988-1996.

Year	Case	Method Bb identified in placenta/fetus/infant/child	Cite:
1988	Tick Bite/EM rash **1st Trimester** Treated Pregnancy Sero + mother Baby born initially healthy but died shortly thereafter	Bb spirochetes identified in neonate brain and liver. Bb identified in paraffin sections of infant brain using **monoclonal antibody H5332**.	7
1989	Mother infected in second trimester. Treated for Lyme. Seronegative.	Baby was born with neurologic dysfunction. Spinal tap on neonate reveals serological evidence of **antibodies specific to borrelia in CSF**.	8
1989	Case series of 14 pregnancies. 3/14 women had history of tick bite/Lyme dx. 8/14 cases where spirochetes/Bb identified in fetal tissue, mother was seronegative.	2/10 SIDS cases identified spirochetes morphologically consistent w Bb in neonate brain. 2 cases of neonatal death, spirochetes identified in tissue (5, 6) 4 cases stillbirth (1, 2, 3, 10); 2 cases miscarriage, Bb identified fetal tissue (4,9) 2 cases miscarriage, spirochetes identified in fetal tissue (7, 8) 2 cases live birth, neonate symptomatic, Bb identified in placenta (11, 12) 1 case live birth, neonate asymptomatic, Bb identified in placenta (13)	9
1992	No maternal tick bite, no EM Asymptomatic, Maternal serology revealed significantly increased IgM titer and slightly increased IgG. Untreated pregnancy	Infant born w neonatal sepsis, treated w antibiotics. **CSF and blood of 3-day old infant revealed increased IgG and IgM Borrelia antibodies**. Total IgM was greatly increased. Syphilis and mononucleosis were negative in mother and child.	10
1994	Maternal tick bite, EM, flu like symptoms in 1968, was not treated. Later developed arthritis, cranial neuritis, meningitis, depression.	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 by immunoblot.	11
1995 / 2001	Mild early Congenital Lyme borreliosis (pt23 + 26)Severe Early Congenital Lyme borreliosis (pt 24) Late Congenital Lyme Borreliosis (patient 25)In all cases, mothers were treated w varying courses of antibiotics for Lyme.	In all cases infants were initially seronegative by ELISA, in one case at 9 months infant had positive EIA. **All infants had positive lymphocyte proliferation assay (LPA)**. In two cases dense sclerotic transverse metaphyseal bands were identified in the long bones which disappeared with IV ceftriaxone.	12
1996	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.	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. Cord blood was negative in all three cases by IgG and IgM Western Blots, normal perinatal outcome was observed.	13

7. 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

8. Dattwyler R, Volkman D, Luft B. Immunologic aspects of Lyme borreliosis. Review of Infectious Diseases, Vol 11(6) 1989.

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

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

11. Gasser R, Dusleag J, Reisinger E, et al. A Most Unusual Case of a Whole Family Suffering from Late Lyme Borreliosis for Over 20 Years. *Angiology*. 1994;45(1):85-86.

12. 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.

13. Figueroa R, Bracero LA, Aguero-Rosenfeld, M et al. 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.

Cases reporting maternal-fetal transmission of Borrelia burgdorferi /spirochetes/borrelia species to offspring and/or placenta ranging between 1997-2011

Year	Case	Method Bb identified in placenta/fetus/infant/child	Cite:
1997	No maternal tick-bite or EM reported. Mother was asymptomatic and seropositive (slightly high IgG 1:128, cutoff 1:64). Untreated pregnancy	Infant w dermatologic manifestations at 3 weeks. **Bb + by PCR of skin** specimen at 9 mths serology neg by IFA, ELISA, WB. At 13 mths neg IFA/EIA but IgG seroconversion Treated w seven courses of antibiotics for recurring skin manifestations.	14
2003	Lyme Dx prior to Pregnancy. Sero + IgG WB. Extensive Treatment prior to pregnancy Miscarriage 18wks PCR positive placenta and fetal tissues	Miscarriage 18wks **PCR Bb positive placenta and fetal tissues at MDL labs**	15
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.	Case history studies on 102 cases of children or adolescents diagnosed with gestational Lyme . Frequency of multi-system symptoms listed. Two cases w detail given including **one case where both amniotic fluid and cord-blood tested positive for Borrelia burgdorferi** and another case of congenital neuroborreliosis marked by hypotonia, drooling, and speech impediment.	16
2005	Mother has tick Bite 1st Trimester, develops high fever, presumed flu. Untreated Pregnancy. After birth dx w tetra paresis, neuroborreliosis ALS.	Child dx w congenital neuroborreliosis w symptoms starting at 2years 10 months, **negative EIA, Bb PCR pos**, child's symptoms improved w antibiotics.	17
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**.	18
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.	Child 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 2: **suspected genome and plasmid in umbilical cord blood and positive genome w suspected plasmid in placenta**.	19
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.** (full description from Maraspin, 2020 – Table 4).	20/21
2011	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.	22

14. 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.

15. 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.

16. Jones, CR., Smith H., Gibb E, Johnson L. Gestational Lyme Disease Case Studies of 102 Live Births. Lyme Times, Gestational Lyme Studies, Summer 2005, pp. 36-38.

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

18. Onk, G., Acun C., Murat K., et al. Gestational Lyme disease as a cause of Congenital Hydrocephalus. J Turkish German Gynecol Assoc. Vol 6(2):156-157.

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

20. Hercogova J, Vanousova D. Syphilis and borreliosis during pregnancy. Dermatol Ther. 2008 May-Jun;21(3):205-9.

21. 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.

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

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

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

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

14 cases of live-birth, neonatal infection and adverse outcomes
2 cases of live-birth, Bb identified by PCR in cordblood of infants whose mothers were treated

17 cases Bb identified by PCR in placentas of treated (15) and untreated (2) women
1 case Bb identified by immunohistochemical techniques in placenta of treated woman
2 cases whereby Bb has been identified in breastmilk by PCR of women with EM rash

IHC = immunohistochemistry
IFA = indirect immunofluorescence
H5332 – monoclonal antibody specific to Bb (Osp A)
https://pubmed.ncbi.nlm.nih.gov/6192088/

8 cases of live birth and subsequent neonatal death

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

1985	Infant born at 35 weeks, died after 39 hours. Mother had EM in first trim. Not treated.	Borrelia compatible w Bb identified in multiple organs. Bb identified in Myocardium later by IHC	Schlesinger et al. MacDonald, 1989
1986	Infant born at 32 weeks, died hours later. Mom had tickbite and EM. Was been treated for Bb, was seropositive.	Darkfield microscopy revealed spirochetes in fetal lung, liver.	Maraspin et al. (1999)
1987	Infant healthy at birth, died at 8 days. Mother had no hx tickbite or EM rash. Was seronegative.	Bb cultured from frontal cerebral cortex. Silver stain confirmed infection in brain ad 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 using monoclonal antibody H5332.	Weber et al (1988)

1989	Two cases of neonatal death Case 5 live birth 39 weeks died shortly thereafter Case 6 live birth 40 weeks died shortly therafter.	Case 5: Spirochetes identified by immunohistochemistry in fetal tissue. Case 6: 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.	MacDonald, 1989

4 Cases of stillbirth

- **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**

1986	33 week stillborn infant. Mother had positive serology (IFA) neg. syphilis. No recall tickbite/symptoms.	Spirochetes identified by darkfield microscopy in lung liver and brain tissue specimens.	Maraspin et al (1999)
1987/1989	(Case 1) 40 week term stillborn infant. Mother had EM rash in first trim. Not treated. Seropos 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
1986/1989	(Case 3) stillbirth 23 weeks. No medical history for Lyme or tickbite, was seronegative for Bb	B. burgdorferi was identified in tissue by indirect immunofluorescence.	Macdonald, 1986/1987.
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

7 cases of miscarriage:

- **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**

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 immunoflourescence.	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 immunoflourescence.	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
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 Lyme 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

14 cases Intrauterine Lyme infection/Fetal borreliosis/Congenital Lyme with adverse outcomes. (suspected and confirmed)

1986	No recall of tick bite or EM rash Asymptomatic mother Untreated pregnancy, later found to be seropositive Bb IgG.	Multi-system inflammatory disease in infant. Elevated IgG ELISA titers repeatedly identified in child's serum which decreased w antibiotic therapy Authors question intrauterine infection with Lyme as precursor to this syndrome.	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 the 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.	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	Infant developed neonatal sepsis, treated w antibiotics. CSF and blood of 3-day old infant revealed increased IgG and IgM Borrelia antibodies. Total IgM was greatly increased. Syphilis and mononucleosis were negative in mother and child.	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 by immunoblot.	Gasser et al, 1994.
1995 /2001	**Mild early Congenital Lyme borreliosis:** (Patient number 23)	See chapter for details	Gardner, 2001
1995, 2001	**Mild Early Congenital Lyme borreliosis:** (Patient number 26)	See chapter for details	Gardner, 2001

1995, 2001	**Severe Early Congenital Lyme borreliosis:** (Patient number 24)	See chapter for details	Gardner 2001
1995, 2001	**Late Congenital Lyme Borreliosis** (Patient number 25)	See chapter for details	Gardner 2001
1997	No maternal tick-bite or EM reported. Mother was asymptomatic and seropositive (slightly high IgG 1:128, cutoff 1:64). Untreated pregnancy	Infant w dermatologic manifestations at 3 weeks. **Bb + by PCR of skin** specimen at 9 mths serology neg by IFA, ELISA, WB. At 13 mths neg IFA/EIA but IgG seroconversion Treated w seven courses of antibiotics for recurring skin manifestations.	Trevison, et al 1997
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.	Details of testing in one case given: Both amniotic fluid and cord-blood of one infant tested positive for Borrelia burgdorferi.	Jones et al, 2005
2005	Mother has tick Bite 1st Trimester, develops high fever, presumed flu. Untreated Pregnancy. After birth dx w tetraparesis, neuroborreliosis ALS.	Child dx w congenital neuroborreliosis w symptoms starting at 2years 10 months, **negative EIA, Bb PCR pos**, child's symptoms improved w antibiotics.	Lazebnik 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

2 cases of Bb identified in cord blood 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

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

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.	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.	Figueroa et al, 1996
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
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

1 case Bb identified in placenta by monoclonal antibody

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.** (full description from Maraspin, 2020 – Table 4).	Hercagova et al, 2008; Maraspin et al, 2020

2 cases Bb identified by PCR in breastmilk

2008	'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.'

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.

Vertical transmission of Borrelia burgdorferi in animals
(note green highlight denotes natural infection, yellow highlight is experimental study)

Animal	Findings	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"	2
Mice 1993	'Transplacental transmission of B. burgdorferi was demonstrated in a M. musculus and in a P. leucopus from Farm 2.	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	"Among 49 infected from groups A and C, 5(10.2%) transmitted Bb to their pups either in-utero or intrapartum. Four of the litters from the mating pairs in group B had infected pups. The described mouse model with further modifications may provide a tool for studying such transmission modes and treatment strategies."	5
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.'	6

1. Anderson JF, Johnson RC, Magnarelli LA. Seasonal Prevalence of Borrelia burgdorferi in Natural Populations of White-Footed Mice, Peromyscus leucopus. Journal of Clinical Microbiology, Vol 25(8)Aug, 1987, p. 1564-1566.

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

3. 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.

4. Silver RM, Yang L, Daynes RA, Branch DW, Salafia CM, Weis JJ. Fetal outcome in murine Lyme disease. *Infect Immun*. 1995;63(1):66-72. doi:10.1128/IAI.63.1.66-72.1995

5. Altaie SS, Mookherjee S, Assian E, Al-Taie F, Nakeeb SM, Siddiqui SY. Transplacental transmission of Bb in a Murine Model. 10th Annual International Scientific Conference on Lyme Disease and other Tick-Borne Disorders, National Institutes of Health, Bethesda MD April 28-30, 1997.

6. 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

Vertical transmission of Borrelia burgdorferi in animals – continued
(note green highlight denotes natural infection, yellow highlight is experimental study)

Animal	Findings	Ref:
Cows 1988	"B. burgdorferi was cultured from the blood of a newborn calf, and an aborted calf had antibodies to B. burgdorferi indicating in-utero infection. 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."	7
Cows 1998	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."	8
Horses 1989	"The demonstration of antibodies in the serum of Foal 2 and the isolation of spirochetes from Foal 1 suggest infection took place in-utero."	9
Dogs 1993	"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."	10/11
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 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	"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."	12

7. Burgess EC. Borrelia burgdorferi infection in Wisconsin horses and cows. Ann N Y Acad Sci. 1988;539:235-43. doi: 10.1111/j.1749-6632.1988.tb31857.x. PMID: 3190095.

8. 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.

9. Burgess EC, Gendron-Fitzpatrick A, Mattison M. Foal mortality associated with natural infection of pregnant Mares with Borrelia burgdorferi. In Proceedings, 5th Int Conf Equine Infectious Dis, 1989, 217-220.

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

11. 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.

12. Burgess EC, Windberg LA. Borrelia SP. Infection in Coyotes, Black-Tailed Jack Rabbits and Desert Cottontails in Southern Texas. Journal of Wildlife Diseases 25(1), 1989, pp. 47-51.

Published Literature with recognition/discussion of maternal-fetal transmission of Borrelia burgdorferi ranging from 1985 to 2020.

Year	Maternal Fetal transmission of Lyme Disease	Cite:
1985	"The **Lyme disease spirochete may also spread transplacentally to organs of the fetus**. The mother in this case developed Lyme disease during the first trimester of pregnancy; spirochetes were seen in the spleen, kidney and bone marrow of the infant at term. In addition, the infant had several cardiac abnormalities" "**If the infant is ill, the diagnosis of congenital Lyme disease should be considered**."	1
1986	'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.'	2
1987	'**Lyme disease in pregnancy may be transmitted from mother to fetus**. Untreated infections have the potential for stillbirth and other adverse outcomes including malformations of the cardiovascular system. One case of cortical blindness has been listed in an infant born to a woman who had Lyme disease during her pregnancy. An additional infant showed reactive Borrelia serology, conjunctivitis, blepharitis, strabismus, mental retardation, cranial enlargement, chronic meningitis, recurrent arthritis and persistent maculopapular rash since birth.'	3
1988	"The organism, like other pathogenic spirochetes, is probably transmissible via the placenta to the fetus. **B. burgdorferi infection of fetuses has been documented**."	4
1988	"Lyme disease has become a prevalent and serious infection. It has been shown to cause fatal myocarditis, respiratory failure, panophthalmitis, leading to blindness, **fetal death** and central nervous system syndromes suggestive of demyelination."	5
1988	'**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..'	6
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. 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."	7

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. Burgdorfer W. The Enlarging Spectrum of Tick-Borne Spirochetoses: R. R. Parker Memorial Address, Reviews of Infectious Diseases, Vol 8, Issue 6, November 1986, 932–940.

3. MacDonald AB. Lyme Disease. A Neuro-ophthalmologic View. Journal of Clinical Neuro-ophthalmology 7(4): 185-190, 1987.

4. Barbour, A G. "Laboratory aspects of Lyme borreliosis." *Clinical microbiology reviews* vol. 1,4 (1988): 399-414. doi:10.1128/cmr.1.4.399

5. Case Records of the Massachusetts General Hospital. Case 51-1988. NEJM Dec 22, 1988. 319(25):1654-1662.

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

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

Year	Maternal Fetal transmission of Lyme Disease	Cite:
1989	"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**."	8
1989	**'Transplacental passage of B. burgdorferi can occur and has been associated with congenital heart disease, developmental delay, cortical blindness, spontaneous abortion, and stillbirth**.' 'Pregnant women with early or late Lyme borreliosis should be treated with high intravenous doses of penicillin G because orally administered therapy may not be sufficient to Prevent infection of the fetus.'	9
1989	"A variety of host factors have the potential to contribute to the spread of the pandemic. **A case of maternal-fetal transmission of the Lyme spirochete was reported when an infant died of congenital heart defects** and the spirochete was found in its spleen, kidney, and bone marrow (but not in its heart). The mother had untreated Lyme disease."	10
1989	"In humans**, B. burgdorferi is capable of infecting the fetus**. Sequelae (including abortion and fetal abnormalities) have been associated with 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 observations)."	11
1989	"**Autopsy and clinical studies have associated gestational Lyme borreliosis with various medical problems** including fetal death, hydrocephalus, cardiovascular anomalies, neonatal respiratory distress, hyperbilirubinemia, intrauterine growth retardation, cortical blindness, sudden infant death syndrome, and maternal toxemia of pregnancy."	12
1989	"Additional **research is needed to define the exact risk of transplacental transmission of Lyme disease, the clinical consequences of such transmission, and the appropriate management of these cases**."	13
1989	"**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." Taken together these data suggest that infection with B. burgdorferi during pregnancy poses a risk to the fetus. It seems prudent for women attempting to conceive to take measures to minimize exposure to ticks. Oral antibiotic treatment has failed in preventing transplacental transmission in one reported case leading to fetal perinatal borreliosis."	14

8. Luft, BJ, Gorevic, PD, Halperin JJ, Volkman DJ, Dattwyler, RJ. A Perspective on the Treatment of Lyme Borreliosis.

9. Eichenfield AH., Athreya BH Lyme disease: Of ticks and titers. The Journal of Pediatrics. 114(2), 1989, p 328-333.

10. Hamilton, D. Lyme Disease. The Hidden Pandemic. Postgraduate Medicine. Vol 85, No 5, April 1989. pp. 303-314.

11. Dattwyler RJ, Volkman DJ, Luft BJ. Immunologic aspects of Lyme borreliosis. Rev Infect Dis. 1989 Sep-Oct;11 Suppl 6:S1494-8. doi: 10.1093/clinids/11.supplement_6.s1494

12. Macdonald, AB. Gestational Lyme borreliosis. Implications for the fetus. Rheum Dis Clin North Am. 1989;15(4):657-77.

13. Cartter ML., Hadler JL., Gerber MA., Mofenson LM. Lyme disease and Pregnancy. Connecticut Medicine, June 1989; 53(6); 341-342.

14. Belani K, Regelmann WE. Lyme Disease in Children. Rheum Dis Clin North Am. Nov. 1989;15(4):679-68

Year	Maternal Fetal transmission of Lyme Disease	Cite:
1989	'The transplacental transmission of B. burgdorferi has now been reported in two infants whose mothers had Lyme borreliosis during the first trimester of pregnancy.'	15
1990	"Transplacental transmission of Lyme disease does appear to occur in human pregnancy. Unequivocal confirmation of B. burgdorferi infection of the fetus by isolation of the organism from fetal tissue obviously is limited to those cases where fetal or neonatal death has occurred. Despite this limitation, several cases of transplacental transmission of B. burgdorferi have been documented."	16
1991	"B. Burgdorferi infection during pregnancy can cause infection of the fetus."	17
1991	"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, stillbirths, 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."	18
1991	'Congenital infection with Borrelia burgdorferi, the agent of Lyme disease, was first reported in 1985. Confirming reports have appeared since. In all these studies the fetal inflammatory response was minimal and did not include any particular reaction in the intestinal tract and the Borrelia organisms were rarely seen in the tissues. These observations are also true in experimental Lyme disease.'	19
1991	"Transplacental transmission was recognized in 5 of 19 pregnancies reported in one study. Injuries there included fetal wastage, syndactyly, cortical blindness, prematurity and neonatal rash. The organism has been cultured from fetal organs and from two neonatal deaths, one resulting from aortic thrombosis". "Of the 19 mothers in the above quoted study on transplacental transmission, 80% were falsely seronegative." "The likelihood of placental infection is highest early in the disease when hematogenous spread is active. Very low-grade spirochetemia likely occurs in later stages and may continue for indefinite periods."	20
1992	'Instances of severe illness in infants following transmission from untreated mothers has already lowered the threshold for more aggressive treatment of pregnant women.'	21
1992	"Spirochetes cross the placenta and have been found in the tissues of stillborn 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 seronegative. It may be preferable to treat pregnant patients on the basis of the described clinical picture prior to development of later maternal disease."	22
1992	"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"	23

15. Steere, AC. Lyme Disease. The New England Journal of Medicine. Aug 31, 1989. Vol 321, No 9. p 586-596.

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

17. Plotkin SA, Peter G., et al. Committee on Infectious Diseases. Treatment of Lyme Borreliosis. Pediatrics. Vol 88 (1), July 1991.

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

19. Abramowsky C, Beyer-Patterson P, Cortinas E. Nonsyphilitic spirochetosis in Second-Trimester Fetuses. Pediatric Pathology, 11, 827-938, 1991.

20. Lavoie, PE. Lyme Disease. In Conn's Current Therapy, 1991. Ed: Robert Rakel. W.B Saunders Company. P. 101-105

21. Kaslow, Richard A. (1992). Current Perspective on Lyme Borreliosis. JAMA: The Journal of the American Medical Association, 267(10), 1381–.1383.

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

23. Bracero L.A, Wormser G.P, Leikin E et al. Prevalence of seropositivity to the Lyme disease spirochete during pregnancy in an epidemic area: A Preliminary Report'. Journal of Maternal-Fetal Investigation.

Year	Maternal Fetal transmission of Lyme Disease	Cite:
1992	"Lyme disease during pregnancy has been associated with neonatal death and congenital heart disease, and the organism has been detected in neonatal brain tissue. Although congenital infection with B. burgdorferi appears to be infrequent, additional studies are needed to determine the incidence and clinical spectrum of congenital Lyme disease. Lyme disease can be established by serologic studies, although such methods have relatively high rates of false-negative or false-positive results. "	24
1992	"The spirochete has been isolated from blood, cerebrospinal fluid and skin lesions of patients with Lyme disease, and maternal-fetal transmission of the spirochete has been demonstrated. Adverse outcomes resulting from maternal transmission may include intrauterine death, prematurity, cortical blindness with developmental delay, hyperbilirubinemia, petechial rash, and congenital cardiac abnormalities."	25
1993	"There have been two cases in which congenital Lyme borreliosis was conclusively diagnosed. The neonates in these cases, both of whom died shortly after birth and whose mothers had erythema migrans during the first trimester of pregnancy were autopsied. The results showed B. burgdorferi infection in different organs (heart, spleen, liver, kidneys, bone marrow and brain), although no signs of tissue inflammation. Possible manifestation of congenital Lyme borreliosis, based on observations in individual cases, are premature or stillbirths, cardiovascular defects and various slight dysplastic stigmata."	26
1993	"Human transplacental transmission of Borrelia type spirochetes can have side effects such as fetal infection in every trimester of pregnancy and sometimes even fetal death. Most often it causes damage to the cardiovascular system of the fetus but can also be isolated from other fetal tissues such as: the liver, the heart, the adrenal gland, the kidneys, meninges, cerebrospinal fluid. Infection during pregnancy can cause abortion, fetal death, premature birth, intrauterine growth failure or acute illness."	27
1993	"In 1974, attention was called to the acronym TORCH to highlight a group of microbes known to cause congenital and perinatal infections, namely Toxoplasma, Rubella, Cytomegalovirus and Herpes Simplex virus." "Now the 'other' component in addition should include Group B streptococci, parvovirus, varicella zolster virus, Neisseria gonorrhea and Borrelia."	28
1993	"there are case reports that have demonstrated the potential of B Burgdorferi to cross the placenta and infect fetal tissue." "these case reports clearly indicate that the bacteria can infect the fetus and that short-term antibiotic treatment of early stage Lyme disease does not necessarily prevent the fetus from becoming infected."	29
1994	"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." "Of fundamental importance is that the possibility of transplacental transmission of Borrelia has been proven; under what conditions it occurs and how often, remains unclear." "The possibility of transplacental transmission of the pathogen from the mother to fetus has been repeatedly proved via the isolation of Borrelia from various fetal tissues. By culturing on a special liquid medium, silver impregnation of histological preparations and other methods, Borrelia has been found in many organs and tissues of fetuses that died in utero, or in newborns in the neonatal period: in the placenta, myocardium, brain, subarachnoid space, liver, spleen, adrenal glands and bone marrow."	30
1995	"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."	31

24. Bale, James F.; Murph, Jody R. (1992). Congenital Infections and the Nervous System. Pediatric Clinics of North America, 39(4), 669–690.

25. McGowan KL., Hodinka RL. Laboratory Diagnosis of Fetal Infections. Clinics in Laboratory Medicine. Vol 12(3), Sept 1992. pp 523-552.

26. Christen HJ, Haneford F, Eiffert H, Thomssen R. Epidemiology and Clinical Manifestations of Lyme Borreliosis in Childhood. Acta Pediatr Suppl 386:1-76, 1993.

27. Jovanovic R, Hajric A, Cirkovic A, Mikovic Z, Dmitrovic R. Lyme Disease and Pregnancy. Serbian Academy of Science and Art. Medical Science Sector, Book 43. Belgrade, 1993. -translated from Serbian

28. Stray-Pederson, B. New Aspects of Perinatal Infections. Annals of Internal Medicine 25: 295-300, 1993).

29. 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.

30. 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

31. 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.

Year	Maternal Fetal transmission of Lyme Disease	Cite:
1995	"As the prevalence of Lyme disease has increased, the concern has grown about the effect of Lyme disease on the fetus and infected mother. As discussed in this review, cases have been reported of transplacental passage of the spirochete, resulting in fetal infections and possibly death." "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."	32
1996	'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."	33
1996	"Several reports of Lyme disease during pregnancy suggest and association between maternal infection and fetal morbidity and mortality. Transplacental transmission has been documented by identifying the spirochete in fetal and placental tissue using immunofluorescence and silver stains."	34
1997	"Maternal-to-fetal transmission has been well documented in only three cases. Two women had erythema migrans in the first trimester, which was not treated. A third woman was given inadequate antibiotic treatment for erythema migrans. The infants born to these three mothers died of respiratory, cardiac or hepatic failure in the first 48 hours of life, and Bb was found in multiple systems. The frequency with which Lyme infection is associated with adverse outcome during the first trimester is not known but thought to be very rare."	35
1999	"In recent years it has been confirmed that during spirochetemia, B. Burgdorferi sensu lato may cross the placental barrier and cause an adverse outcome of pregnancy."	36
1999	"Spirochetes have been observed in tissues taken from fetuses and neonates who died in the perinatal period when the mother has had Lyme disease during pregnancy."	37
1999	"Perinatal transmission. Although like syphilis, Lyme disease has a potential for transplacental transmission, there is no recognized congenital Lyme disease syndrome, and there are only a few well-documented reports of congenital B. burgdorferi infection. At least two were in women with untreated infection during the first trimester, and in one B. burgdorferi was recovered from the fetal liver of the stillborn baby." "It is clear from some of these reports that Bb can be transmitted transplacentally."	38
2001	"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."	39

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

33. Maraspin V, Cimperman J, Lotric-Furlan S et al. Treatment of Erythema Migrans in Pregnancy. Clinical Infectious Diseases 1996; 22, 788-93.

34. Figueroa R, Bracero LA, Augero-Rosenfeld, M et al. 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.

35. Krause PJ., Telford SR. Emerging Tick-Borne Zoonoses: Lyme Disease, Babesiosis, Human Granulocytic Ehrlichiosis. Seminars in Pediatric Infectious Diseases, Vol *, No 1 (January), 1997: pp 34-43.

36. Maraspin V, Cimperman J, Lotric-Furlan, S et al. Erythema migrans in pregnancy. Wein KlinWochenschr (1999) 111/22-23:933-940.

37. Strobino B, Abid S, Gewitz M. Maternal Lyme disease and congenital heart disease: A case-control study in an endemic area. Am J Obstet Gynecol. March 1999. Vol 180, Number 3, Part 1.

38. Sood SK. Lyme disease. The Pediatric Infectious Disease Journal. 18(10), October 1999, pp 913-925.

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

Year	Maternal Fetal transmission of Lyme Disease	Cite:
2001	Although a homogeneous congenital Lyme borreliosis syndrome has not yet emerged, there are several features that are common among the 66 adverse outcomes of pregnancies complicated by gestational Lyme Borreliosis'; 'Although relatively few cases of congenital Lyme borreliosis have been studied pathologically, comparisons with congenital syphilis may be appropriate.'	40
2001	"There is little doubt 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.'	41
2003	"Pregnant women should be especially careful to avoid ticks in Lyme disease areas because infection can be transferred to an unborn child. Although rare, such a prenatal infection may make the woman more likely to miscarry or deliver a stillborn baby."	42
2003	"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."	43
2003	"The listed cases highlight 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. In addition, bacteremia of clinically manifest Lyme borreliosis can long precede the failure of antibiotic treatment to reduce fetal infection despite successful therapy of maternal disease. At the current state of affairs would at least be required to treat the expectant mother in a tick bite during pregnancy prophylactically antibiotic and abandon the usual wait-and-see attitude. Possible benefits of this, however, would only those pregnant women who are aware of a tick bite and go to the doctor."	44
2005	It is known that transplacental transmission of the spirochete from mother to fetus is possible. Many studies have associated gestational LD with fetal death, hydrocephalus, cardiovascular anomalies, neonatal respiratory distress, hyperbilirubinemia, intrauterine growth retardation, cortical blindness, sudden infant death syndrome and maternal toxemia of pregnancy."	45
2005	'The insidious nature of gestational Lyme disease can present a complicated diagnosis due to the delay of presentation, the multi-systemic often transient nature of symptoms that can vary in severity and change with progression of the disease, and finally, the unreliability of standard diagnostic tests.'	46
2007	'Toxoplasma gondii, leptospirosis, Listeria monocytogenes and the organisms which cause leptospirosis, Q fever and Lyme disease have all been implicated as etiologic for stillbirth.'	47

40. 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.

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

42. US Department of Health and Human Services. National Institutes of Health. Lyme Disease: The Facts, the Challenge. NIH Publication No. 03-7045, April 2003.

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

44. Horst, H. Borrelieninfektion in der Schwangerscharft und durch Bluttransfusionen. In H. Horst (ed.) Zeckenborreliose Lyme-Krankheit bei Mensch und Tier (4th ed., pp. 132-137). Balingn, Germany: Spitta Vergag GmbH & Co., KG. **translated from German

45. Onk G, Acun C, Kalayci M et al. Gestational Lyme Disease as a rare cause of congenital hydrocephalus. J Turkish German Gynecol Assoc, Vol 6(2); 2005-156-157.

46. Jones, CR, Smith H, Gibb E, Johnson L. Gestational Lyme Disease Case Studies of 102 Live Births. Lyme Times. 2005(summer):36-38

47. 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.

Year	Maternal Fetal transmission of Lyme Disease	Cite:
2008	"They Lyme disease spirochete was found to be disseminated through bites from species of deer tick found throughout North America. During the subsequent epidemiologic characterization of Lyme disease, it was shown to cause transplacental infection of the fetus and was associated with stillbirth. Multiple reports of congenital Lyme disease prompted large serosurveys of pregnant women; these studies also suggested a link with pregnancy wastage and congenital defects."	48
2008	"The present authors believe that taxonomical relationship of T. Pallidum and B. burgdorferi is responsible for similar clinical course of syphilis and Lyme borreliosis, including congenital infections. Further studies are needed to answer the question of a possible teratogenic effect of B. burgdorferi in humans."	49
2009	"Another spirochetal infection associated with stillbirth is Lyme disease, a systemic illness caused by the tick-borne spirochete Borrelia burgdorferi. The first case of stillbirth associated with Lyme disease was described in 1987. In that case, the mother acquired the disease in the first trimester, and at 34 weeks was delivered of a stillborn infant who had B. burgdorferi in the placenta and internal fetal organs."	50
2010	'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. '	51
2010	Transplacental infections associated with IUFD include cytomegalovirus(Evidence level 2+), syphilis (Evidence level 1+) and parvovirus B19 (Evidence level 2++) as well as listeria (Evidence level 2+),rubella (Evidence level 3), toxoplasmosis (Evidence level 2+), herpes simplex (Evidence level 2+),coxsackievirus, Leptospira, Q fever, and Lyme disease.'	52
2011	"..B. burgdorferi can cross the placenta, presumably during a period of spirochetemia. The frequency and clinical significance of transplacental transmission are unclear however."	53
2011	"The likelihood of a transplacental infection is probably higher at the beginning of pregnancy than in the remaining duration of pregnancy. Besides abortion, malformations such as syndactyly, ventricular septum defect and heart rate defects have been described."	54
2011	"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."	55

48. Theiler RN., Rasmussen SA et al. Emerging and Zoonotic Infections in Women. Infect Dis Clin North Am. Dec 2008; 22(4) 755-viii.

49. Hercogova J, Vanousova D. Syphilis and borreliosis during pregnancy. Dermatologic Therapy, Vol. 21, 2008, 205-209.

50. McClure E, Goldenberg R. Infection and stillbirth. Semin Fetal Neonatal Med. August; 2009 14(4): 182–189

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

52. Late Intrauterine Fetal Death and Stillbirth. Royal College of Obstetricians and Gynecologists. Greentop Guideline No. 55, October 2010.

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

54. Mylonas I. Borreliosis during pregnancy: a risk for the unborn child? Vector borne zoonotic dis.2011;11(7):891-8.

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

Year	Maternal Fetal transmission of Lyme Disease	Cite:
2011	"Transplacental transmission occurs as is evidenced by the presence of B. burgdorferi organisms isolated from postmortem and placental tissue." "In those reported cases of Lyme disease associated with neonatal death, the mother had received inadequate treatment with only penicillin or no treatment at all. In a 1989 case report, MacDonald demonstrated successful treatment of Lyme Disease during pregnancy and a healthy infant outcome. The case reports are too few to draw any definitive conclusion about the risk of Lyme disease to the fetus or any specific correlation with congenital anomalies. However, prompt diagnosis and treatment are recommended."	56
2013	"Data regarding pregnancy outcomes are mixed. Borrelia burgdorferi (the bacterial strain seen in the United States) does appear to cross the placenta and infect the fetus. There are data to suggest an increased incidence of spontaneous abortion, stillbirth, and congenital malformations associated with Lyme disease. In contrast, multiple other studies have found no increased risk of fetal death or cardiac anomalies. The overall conclusion from these data seems to be that transplacental passage is extremely rare, and infection early in pregnancy is more likely to be associated with adverse outcomes."	57
2015	"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. 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. 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."	58
2015	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."	59
2015	"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."	60
2016	Other fatal complications reported include a case of acute respiratory distress syndrome, and neonatal death after transplacental transmission.'	61
2017	"Intra-human transfer of Borrelia can be initially silent or unrecognized, and if not successfully treated, infection can be life long and latency, late activation and reactivation are common. Therefore, continued investigation into new cases of pregnancies acutely afflicted by Lyme disease and reporting of such cases is in order to add to the growing body of evidence regarding the pathophysiology and clinical outcomes of congenital Lyme disease. Thankfully, through the already available case reports, animal studies and epidemiological studies, we have gained valuable insight. The similarities of the clinical presentation of congenital syphilis to pregnancies with acute Lyme disease helps guide ante partum management. Due to the severity of previously documented cases, there should be a low threshold of suspicion to diagnose cases of Lyme disease in pregnancy.	62

56. Qasba N, Shamshirsaz AA, Feder HM, Campbell WA, Egan JF, Shamshirsaz AA. A case report of human granulocytic anaplasmosis (ehrlichiosis) in pregnancy and a literature review of tick-borne diseases in the United States during pregnancy. Obstet Gynecol Surv. 2011 Dec;66(12):788-96.

57. Dotters-Katz SK, Kuller J, Heine RP. Arthropod-borne bacterial diseases in pregnancy. Obstet Gynecol Surv. 2013 Sep;68(9):635-49

58. 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.

59. Feder H. Borrelia Infections: Lyme Disease and Relapsing Fever. (Chapter 17). Found in Remington and Klein's Infectious Diseases of the Fetus and Newborn Infant, 8th ed., 2015.

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

61. Muehlenbachs A, Bollweg BC, Schulz TJ, et al. Cardiac Tropism of Borrelia burgdorferi: An Autopsy Study of Sudden Cardiac Death Associated with Lyme Carditis. Am J Pathol. 2016 May;186(5):1195-205.

62. O'Brien JM., Hamidi OP. Borreliosis Infection during pregnancy. (2017). Ann Clin Cytol Pathol 3(8; 1085.

Year	Maternal Fetal transmission of Lyme Disease	Cite:
2018	'Across 59 cases, negative outcomes for the fetus or newborn occurred in 36 (61%) pregnancies. Negative outcomes ranged from spontaneous miscarriage (termination of pregnancy prior to when the fetus is considered viable, approximately 28weeks) (n = 10), fetal death and stillbirth after 28 weeks (n = 2) and death shortly following birth (n = 8, four were premature, born before 36 weeks gestation), to a range of congenital abnormalities and health issues (n = 16) including hyperbilirubinemia, respiratory distress, syndactyly, and ureter and heart abnormalities.' '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.'	63
2018	'Congenital LB infections can contribute to developmental disorders and neuropsychiatric impairments. Congenital transmission of Bartonella has also been documented. Since 1985 there are over 60 references documenting congenital transmission and associated pathological outcomes with LB/TBD. The most comprehensive study was a review of 263 cases and included cases of miscarriage, stillbirth, perinatal death, congenital anomalies, systemic illness, early onset fulminant sepsis and later-onset chronic progressive symptoms associated with gestational LB.'	64
2020	"The literature on "Congenital Lyme" is at present incomplete due to lack of intensive investigations, and lack of longitudinal follow up of exposed infants, as has been done for another spirochete, syphilis. There is no doubt that congenital infection occurs with Borrelia; whether a congenital syndrome occurs as a result of this in utero infection remains to be further investigated."	65
2020	'During spirochetemia in the acute phase of infection, B burgdorferi sl may spread transplacentally, and evidence for congenital infection has indeed been reported in a few cases where Borrelia species were cultured from the newborn post mortem.'	66
2020	'Untreated Lyme disease during pregnancy can lead to infection of the placenta. Spread from mother to fetus is possible but rare. Fortunately, with appropriate antibiotic treatment, there is no increased risk of adverse birth outcomes.* There are no published studies assessing developmental outcomes of children whose mothers acquired Lyme disease during pregnancy.'	67

63. 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.

64. Bransfield RC. Neuropsychiatric Lyme Borreliosis: An Overview with a Focus on a Specialty Psychiatrist's Clinical Practice. Healthcare (Basel). 2018 Aug 25;6(3):104. doi: 10.3390/healthcare6030104.

65. 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. doi:10.3389/fmed.2020.00072

66. Kullberg B J, Vrijmoeth H D, van de Schoor F, Hovius J W. Lyme borreliosis: diagnosis and management *BMJ* 2020; 369 :m1041 doi:10.1136/bmj.m1041

67. US CDC. https://www.cdc.gov/lyme/resources/toolkit/factsheets/Pregnancy-and-Lyme-Disease-508.pdf

Research Priorities/Opportunities:

- **Patient-Centered inclusive research partnerships** which welcome and value patient/family priorities.
- **Developing interim guidelines for assessing/testing/treating infants** born to mothers with Lyme disease and as more data emerges, developing a case definition for congenital Lyme.
- **Multi-center long-term prospective follow-up studies of mother-baby** pairs to determine maternal cofactors (acute vs chronic infection) related to maternal-infant transmission and short and long-term maternal and infant outcomes.
- **Novel diagnostic methods to detect Borrelia-infected mothers and infants** including comparative antibody studies, identifying immunodominant antigens in WB, potential biomarkers, T-cell testing, nucleic acid testing, culture, PCR, whole genome sequencing in serum, cord-blood, amniotic fluid, urine, CSF.
- **Study of the sensitivity and specificity of current laboratory** tests in pregnant women and neonates for diagnosing Lyme infection
- **Lyme and Pregnancy Registries**: National/State/Provincial
- **Biorepositories**: Samples of pregnant people with acute Lyme, late-stage Lyme, subclinical Lyme and post-treatment Lyme Disease including serum, amniotic fluid, placenta, products of conception. Samples of offspring exposed to Lyme in-utero including cord blood, serum, urine.
- **Screening:** Effective approaches for Borrelia burgdorferi screening in pregnant women
- **Detailed Histopathologic evaluation** of any placenta, miscarriage, stillbirth or perinatal death from a pregnancy complicated by Lyme borreliosis.
- Study of **Maternal and neonate immune response** to Bb infection in pregnancy and identification of possible biomarkers to identify Bb infection in both cohorts.
- **Breast-milk studies** from lactating mothers with Lyme borreliosis (acute or chronic) using culture and PCR and risk assessment regarding potential transmissibility 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 Lym

Current Lyme and Pregnancy Research Opportunity - Recruiting participants:

McMaster Lyme and Pregnancy Research Study in English:
https://obsgynresearch.mcmaster.ca/surveys/index.php?s=MN9CCXDTW9

McMaster Lyme and Pregnancy Research Study in French:
https://obsgynresearch.mcmaster.ca/surveys/?s=KWJT9K9TR9

Overview of Lyme and Pregnancy Study:
https://www.lymehope.ca/news-and-updates/ground-breaking-lyme-and-pregnancy-research-launches